A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP13254.

Heat Exposure and Cause-Specific Hospital Admissions in Spain: A Nationwide Cross-Sectional Study

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Background: More frequent and intense exposure to extreme heat conditions poses a serious threat to public health. However, evidence on the association between heat and specific diagnoses of morbidity is still limited. We aimed to comprehensively assess the short-term association between cause-specific hospital admissions and high temperature, including the added effect of temperature variability and heat waves and the effect modification by humidity and air pollution.

Methods: We used data on cause-specific hospital admissions, weather (i.e., temperature and relative humidity), and air pollution [i.e., fine particulate matter with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$), fine particulate matter with aerodynamic diameter ≤10 μm (PM_{10}), NO_2, and ozone (O_3)] for 48 provinces in mainland Spain and the Balearic Islands between 1 January 2006 and 31 December 2019. The statistical analysis was performed for the summer season (June–September) and consisted of two steps. We first applied quasi-Poisson generalized linear regression models in combination with distributed lag nonlinear models (DLNM) to estimate province-specific temperature–morbidity associations, which were then pooled through multilevel univariate/multivariate random-effect meta-analysis.

Results: High temperature had a generalized impact on cause-specific hospitalizations, while the added effect of temperature variability [i.e., diurnal temperature range (DTR)] and heat waves was limited to a reduced number of diagnoses. The strongest impact of heat was observed for metabolic disorders and obesity [relative risk (RR) = 1.978; 95% empirical confidence interval (eCI): 1.772, 2.208], followed by renal failure (1.777; 95% eCI: 1.629, 1.939), urinary tract infection (1.746; 95% eCI: 1.578, 1.933), sepsis (1.543; 95% eCI: 1.387, 1.718), urolithiasis (1.490; 95% eCI: 1.338, 1.658), and poisoning by drugs and nonmedicinal substances (1.470; 95% eCI: 1.298, 1.665). We also found differences by sex (depending on the diagnosis of hospitalization) and age (very young children and the elderly were more at risk). Humidity played a role in the association of heat with hospitalizations from acute bronchitis and bronchiolitis and diseases of the muscular system and connective tissue, which were higher in dry days. Moreover, heat-related effects were exacerbated on high pollution days for metabolic disorders and obesity ($PM_{2.5}$) and diabetes (PM_{10}, O_3).

Discussion: Short-term exposure to heat was found to be associated with new diagnoses (e.g., metabolic diseases and obesity, blood diseases, acute bronchitis and bronchiolitis, muscular and connective tissue diseases, poisoning by drugs and nonmedicinal substances, complications of surgical and medical care, and symptoms, signs, and ill-defined conditions) and previously identified diagnoses of hospital admissions. The characterization of the vulnerability to heat can help improve clinical and public health practices to reduce the health risks posed by a warming planet. https://doi.org/10.1289/EHP13254

Introduction

Climate change is increasing the frequency and intensity of exposure to extreme heat conditions, which poses a serious threat to public health globally.[1] In some high-income regions such as Europe and the United States, heat waves are already by far the largest cause of mortality related to extreme weather events, causing thousands of premature deaths each year.[2–4] But in addition to mortality, high ambient temperatures also contribute to the burden of morbidity, including emergency department visits[5] and hospital admissions.[6] The health impacts of heat are, however, unequal across population subgroups, being the elderly, infants, and people with cardiorespiratory and other chronic diseases at highest risk of hospitalization or death, irrespective of the geographical region.[1] Unless strong global climate change mitigation actions are put in place, temperatures are projected to increase at an accelerated rate in the future,[7] which in conjunction with a rapidly ageing population[8] and urbanization (i.e., urban heat island),[9] could exacerbate the heat-related risks and impacts. Nonetheless, this scenario is subject to a high level of uncertainty, given that the eventual impact of heat will greatly depend on the degree of societal adaptation to climate change.[10,11]

To date, epidemiological studies focusing on the association of high temperature with hospitalizations have documented heat effects for several large groups of disease (cardiovascular, respiratory, urinary, endocrine and metabolic, infectious, skin, mental, neoplasms), both in developing and developed countries.[12–17] However, although analyses have been conducted for some more specific diagnoses of hospital admission (such as pneumonia,[18] chronic obstructive pulmonary disease,[19] asthma,[20,21] diabetes,[22] renal failure,[23,24] gastroenteritis,[25] heart and cerebrovascular diseases[26,27]), there are still many causes of morbidity that have not been analyzed so far. Furthermore, while the independent impacts of heat on morbidity are well established, it remains uncertain whether those are modified by humidity and air pollution. This issue is of especial relevance because, from a physiological perspective, the exposure to higher levels of humidity should worsen heat stress by decreasing sweat evaporation,[28] and because the compound heat–humidity extremes and heat–pollution extremes (especially heat–ozone) are projected to increase under global warming.[29–31] A more comprehensive assessment is therefore needed to fill the literature gaps, and thus inform health adaptation policies to best tackle the detrimental health consequences of climate change.

In the present study, we aimed to analyze the short-term association between high temperatures and cause-specific hospital admissions in Spain, a country that emerges as a major hotspot in terms of both the impact of global warming[32] and human longevity.[33] The analysis also included the added contributions of heat

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Supplemental Material is available online (https://doi.org/10.1289/EHP13254).

The authors declare they have no conflicts of interest related to this work to disclose.

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Received 2 May 2023; Revised 20 March 2024; Accepted 2 April 2024; Published 22 May 2024.

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waves, temperature variability, and compound hot and humid/polluted events, which are all projected to increase in a warmer world.[31,34–36]

Methods

Data Sources

This country-wide cross-sectional study used data on hospital admissions, weather (i.e., temperature and relative humidity), air pollution [i.e., fine particulate matter with aerodynamic diameter $\leq$2.5 μm ($PM_{2.5}$), fine particulate matter with aerodynamic diameter $\leq$10 μm (PM_{10}), NO_2, and ozone (O_3)], and relevant contextual indicators for 48 provinces in mainland Spain and the Balearic Islands (see map in Figure S1). There were no missing values for any of the used data.

Health data. Individual-level records of hospital admissions both from public and private hospitals between 1 January 2006 and 31 December 2019 were provided by the Spanish National Institute of Statistics (INE). The database included the following variables for the patients: sex, age, date of admission and discharge, province of residence and hospitalization, type of admission [i.e., planned (scheduled) or emergency (unscheduled)], primary diagnosis of admission, type of discharge (i.e., recovery, death, transfer, other), and length of hospital stay (in days). The database did not include unique identifier of patient, and therefore, readmissions or admissions belonging to the same subject could not be identified. Individual records of patients residing in the same province where they were hospitalized were aggregated by date of admission and province of residence-hospitalization in order to conduct the statistical analyses described below. The analysis was restricted to emergency hospital admissions. Note that a patient is considered admitted to the hospital when that person has spent at least one night in the health center.

