HEAT WAVES AND CAUSE-SPECIFIC MORTALITY IN ADULTS AND INFANTS

eAppendix 1. Imputation of missing weather data

Maximum and minimum daily temperature data were obtained for 66 weather stations covering Catalonia, with at least one station in each of the 14 climatic regions (eFigure 1). Twenty-one of the stations covered the entire period and had less than 2% of days missing, but many stations did not have data for all years of study. Overall, 34% of the temperature data was missing. Ten out of the fourteen climatic zones had at least one station covering the entire period. The remaining four zones, which were the least populated zones with only 1.4% of the total deaths, had gaps of one (two zones), four and thirteen years. The imputation process began by calculating the correlations between all pairs of stations. To impute the missing temperatures for a given station, the station with complete data that had the highest correlation with the station being predicted and that belonged to the same climatic zone was chosen as a predictor variable in a regression model. When a complete series did not exist in the same climatic zone, a station in a neighboring zone was chosen. The regression model used to predict missing temperature included as predictors temperature in the chosen station, season and the interaction of the two variables. Imputations were validated by comparing predictions to real data values for a year that had data available but that was withheld in the modeling step. The comparison of predictions to actual values returned R^2 values above 85% for all stations.

Humidity data were also obtained for 50 stations. Only six stations had data for the entire period, with less than 10% of the days with missing data. Overall, 61% of the days had missing humidity. A similar process as the one used to predict temperature was used to impute missing humidity. Imputations were obtained from a regression model including humidity and maximum temperature variables from the two weather stations that showed the highest correlation with the station being predicted. In this case, 66% of the validation R^2 were above 75%, while the lowest value was 64%.

eAppendix 2. Modeling the effect of temperature using linear splines

In order to facilitate the comparison of our results with other studies, we repeated the analysis using a two-piece linear spline to describe the effects of temperature on mortality.[1] As in the main analysis, we assumed that there were no effects below the 95th percentile of temperature, but now assumed that the effect was linear once the threshold was exceeded. Lags 0 to 6 were included in a lag-stratified distributed lag model, where the coefficients for lags 0-2 were constrained to be equal and likewise for the coefficients for lags 3-6, and the cumulative effect of each of the two lag intervals was reported. The first estimate (lags0-2) represents the increase in mortality risk per 1ºC increase over the threshold sustained over lags 0 to 2, while the second one (lags3-6) represents the increase in mortality per 1ºC increase over the threshold sustained over lags 3 to 6. Applying this model to all cause mortality resulted in a mortality increase of 9.6% per degree over the threshold sustained over lags 0 to 2, and a 4.9% increase per degree over the threshold sustained over lags 3 to 6. The cause-specific RRs based on this model are shown in eFigure6 and eFigure7. Results were very similar to the ones reported in the paper.

eAppendix 3. Stata code for the analysis

Variables:

tmax_heat95: indicator variable that takes value 1 if the day was extremely hot according to maximum temperature (days above the historic 95th percentile)

tmax_heat95_L1, tmax_heat95_L2, tmax_heat95_L3, tmax_heat95_L4, tmax_heat95_L5, tmax_heat95_L6: lags 1, 2, 3, 4, 5 and 6 of tmax_heat95

case: indicador variable to identify case periods (case=1) from referent periods (case=0)

id: variable that identifies the rows that belong to the same deceased person. In general every deceased person has 4 or 5 rows, one as a case period, and 3 or 4 as referent periods (days with the same day of the week of the same month and year than the date of death)

Analysis code:

There are two ways to fit the lag-stratified distributed lag model:

Option 1:

```
constraint define 1  tmax_heat95= tmax_heat95_L1
constraint define 2  tmax_heat95= tmax_heat95_L2
constraint define 3  tmax_heat95_L3= tmax_heat95_L4
constraint define 4  tmax_heat95_L3= tmax_heat95_L5
constraint define 5  tmax_heat95_L3= tmax_heat95_L6

clogit  case tmax_heat95 tmax_heat95_L1 tmax_heat95_L2  tmax_heat95_L3
tmax_heat95_L4 tmax_heat95_L5 tmax_heat95_L6 ,group(id) constraints(1 2 3
4 5)

* Obtain cumulative estimates

lincom tmax_heat95 +tmax_heat95_L1+ tmax_heat95_L2,eform
lincom tmax_heat95_L3+ tmax_heat95_L4 + tmax_heat95_L5 +
       tmax_heat95_L6,eform
```

Option 2:

```
gen heat012=(tmax_heat95+tmax_heat95_L1+tmax_heat95_L2)/3
gen heat3456=(tmax_heat95_L3 + tmax_heat95_L4 + tmax_heat95_L5 +
              tmax_heat95_L6)/4

clogit case heat012 heat3456,group( id_persona)
clogit,or
```

eTable 1. Condensed list of 66 causes of death, their corresponding ICD codes and mortality counts.