Environmental data. Gridded ($0.10^\circ \times 0.10^\circ$) observations of daily mean, minimum, and maximum 2-meter temperature (°C) and daily mean relative humidity (%) were derived from an E-OBS (version 24.0e) dataset.[37] The diurnal temperature range (DTR) was computed as the difference between the daily maximum and minimum temperatures, whereas the interday temperature variation (ITV) was defined as the difference between the daily mean temperature of two consecutive days. As previously described,[38] daily mean concentrations of $PM_{2.5}$, PM_{10}, NO_2, and daily maximum 8-h averages of O_3 across Spain were estimated using a quantile machine learning (QML) model framework at a spatial resolution of 10 km × 10 km. The model's development involved integrating various data sources, including ground monitoring measurements,[39] fine-mode and course-mode aerosol optical depth (AOD),[40] climate and air quality reanalysis data,[41–43] and geographical features (e.g., land-use, topography, road traffic).[44,45] The model was trained using data from across Europe, covering the period from 1 January 2003 to 31 December 2020. To assess the accuracy of the model, we conducted a 10-fold validation. The results showed good performance, with correlation coefficients of 0.80, 0.79, 0.79, and 0.90 for $PM_{2.5}$, PM_{10}, NO_2, and O_3, respectively, when compared with site observations in Europe. The normalized root mean square error (NRMSE) for $PM_{2.5}$, PM_{10}, NO_2, and O_3 predictions in Europe were found to be 1.84%, 2.07%, 8.99%, and 3.35%, respectively, in comparison to site observations. Both meteorological and air pollution data were transformed into provincial estimates by weighting the values with 1 km × 1 km gridded population counts for the year 2011 from INE.[46]

Contextual indicators. Based on plausible relations identified in the existing literature and subject to data availability, we considered several province-level factors that might explain geographical differences in heat-related morbidity risks, which encompass aspects related to health, demography, housing, and socioeconomics. As in a previous study,[47] we extracted the following variables (expressed as a percentage of the provincial population) from the Spanish Population and Housing Census conducted by INE in 2011[46]: population ≥65 years old (to represent ageing), population ≥65 years old living alone (to represent isolation), population living in municipalities of <10,000 inhabitants (to represent the degree of rurality/urbanicity), houses with air conditioning (not available in 2011 Census, and we used instead data from 2001 Census), houses constructed before 1971 (to represent the age of the housing stock), owned dwellings (to represent the prevailing dwelling tenancy regime), and population with tertiary education (to represent the educational level). We also obtained from INE the life expectancy at birth (to represent the health status)[48]; the mortality rate from trachea, bronchi and lung cancer (to represent smoking status)[49]; average net income per capita/household and Gini index (to represent income inequality)[50]; and gross domestic product (GDP) per capita.[51] The average retirement income/pension was derived from the National Social Security Institute (INSS).[52]

Statistical Analysis

The statistical analysis was restricted to emergency (i.e., nonplanned) hospital admissions during the summer season (June–September; 2006–2019) and stratified by diagnosis codes for hospitalizations (see ICD codes in Table S1), sex, and age group.

Time-series regression analysis. In the first step, we estimated province-specific temperature-morbidity associations using a quasi-Poisson generalized linear regression in combination with distributed lag nonlinear models (DLNM). Specifically, the regression model included: *a*) an intercept; *b*) a categorical variable of day of the week to take into account the weekly cycle in morbidity; *c*) a natural cubic B-spline of day of the season with 4 degrees of freedom (df) to control for the seasonality, which was interacted with an indicator of summer/year to relax the assumption of a constant seasonal trend[10]; *d*) a natural cubic B-spline of time with 1 df per decade to account for the long-term trend; *e*) a natural cubic B-spline with 2 df for relative humidity; and *f*) a cross-basis function of temperature produced by DLNM[53] using a natural cubic B-spline both for the exposure–response and lag–response dimensions. The baseline model equation can be written as:

$$\log(\mu) = \alpha + \text{dow} + ns(\text{dos}) \times \text{factor}(\text{year}) + ns(\text{time}) + ns(\text{humidity}) + cb(\text{temp}), \quad (1)$$

where μ denotes the expected number of hospital admissions, α the intercept, dow the day of the week, *ns* the natural cubic splines, dos the day of the season, and *cb* the cross-basis function. The spline representing the exposure–response dimension in the cross-basis was modeled with one internal knot placed at the 90th percentile of the daily mean temperature distribution of June–September. The spline representing the lag–response dimension was modeled with an intercept and one internal knot placed at equally spaced values in the log scale and a lag period extending up to 1 week. The province-specific temperature–hospitalization associations captured by the cross-basis were summarized as relative risk (RR) across the whole range of summer temperatures vs. the province-specific minimum morbidity temperature (MMT) from the cross-basis, with 95% empirical confidence interval (eCI). Sex-specific estimates were calculated with models additionally considering an interaction of the cross-basis with a dummy variable of sex, which can be interpreted as ratio of RR (RRR) with 95% eCI.

Conversely, to test the potential confounding effect of air pollution on heat–morbidity association, we introduced separately in the baseline model (i.e., Equation 1) a linear term for $PM_{2.5}$,

PM_{10}, NO_2, and O_3. To assess the effect modification of heat by relative humidity and air pollutants, we included separately in the baseline model (i.e., Equation 1) an interaction between the cross-basis function of temperature and dummy variables representing humidity and air pollution categories [low (below the province-specific median) and high (above the province-specific median)], and a linear term for the air pollutants in order to account for potential residual confounding. In other words, we stratified the temperature–morbidity associations by humidity/pollutant exposures (days below and above the province-specific median). To examine whether heat waves lead to an additional risk (i.e., added effect) on hospitalizations due to the persistence of extreme temperatures, we included in the baseline model (i.e., Equation 1) a dummy or binary variable with value equal to 1 only for all the heat wave days. We here defined heat wave as a set of at least 2, 3, or 4 consecutive days with daily mean temperatures higher than the province-specific 95th percentile of June–September days. Lastly, to analyze the association between temperature variability and hospital admissions, we introduced in the baseline model (i.e., Equation 1) cross-basis functions of DTR and ITV by using a linear term for the exposure–response dimension and a natural cubic B-spline for the lag–response dimension. The lag–response function was modeled with an intercept and one internal knot placed at equally spaced values in the log scale and a lag period extending up to 1 week. However, given that we found no association between ITV and hospital admissions for any diagnosis, we finally removed this variable from the model. The effect of DTR was expressed as RR increase in hospitalization per 1°C increase in daily DTR with 95% eCI.

The models described above allowed us to obtain sets of coefficients representing, respectively, the associations in each province between morbidity and temperature (including effect modification by relative humidity and air pollution), heat waves, and DTR, as well as their (co)variance matrices.

Meta-analysis and meta-regression. In the second step, we used *a*) univariate (i.e., for heat wave associations) and multivariate (i.e., for temperature and DTR associations) multilevel meta-analysis[54] to pool the province-specific estimates obtained in the previous stage, thus obtaining the average associations across the country, and *b*) multilevel multivariate meta-regression[55] to evaluate the effect modification of the contextual factors on temperature–morbidity associations. Algebraically, the meta-regression model can be written as:

$$\theta_{ij} = \beta_0 + \beta X_j + \gamma_i Y_i + \delta_j Z_{ij} + \varepsilon_{ij},$$
$$\gamma_i \sim N(0, \tau_1^2), \delta_j \sim N(0, \tau_2^2), \varepsilon_{ij} \sim N(0, s_{ij}^2) \quad (2)$$

where θ_{ij} denotes the matrix of spline coefficients representing the temperature–morbidity association accumulated across the lag period in province j ($n = 48$) within region i ($n = 16$); X_j the matrix of meta-predictors with fixed effect coefficients β; Y_i the matrix of indicators of region with random coefficients γ_i; Z_{ij} the matrix of indicators of province with random coefficients δ_j; and ε_{ij} the error term distributed with province-period (co)variance matrices s_{ij}^2. The random coefficients had unstructured (co)variance matrices τ^2. The model with no predictors and only intercepts (i.e., meta-analysis) produced pooled estimates of the coefficient representing the average temperature-health associations across the whole country. Residual heterogeneity was tested and quantified by the multivariate extension of the Cochran Q test and I^2 statistic, respectively. Moreover, a test on the significance of the multivariate association between the outcome parameters and each province-level meta-predictor was carried out by applying a Wald test on the related subset of coefficients.

All statistical analyses were done with R software (version 3.4.3) using the packages *dlnm* (for the first-stage regression) and *mixmeta* (for the second-stage meta-analysis and meta-regression).

Results

Our study included a total of 11,274,252 emergency hospital admissions during the summer season between 2006 and 2019, of which 54.8% corresponded to women. The four leading causes of hospitalization were maternal obstetric causes (16.2%) cardiovascular diseases (14.7%), digestive diseases (12.8%), and respiratory diseases (11.0%). Male patients were more likely to be admitted to the hospital from respiratory diseases (59.7%) and neoplasms (59.2%) than females. More information on the distribution of hospital admission counts by sex, age group, and specific diagnoses is available in Tables S2–S4. The average values (interprovince range) of environmental covariates were as follows: daily mean population-weighted temperature of 22.2°C (18.5 to 26.5), DTR of 13.0°C (7.7 to 16.2), relative humidity of 59.5% (40.4 to 79.8), $PM_{2.5}$ of 10.2 $\mu g/m^3$ (7.2 to 15.2), PM_{10} of 21.4 $\mu g/m^3$ (13.2 to 31.1), NO_2 of 11.2 $\mu g/m^3$ (9.0 to 13.7), and O_3 of 84.6 $\mu g/m^3$ (73.6 to 90.6), during the warm season. As expected, there was an inverse correlation between the daily temperature and daily relative humidity in summer (Pearson correlation $= -0.60$), given that *a*) soil moisture dampens temperatures through evaporation and the release of absorbed incoming solar radiation as latent heat, and *b*) coastal regions are affected by wind breezes, which in summer drive relatively cool and wet air masses from the ocean/sea. Descriptive statistics of the contextual indicators considered in the analysis show a large socioeconomic disparity among the 48 Spanish provinces (Table 1). For example, the life expectancy at birth varied from 80.2 years to 83.7 years; the average net income per household varied from €18,249 to €37,141; the percentage of

Table 1. Summary statistics of emergency hospital admissions in Spain,[a] June–September, 2006–2019 ($n = 11,274,252$).

Variables	Years	Mean (interprovince range)
Hospitalizations		
Daily counts	2006–2019	137.5 (15.6–907.3)
Weather		
Daily mean temperature (°C)	2006–2019	22.2 (18.5–26.5)
Daily relative humidity (%)	2006–2019	59.5 (40.4–79.8)
Air pollution		
Daily $PM_{2.5}$ ($\mu g/m^3$)	2006–2019	10.2 (7.2–15.2)
Daily PM_{10} ($\mu g/m^3$)	2006–2019	21.4 (13.2–31.1)
Daily NO_2 ($\mu g/m^3$)	2006–2019	11.2 (9.0–13.7)
Daily maximum 8-hour O_3 ($\mu g/m^3$)	2006–2019	84.6 (73.6–90.6)
Socioeconomic indicators		
Life expectancy (years)	2004–2019	82.1 (80.2–83.7)
Population ≥65 years (%)	2011	18.9 (13.1–28.8)
Population ≥65 years living alone (%)	2011	21.5 (15.1–24.2)
Trachea, bronchi, and lung cancer mortality rate (per 100,000 people)	2004–2019	48.9 (37.0–70.3)
Population in municipalities of ≤10,000 inhabitants (%)	2011	34.4 (4.5 to 66.6)
Houses with air conditioning (%)	2001	11.2 (1.0–48.0)
Houses constructed before 1971 (%)	2011	32.5 (20.2–52.4)
Owned dwellings (%)	2011	49.8 (38.3–64.1)
Population with tertiary education (%)	2011	14.4 (10.4–23.3)
Average retirement income (€)	2004–2019	864 (637–1,163)
Average net income per capita	2015–2018	10,469 (7,847–15,002)
Average net income per household	2015–2018	25,171 (18,249–37,141)
Gini Index	2015–2018	29.9 (27.2–33.6)
GDP per capita (€)	2004–2018	21,656 (15,996–34,112)

Note: €, euros; GDP, gross domestic product; NO_2, nitrogen dioxide; O_3, ozone; PM, particulate matter.
[a]Forty-eight provinces in mainland Spain and the Balearic Islands.