Code	Groups of mortality causes	ICD-10 codes	ICD-9 codes	Deaths	Deaths %
	Infectious diseases	**A00-B99**	**001-139**	**6526**	**1.30**
1	Intestinal infections	A00-A09	001-009	348	0.07
2	Viral hepatitis and AIDS	B15-B19, B20-B24	042, 070	1747	0.35
3	Respiratory tuberculosis	A15-A16	010-012	705	0.14
4	Other tuberculosis	A15-A19, B90	013-018, 137	253	0.05
5	Other bacterial infections	A20-A28, A30-A49, A50-A58, A65, A66-A69, A70-A74, A75-A79, B92, B95-B96	005, 007, 020-027, 030-041,080-083, 087, 090-098	2722	0.54
6	Other infectious diseases	A60, A90-A99, B00-B09, B25-B34, A80-A89, B91, B97 A59,A63-A64, B35-B49, B50-B64, B65-B83, B85-B89, B94, B99	Rest of 001-139	751	0.15
	Neoplasms	**C00-D48**	**140-239, 273.1.3, 289.8**	**143282**	**28.47**
7	Pancreas	C25	157	5895	1.17
8	Skin and soft tissue	C43-C47, C49	171-173	1984	0.39
9	Cervix uteri	C53	180	869	0.17
10	Kidney and other urinary tract	C64-C66, C68	189.0	990	0.20
11	Lip, oral cavity and pharynx	C00-C14	140-149	3340	0.66
12	Other, specified sites	C30-C31, C37-C39, C40-C41, C51-C52, C57-C58, C60, C62-C63, C69-C70, C72, C73-C75, C76-C80, C97	rest of 170, 160, 163-165, 171, 183, 184, 186-198	13966	2.78
13	Secondary and unspecified sites	C77-C80	199	5427	1.08
14	Rectum and anus	C19-C21	154	4652	0.92
15	Ovary	C56	183.0	846	0.17
16	Other uterus	C54, C55	179,182	2093	0.42
17	Esophagus	C15	150	2859	0.57
18	Breast	C50	174,175	9816	1.95
19	Stomach	C16	151	9731	1.93
20	Trachea, bronchus and lung	C33, C34	162	26151	5.20
21	Liver	C22	155	7253	1.44
22	Leukemia	C91-C95	204-208	4785	0.95
23	Colon	C18	153	12856	2.55
24	In situ and uncertain behavior	D00-D09, D37-D48	230-234, 289.8, 235-239, 273.1	3581	0.71
25	Larynx	C32	161	2523	0.50
26	Other digestive system	Rest of C15-C26, C45.1, C48	Rest of 150-159	3349	0.67
27	Brain	C71	191	3308	0.66
28	Bladder	C67	188	2254	0.45
29	Prostate	C61	185	7499	1.49
30	Gallbladder and biliary tract	C23-C24	156	760	0.15
31	Lymphoid, haematopoietic and related tissue	C81-C90, C96	200-203, 273.3	6004	1.19
32	Benign	D10-D36	210-229	491	0.10
	Endocrine diseases	**D50-D89, E00-E90**	**240-289**	**19716**	**3.92**
33	Other endocrine, nutritional and metabolic	E00-E07, E15-E90	240-246, 251-279	5514	1.10
34	Blood, blood-forming organs and immunity disorders	D50-D77, D80-D89	280-289	2203	0.44
35	Diabetes	E10-E14	250	11999	2.38
	Mental and nervous system disorders	**F00-H95**	**290-389**	**32586**	**6.47**
36	Nervous system, eye, ear and mastoid process	G00-H95	320-389	14041	2.79
37	Mental and behavioral disorders	F00-F99	290-319	18545	3.68
	Cardiovascular diseases	**I00-I99**	**390-459**	**176830**	**35.13**
38	Chronic rheumatic heart diseases	I05-I09	393-398	2070	0.41
39	Other circulatory system diseases	I71-I99	441-459	9072	1.80
40	Ischaemic heart diseases	I20-I25	410-414	48237	9.58
41	Cerebrovascular diseases	I60-I69	430-434, 436-438	54604	10.85
42	Hypertensive disease	I10-I15	401-405	6555	1.30
43	Heart failure and other heart diseases	I50	428	43877	8.72