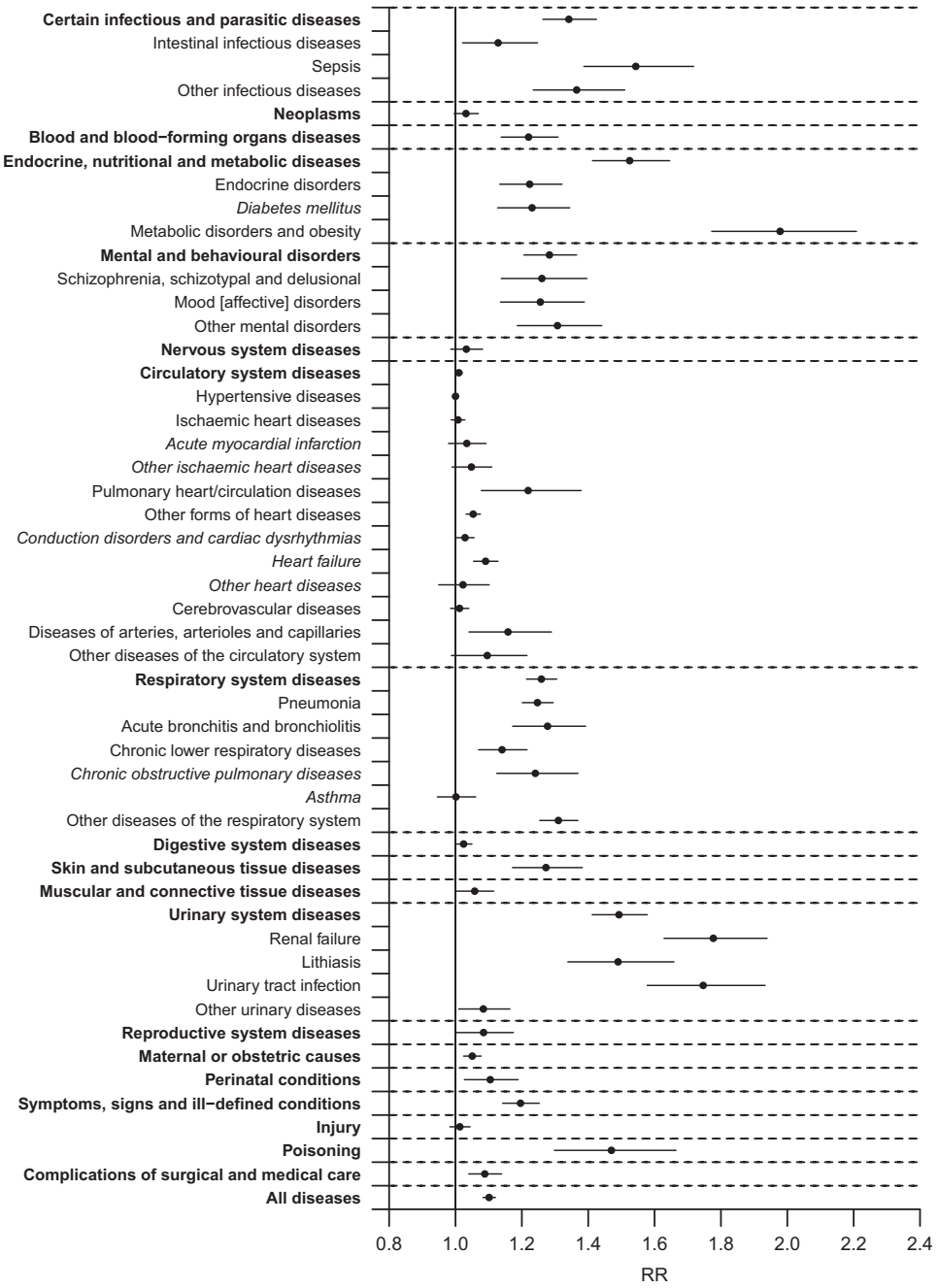

Figure 1. Risk of cause-specific morbidity associated with heat. Relative risk (RR) and 95% confidence intervals (error bars) of hospital admission at the 99th percentile of the distribution of daily June-to-September temperatures vs. the minimum morbidity temperature (MMT). Numerical information is reported in Table S7.

population with tertiary education varied from 10.4% to 23.3%; and the proportion of houses with air conditioning varied from 1.0% to 48.0%. The dependence between the province-level variables is displayed in the correlation matrix (Figure S2).

Figure 1 shows the RR of cause-specific hospital admission at the 99th percentile of the distribution of daily June-to-September temperature with regard to the MMT (see Table S5). The associations for the whole range of summer temperature values are additionally shown in Figure S3. Heat statistically significantly contributed to an increase in the risk of hospitalization for all of the diagnosis code groups, except for neoplasms, nervous system diseases, asthma, digestive system diseases, injuries, and a subset of cardiovascular diseases (hypertension, ischemic heart diseases, and cerebrovascular diseases). The strongest impact of heat was observed for metabolic disorders and obesity [RR = 1.978 (95% eCI: 1.772, 2.208)], followed by renal failure [1.777 (1.629, 1.939)], urinary tract infection [1.746 (1.578, 1.933)], sepsis [1.543 (1.387, 1.718)], urolithiasis [1.490 (1.338, 1.658)] and poisoning by drugs and nonmedicinal substances [1.470 (1.298, 1.665)]. By contrast, heat was only slightly associated with the risk of hospitalization for heart diseases [conduction disorders and cardiac dysrhythmias [1.029 (1.002, 1.056)] and heart failure [1.091 (1.055, 1.128)], complications of surgical and medical care [1.088 (1.040, 1.139)], reproductive system diseases [1.085 (1.002, 1.175)], muscular and connective tissue diseases [1.058 (1.003, 1.115)], and maternal or obstetric causes [1.051 (1.024, 1.077)].

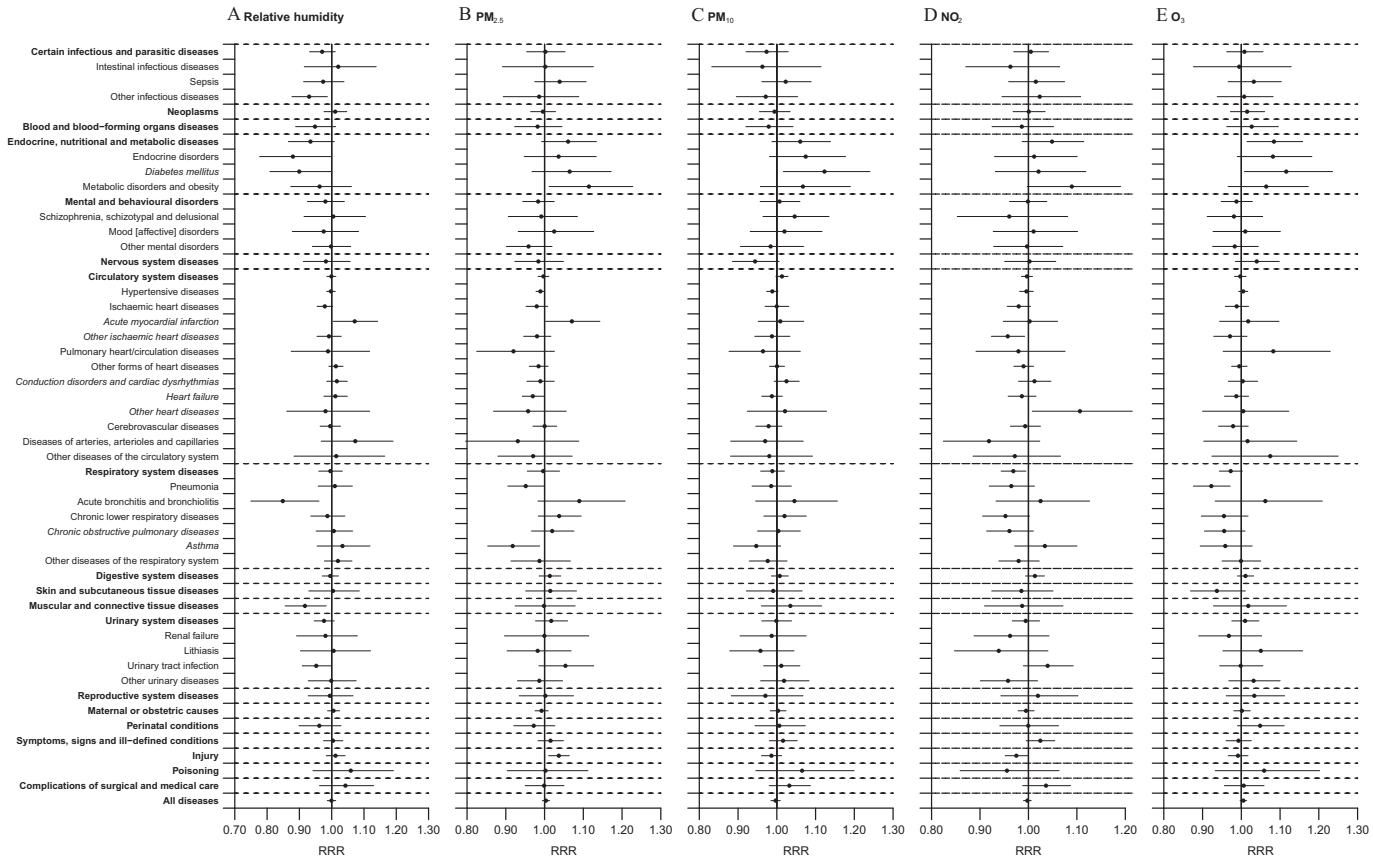

Figure 2. Ratio of heat-related morbidity risk between high and low relative humidity and air pollution days. Ratio of relative risk (RRR) and 95% confidence intervals (error bars) of hospitalization at the 99th percentile of the distribution of daily June-to-September temperature with regard to the minimum morbidity temperature (MMT) between high (above province-specific median) and low (below province-specific percentile) relative humidity and air pollution days. Numerical information is reported in the Table S8. Note: PM, particulate matter; NO_2, nitrogen dioxide; O3, ozone.

Generally, the reported estimates hardly changed after adjustment for air pollutants (Figure S4). Regarding the distribution of the risk across the lag period, in most of the diagnoses it is limited to the first 7 d or less, although for certain diseases (e.g., endocrine, nutritional and metabolic diseases, mental disorders) the risk extended beyond this time window (Figure S5). Province-specific estimates showed substantial spatial heterogeneity in the effect of heat on all-cause hospitalizations (Table S6 and Figure S6). The potential contextual factors contributing to this geographical heterogeneity are analyzed in the last paragraph of this section.

Figure 2 depicts the ratio of RR of hospitalization at the 99th percentile of the distribution of daily June-to-September temperature with regard to the MMT between high (above province-specific median) and low (below province-specific median) relative humidity and air pollution days. Interestingly, humidity played no statistically significant role in the association of heat with morbidity, except for acute bronchitis and bronchiolitis and diseases of the muscular system and connective tissue, which showed a stronger association with heat on days with low humidity [ratio of RR between humid and dry days of 0.849 (0.750, 0.961) and 0.917 (0.856, 0.983), respectively]. Conversely, the heat-related hospitalization risk from metabolic disorders and obesity [ratio of RR for $PM_{2.5} = 1.114$ (1.012, 1.228)] and diabetes [ratio of RR from $PM_{10} = 1.123$ (1.017, 1.240); ratio of RR from $O_3 = 1.116$ (1.008 to 1.236)] were higher on days with elevated pollution. The RR ratios across the whole range of summer temperatures are provided in Figure S7.

Figure 3 displays the risk of cause-specific hospital admission associated with different criteria of heat wave persistence. Heat waves had a small added effect on some causes of hospitalization when the extreme heat episode lasted at least 4 d. This is the case for nonrespiratory infectious diseases [increase in risk of 4.3% (0.4, 8.4)]; endocrine and metabolic disorders [7.7% (2.3, 13.2)]; nervous system diseases [6.5% (0.7, 12.7)]; cardiovascular diseases [2.7% (0.6, 4.9)]; reproductive system diseases [8.0% (0.2, 16.4)]; and symptoms, signs, and ill-defined conditions [5.0% (1.6, 8.6)].

Figure 4 summarizes the associations between DTR and cause-specific hospitalizations after accounting for the effects of daily mean temperature, representing the RR increase in hospitalization per 1°C increase in daily DTR. Unlike daily mean temperature, DTR was only associated with respiratory and urinary diseases, such as pneumonia [1.0075 (1.0016, 1.0135)], acute bronchitis and bronchiolitis [1.0142 (1.0010, 1.0275)], chronic lower respiratory diseases [1.0086 (1.0006, 1.0165)], renal failure [1.0103 (1.0006, 1.0201)], and urinary tract infection [1.0118 (1.0034, 1.0203)]. The effect of DTR on respiratory and urinary diseases was delayed and lasted up to 1 week (Figure S8).

Figure 5 shows the ratio of RR of hospitalization at the 99th percentile of the distribution of daily June-to-September temperature vs. the MMT between women and men by diagnosis of admission, and Figure 6 shows the RR of hospital admission at the 99th temperature percentile vs. the MMT by age group. Women had a statistically significantly higher risk of hospitalization from infectious and parasitic diseases [ratio of RR = 1.185 (1.041, 1.349)]; endocrine and metabolic diseases [ratio of RR = 1.156 (1.019, 1.312)]; respiratory diseases [ratio of RR = 1.078 (1.038, 1.119)]; urinary diseases [ratio of RR = 1.102 (1.007,

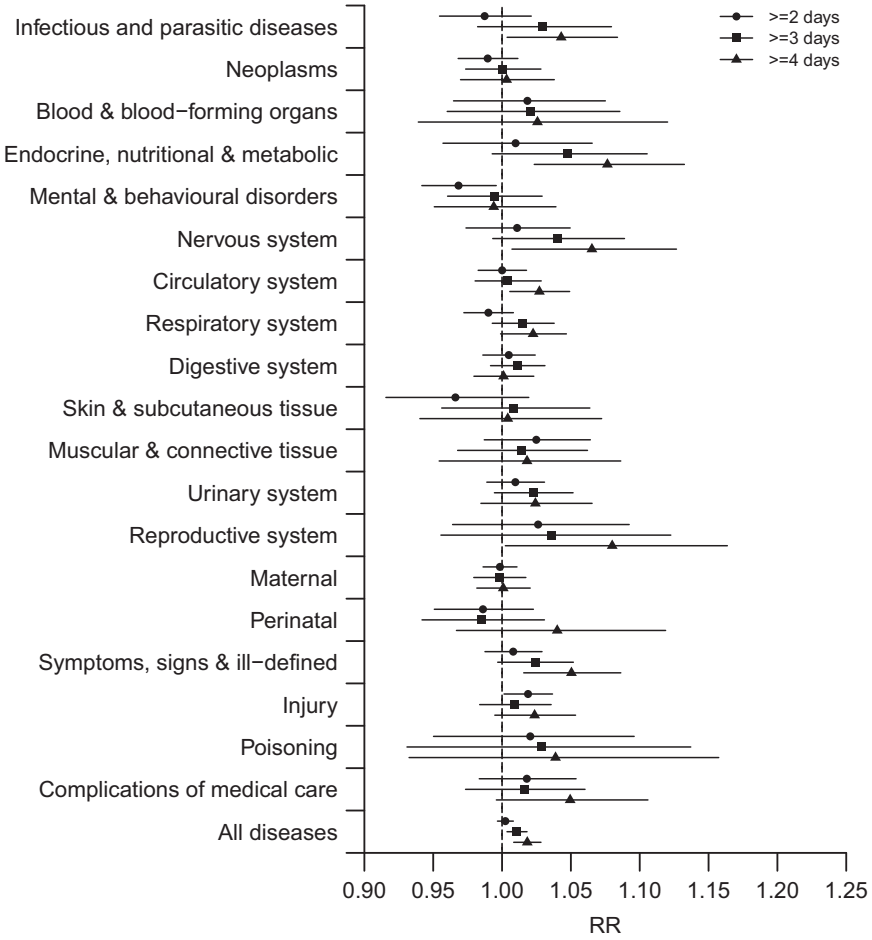

Figure 3. Risk of cause-specific morbidity associated with heat wave duration. Relative risk (RR) and 95% confidence intervals (error bars). Numerical information is reported in Table S9.