Code	Groups of mortality causes	ICD-10 codes	ICD-9 codes	Deaths	Deaths %
44	Atherosclerosis	I70	440	12415	2.47
	Respiratory diseases	**J00-J99**	**460-519**	**38843**	**7.72**
45	Acute respiratory infections	J00-J06, J10, J11, J20-J22	460-466, 487	685	0.14
46	Pneumonia	J12-J18	480-486	6419	1.28
47	Bronchitis, emphysema, asthma and COPD	J40-J47	490-496	19192	3.81
48	Other respiratory diseases	J60-J99, J30-J39	470-478, 500-508, 510-519	12547	2.49
	Digestive system	**K00-K93**	**520-579**	**27664**	**5.50**
49	Gastritis, duodenitis and peptic ulcer	K25-K29	531-535	1431	0.28
50	Diseases of liver	K70-K77	571	11765	2.34
51	Other digestive system diseases	rest of K00-K93	rest of 520-579	14468	2.87
	Other internal diseases	**L00-R99**	**580-799**	**27871**	**5.54**
52	Genital, pelvic organs, breast	N40-N98	600-608, 610, 611, 614-629	405	0.08
53	Congenital	Q00-Q99	740-759	1802	0.36
54	Kidney and urinary system	N00-N39, N99	580-599	10588	2.10
55	Musculoskeletal system and connective tissue	M00-M99	710-739	3952	0.79
56	HIV and not elsewhere classified	R00-R99	780-799	8775	1.74
57	Skin and subcutaneous tissue	L00-L99	680-709	824	0.16
58	Conditions originating in the perinatal period	P00-P96	760-779	1525	0.30
	External causes	**V01-Y89**	**E800-E999**	**30050**	**5.97**
59	Homicide	X85-Y09	E960-E969	651	0.13
60	Other external causes	rest of V00-Y89	rest of E800-E999	8084	1.61
61	Accidental poisoning	X40-X49	E850-E869	1994	0.40
62	Traffic accidents	V02-V04 (.1-.9), V09 (.2-.3), V12-V14 (.3-.9), V19 (.4-.6), V20-V28 (.3-.9), V29-V79 (.4-.9), V80 (.3-.5), V81.1, V82.1, V83-V86 (.0-.3), V87 (.0-.8), V89 (.2), V89 (.9).	E810-E825	9519	1.89
63	Intentional self-harm	X60-X84	E950-E959	4586	0.91
64	Falls	W00-W19	E880-E888	3241	0.64
65	Complications of medical and surgical care	Y40-Y84	E870-E879, E930-E949	495	0.10
66	Accidental drowning and submersion	W65-W74	E910	1480	0.29

eTable 2. ICD codes for the infant mortality categories used in Table 2.

Infant Mortality[a]	ICD-10 codes	ICD-9 codes
Conditions not originating in the perinatal[b] period	All causes except P00-P96	All causes except 760-779
Congenital malformations, deformations and chromosomal abnormalities	Q00-Q99	740-759
Other	All causes except P00-P96, Q00-Q99	All causes except 740-779
Conditions originating in the perinatal[b] period	P00-P96	760-779
Conditions related to duration of gestation	P05-P08	764-766
Cardiovascular & respiratory	P20-P29	768-770,779.8
Infections specific to the perinatal period	P35-P39	771
Haemorrhagic and haematological disorders	P50-P61	772-774, 776
Digestive system	P75-P78	777
Other	rest of P00-P96	rest of 760-779