1.207)]; and symptoms, signs, and ill-defined conditions [ratio of RR = 1.122 (1.041, 1.210)] compared to men but a statistically significant lower risk of hospital admission from injuries [ratio of RR 0.848 (0.784, 0.917)]. The risk of hospitalization due to heat increased in all the age groups, although the highest increases in risk of hospitalization were among the very young children (<1 year old) and very old people (≥85 years old), with smaller risks for younger adults (20–34 years old) and people 65–74 years old.

Results from the analysis of heterogeneity for the overall temperature—morbidity association are reported in Table S13, both for multivariate meta-analysis (no meta-predictor) and multivariate meta-regression with a single meta-predictor. In the former model, the multivariate Cochran Q test for heterogeneity was highly significant (p-value <0.001), and the related I^2 statistic indicated that 48.4% of the variation was due to heterogeneity between provinces. In meta-regression models, the association between heat and hospitalization was statistically significantly modified (Wald test p-value <0.05) by the proportion of houses constructed before 1971. However, this variable only explained a very small amount of the residual heterogeneity across provinces, with an overall I^2 of 41.8% compared with the 48.4% of the model with no meta-predictor (i.e., meta-analysis), and highly significant Cochran Q test (p-value <0.001). Regarding the direction of the effect modification, the exposure–response associations predicted from meta-regression at the 10th and 90th percentile values of the independent variable (i.e., proportion of houses constructed before 1971) indicated a lower morbidity risk of heat in provinces with a lower proportion of houses constructed before 1971 (Figure S9). It is important to highlight that no association was found between the degree of rurality/urbanicity of the province (i.e., the proportion of population of the province living in municipalities of <10,000 inhabitants) and the heat-related morbidity risks.

Discussion

To the best of our knowledge, this is the most comprehensive assessment on the short-term association between cause-specific hospital admissions and high temperatures, including the added effect of heat waves, temperature variability, and compound hot and humid or high pollution events. Our findings showed a generalized impact of high temperature on hospitalizations, while the added effect of heat waves, temperature variability (i.e., DTR), and compound hot and humid or high pollution events was limited to a reduced number of diseases. We also found that the health risks associated with heat varied widely depending on the diagnosis of admission to hospital, with the metabolic and urinary disease risks being the most affected. Moreover, there were differences by sex (depending on the diagnosis of hospitalization) and age (very young children and the elderly were more at risk).

The underlying physiological mechanisms by which heat triggers adverse health outcomes remain unclear, but they seem to be largely mediated by a thermoregulatory pathway.[1,56–58] Under conditions of heat stress, the body activates heat loss responses of cutaneous vasodilation and sweat production (which subsequently evaporates and removes body heat) to limit elevations in core temperature, which can affect people differently based on, for example,

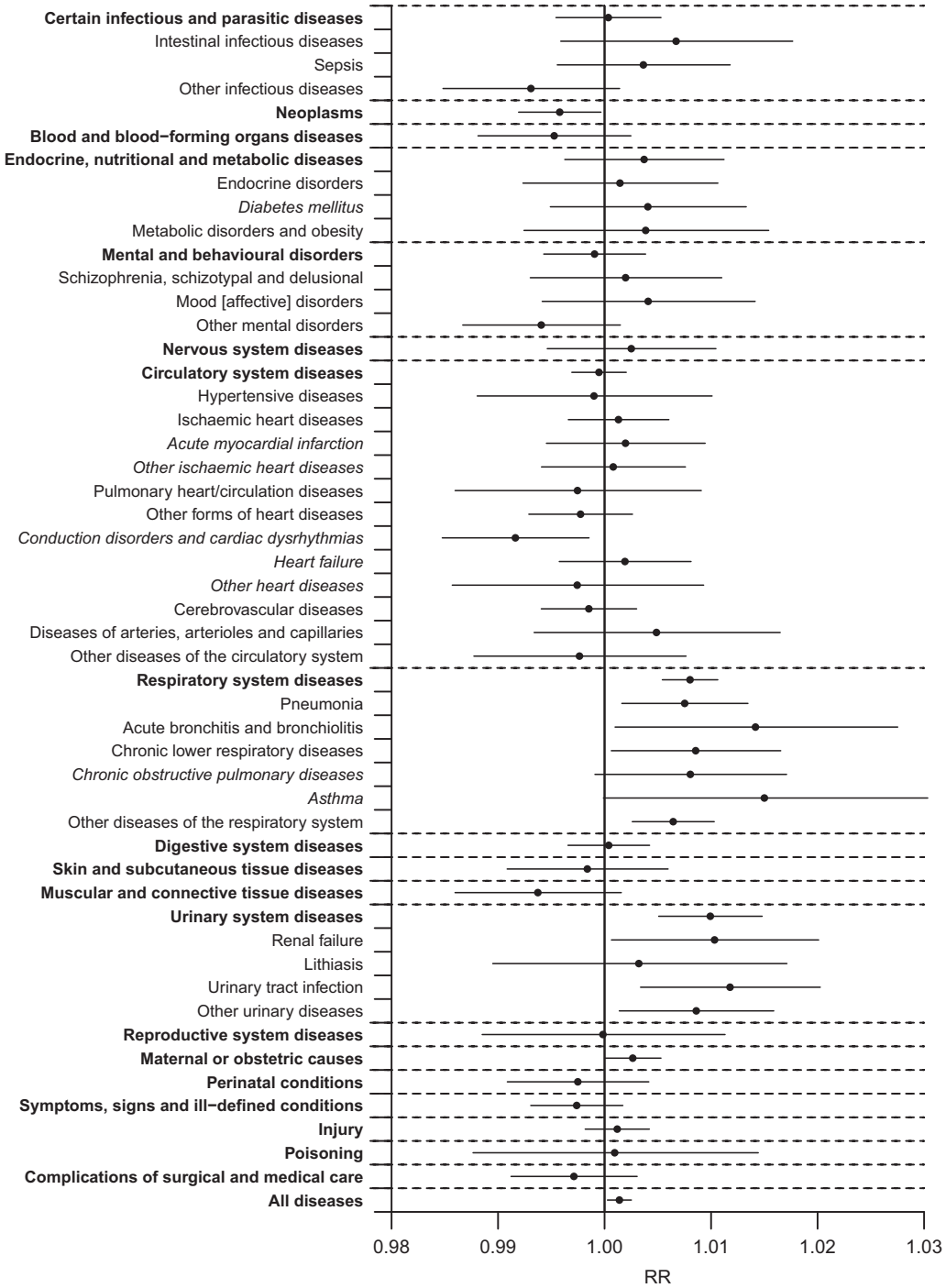

Figure 4. Risk of cause-specific morbidity associated with diurnal temperature range (DTR). Relative risk (RR) and 95% confidence intervals (error bars) per 1°C increase in DTR. Numerical information is reported in Table S10.

age, preexisting health conditions (e.g., chronic cardiovascular–respiratory–kidney diseases, obesity, diabetes, etc.), or even the use of certain medication.[59] Vasodilation increases blood flow from the core to the skin and this allows more heat to be dissipated to the environment. Consequently, central blood volume is decreased and can be further reduced if sweating is not compensated by appropriate fluid intake (i.e., dehydration). In response to this, heart rate and contractility increase, leading to a higher cardiac oxygen demand, which predisposes individuals with limited coronary flow reserve to ischemia (i.e., inadequate blood flow to other organs). Compounding factors of ischemia and severe hyperthermia can cause cell damage (i.e., necrosis), affecting critically the functioning of several vital organs, with the brain, heart, kidneys, intestines, liver, pancreas, and lungs at greatest risk. Hyperthermia and ischemia can also break down *a*) cell membranes rendering the organs more permeable to pathogens and toxins, which induce a systemic inflammatory response that can activate a hypercoagulable state, potentially resulting in thrombosis; and *b*) skeletal muscle cells (i.e., rhabdomyolysis), thereby releasing myoglobin that can cause acute renal failure by obstructing kidney tubules. Moreover, exposure to high ambient temperature in people with diabetes resulted in a greater insulin peak, thereby increasing the risk of a

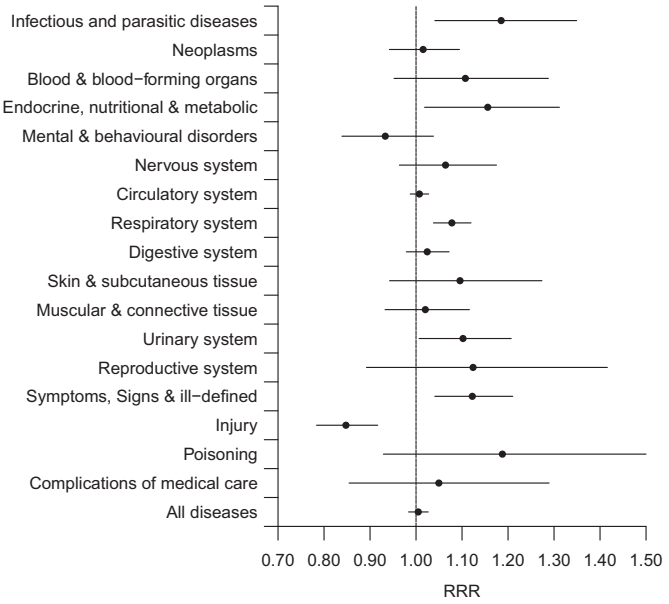

Figure 5. Ratio of heat-related morbidity risk between women and men. Ratio of Relative Risk (RRR) and 95% confidence intervals (error bars) of hospitalization (accumulated across the lag period) at the 99th percentile of the distribution of daily June-to-September temperature vs. the minimum morbidity temperature (MMT) between women and men. Numerical information is reported in Table S11.

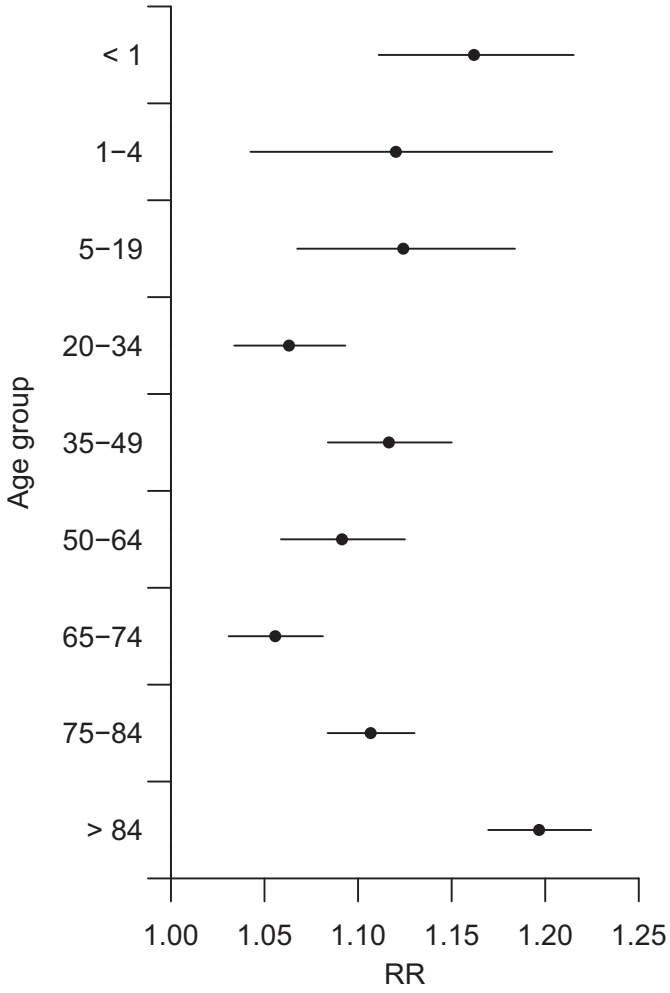

Figure 6. Heat-related morbidity risk according to age group. Relative risk (RR) and 95% confidence intervals (error bars) of hospital admission at the 99th percentile of the distribution of daily June-to-September temperatures vs. the minimum morbidity temperature (MMT). Numerical information is reported in Table S12.

hypoglycemic event,[60,61] whereas, in people with obesity, exposure resulted in lower heat loss (as subcutaneous fat reserves act as layer of insulation), thus increasing the susceptibility to heat disorders.[62] Nevertheless, although adverse effects related to impaired thermoregulation may play an important role in heat-related respiratory diseases, a direct effect of breathing hot air is also plausible.[63] For example, a study found that the inhalation of hot air triggered bronchoconstriction in patients with asthma.[64]

We found sex-specific differences in heat-hospitalization associations according to the diagnosis of admission. Compared to men, women had a higher risk of being admitted to the hospital from infectious and parasitic diseases, endocrine and metabolic disorders, respiratory diseases, and urinary diseases. This situation might partly be linked to sex-specific physiological differences in thermoregulation. 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.[65] By contrast, women had a lower risk of hospital admission from injuries, which could be explained by their lower likelihood of engaging in risky behaviors[66] and outdoor work.[67] Conversely, regarding differences by age, the very young children and the elderly were more at risk of hospitalization because of heat exposure. This is likely linked to age-specific physiological differences in thermoregulation. It is well known that the thermoregulatory capacity is not completely developed during early childhood, and naturally deteriorates with advancing age (e.g., decreased sweat output, impaired cutaneous vasomotor control, etc.), thus affecting the ability of the very young children and the elderly to maintain their body temperature when exposed to hot environments.[68,69]

Numerous studies have documented associations between high temperature and hospital admissions from different causes of disease both in developing (Brazil[14,22,24,27] and China[18]) and developed countries (USA,[6,12] UK,[19,21] Canada,[26] Australia,[20,23] Switzerland,[70] Spain[13,25]), and our results are generally in agreement with them. In these investigations, heat increased the risk of hospitalization for respiratory diseases (pneumonia,[18] chronic obstructive pulmonary disease,[19] asthma[20,21]), nonrespiratory infectious diseases (intestinal,[25] sepsis[6]), urinary diseases (renal failure,[24] lithiasis,[23] urinary tract infections[23]), diabetes,[22] mental disorders (schizophrenia[70]), and skin diseases[14] and neoplasms.[27] However, our study adds to this long list with new diagnoses, such as metabolic diseases and obesity (which are by far the most affected by heat); blood diseases; bronchitis and bronchiolitis; muscular and connective tissue diseases; symptoms, signs, and ill-defined conditions; poisoning by drugs and nonmedicinal substances; and complications of surgical and medical care, and provides information on more specific cardiovascular diagnoses. We also analyzed nervous system, digestive diseases, and injuries, which were not statistically significantly associated to heat. Moreover, we did these analyses by including the added effect of heat waves, temperature variability, and compound hot and humid/polluted events.

In line with the existing literature and in contrast to cold temperatures, heat did not impact cardiovascular hospitalizations,[13,26,27] although we found a small but statistically significant effect for some heart diseases (conduction disorders and cardiac dysrhythmia and heart failure); pulmonary circulation diseases; and diseases of the arteries, arterioles, and capillaries. A possible reason for this is that many heat-related cardiovascular deaths occur suddenly, before the patients get medical attention or are admitted to the hospital.

This hypothesis seems to be supported by the lower increase in cardiovascular hospitalizations observed in women (compared to men), who have been systematically reported to be much more susceptible to heart-related mortality than males.[71,72]

This study is the first to examine potential effect modification of the heat–morbidity association by humidity and air pollution levels for a wide spectrum of cause-specific diseases. We found no interaction of heat with humidity, except for hospital admissions from acute bronchitis and bronchiolitis and muscular and connective tissue diseases, which showed a stronger association with heat on days with lower humidity. One plausible explanation for the association with acute bronchitis and bronchiolitis is that, in a hot–dry environment, the fluid that hydrates the bronchial tubes can quickly evaporate, leaving the airways vulnerable to irritation. Although our findings are counter to expectations from a physiological perspective, given that heat loss by sweat evaporation is reduced in a more humid environment, they are instead consistent with a recent multicounty multicity study on all-cause mortality,[73] which found that neither relative humidity nor mass-based measures of humidity (dew point temperature and specific humidity) had an additional effect on heat–mortality association. Baldwin et al.[28] exposed several potential reasons for the little or no role of humidity in the association of high temperature with morbidity and mortality in population-scale epidemiological studies. Conversely, the effect modification by air pollution was quite limited, as we only observed higher heat-related hospitalization risks on high-pollution days for metabolic disorders and obesity ($PM_{2.5}$) and diabetes (PM_{10} and O_3). Interestingly, high levels of NO_2 did not exacerbate the association between heat and any cause of hospitalization. Effect modification by air pollution on heat–morbidity relationship has been barely investigated, but former multicountry multicity studies on mortality found a considerable modification of the heat effects on overall cardiovascular and respiratory mortality by elevated levels of air pollutants ($PM_{2.5}$ and PM_{10} and O_3).[74–76]

Our study showed that the effects of extreme high temperatures over consecutive days (i.e., heat waves) had a small added effect on morbidity and only for subset of diseases, mainly nonrespiratory infectious diseases; endocrine and metabolic disorders; nervous system diseases; cardiovascular diseases; reproductive system diseases; and symptoms, signs, and ill-defined conditions. Based on these results, which are similar to those reported in prior investigations for broad causes of morbidity[12,14] and mortality,[77] current Heat Health Warning Systems should be activated not only during heat waves but also during nonpersistent extreme temperatures to reduce the health risks.

The analysis of temperature variability during the summer season in relation to morbidity indicated a consistent contribution of DTR to the risk of hospital admissions for respiratory (pneumonia, acute bronchitis, and bronchiolitis) and urinary diseases (renal failure and urinary tract infection), while no effect was found for temperature change between adjacent days (i.e., ITV). Former studies describing associations between DTR and morbidity were mostly focused on respiratory and cardiovascular diseases,[16,78–80] whereas the present study extends the assessment to the rest of diagnoses of hospital admission, thus providing complete and more comprehensive picture of the impacts of temperature variability on morbidity. Some evidence suggests that the thermoregulatory system might not respond efficiently to a sudden change in temperature,[81,82] which can induce the onset of adverse health events, although behavioral patterns might also play an important role (i.e., people are not behaviorally prepared for rapidly changing temperature).

Finally, this study had strengths and limitations. On the one hand, we analyzed high-quality morbidity and environmental data spanning 14 years, which allowed us to accurately characterize the association between high temperature and cause-specific hospital admissions. Additionally, we used the most advanced modeling approaches, based on state-of-the-art methodologies in environmental epidemiology, which allowed us to obtain robust estimations while accounting for complex temporal patterns in the data. On the other hand, health data were not available at a finer geographical or administrative scale (e.g., municipalities), and therefore, we were not able to differentiate the temperature–health associations between urban and rural areas (urban heat island). However, in the second-stage meta-regression, we found no association between an indicator of the degree of rurality/urbanicity of the province (i.e., the proportion of population of the province living in municipalities of <10,000 inhabitants) and the heat-related morbidity risks. Please note that throughout the results, some of the statements on associations are only based on statistical significance, which can depend on the statistical power. Moreover, the use of hospital admissions as the only health outcome did not allow us to capture the less severe morbidity effects of heat (e.g., emergency department visits). Lastly, our study includes data for a single country, and therefore, the generalizability our findings might be limited.

Acknowledgments

H.A. designed the study, did the statistical analysis, and wrote the manuscript. G.R. and J.B. contributed to the study design and edited the manuscript. Z.C. produced the air pollution data. S.J.L. and M.Q.Z. edited the manuscript. R.F.M.T. processed the meteorological data. All authors revised the manuscript and approved the final version.

We acknowledge the E-OBS dataset from the EU-FP6 project UERRA (http://www.uerra.eu) and the Copernicus Climate Change Service, and the data providers in the ECA&D project (https://www.ecad.eu).

H.A., Z.C., M.Q.Z., S.J.L., R.F.M.T., and J.B. acknowledge funding from the European Union's Horizon 2020 research and innovation program under grant agreement no. 865564 (European Research Council Consolidator Grant EARLY-ADAPT, https://early-adapt.eu). H.A. also acknowledges funding from the European Union's Horizon Europe research and innovation program under grant agreement no. 101065876 (MSCA Postdoctoral Fellowship TEMPMOMO). Z.C. also acknowledges support from the grant PRE2020-091985 funded by "MCIN/AEI/10.13039/501100011033 and by European Social Fund invests in your future". J.B. also acknowledges funding from the European Union's Horizon Europe research and innovation program under grant agreement no. 101069213 (European Research Council Proof-of-Concept HHSEWS, https://forecaster.health) and 101123382 (European Research Council Proof-of-Concept FORECAST-AIR), and from the Spanish Ministry of Science and Innovation under grant agreement no. RYC2018-025446-I (program Ramón y Cajal). ISGlobal authors acknowledge support from the grant CEX2018-000806-S funded by MCIN/AEI/10.13039/501100011033 and support from the Generalitat de Catalunya through the CERCA Program.

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