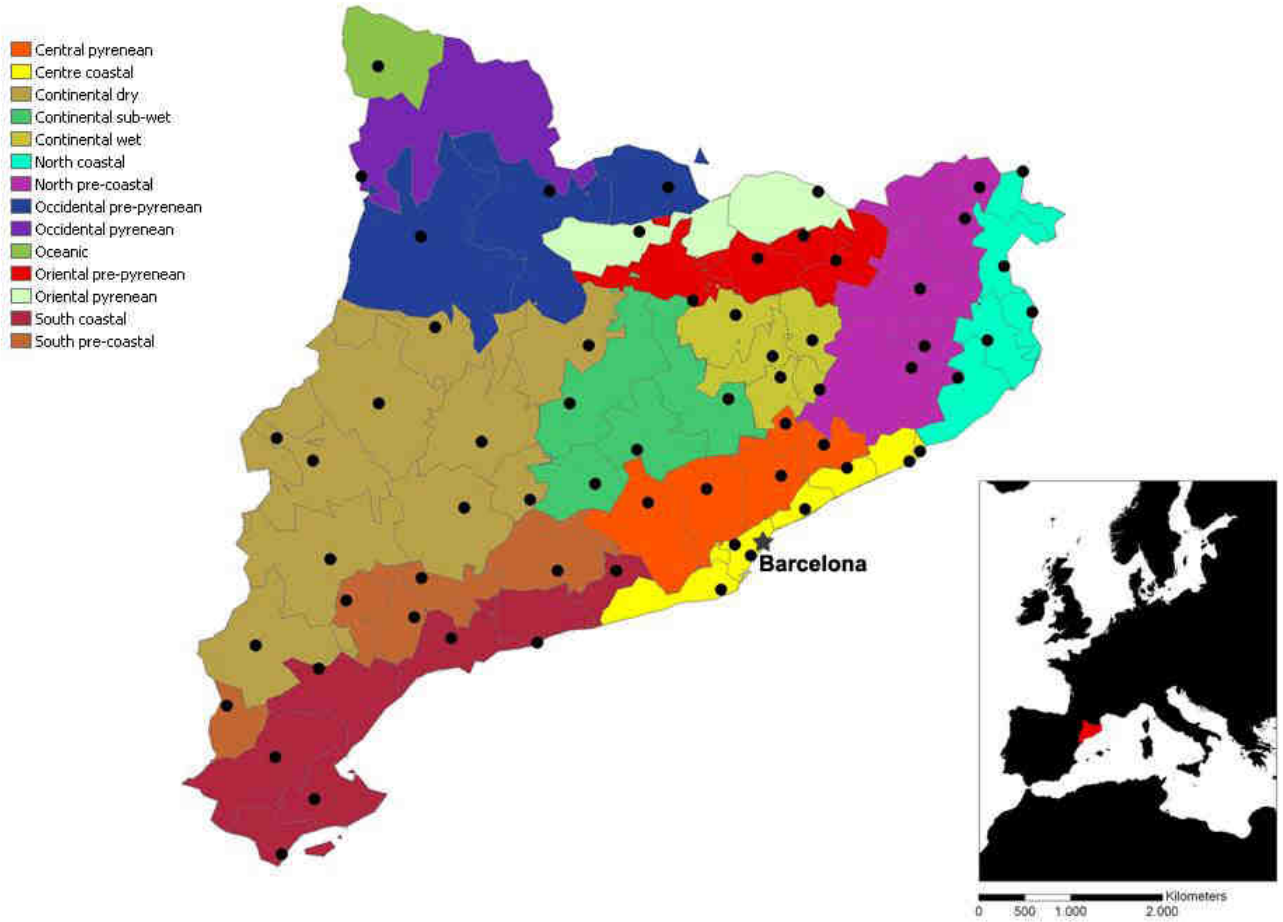
[a] Mortality before one year of age.
[b] The perinatal period commences at 22 completed weeks of gestation and ends seven completed days after birth.

eTable 3. Association between mortality and extremely hot days according to maximum temperature with and without adjustment for humidity. Cumulative lag0-2 and lag3-6 relative risk (RR) estimates and 95% confidence intervals (CI) from a lag-stratified distributed lag model are reported.

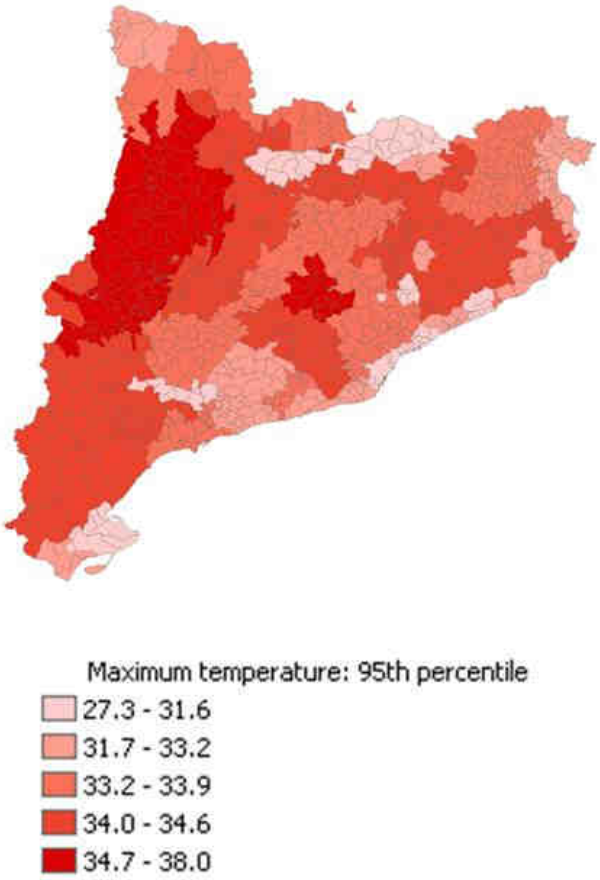
Variable	Without adjustment	Adjusted for humidity[a]
Lags 0-2	1.19 (1.17, 1.22)	1.19 (1.17, 1.22)
Lags 3-6	1.13 (1.11, 1.16)	1.11 (1.09, 1.14)

[a] The model included the average relative humidity in lags 0-2 and in lags 3-6 as continuous variables

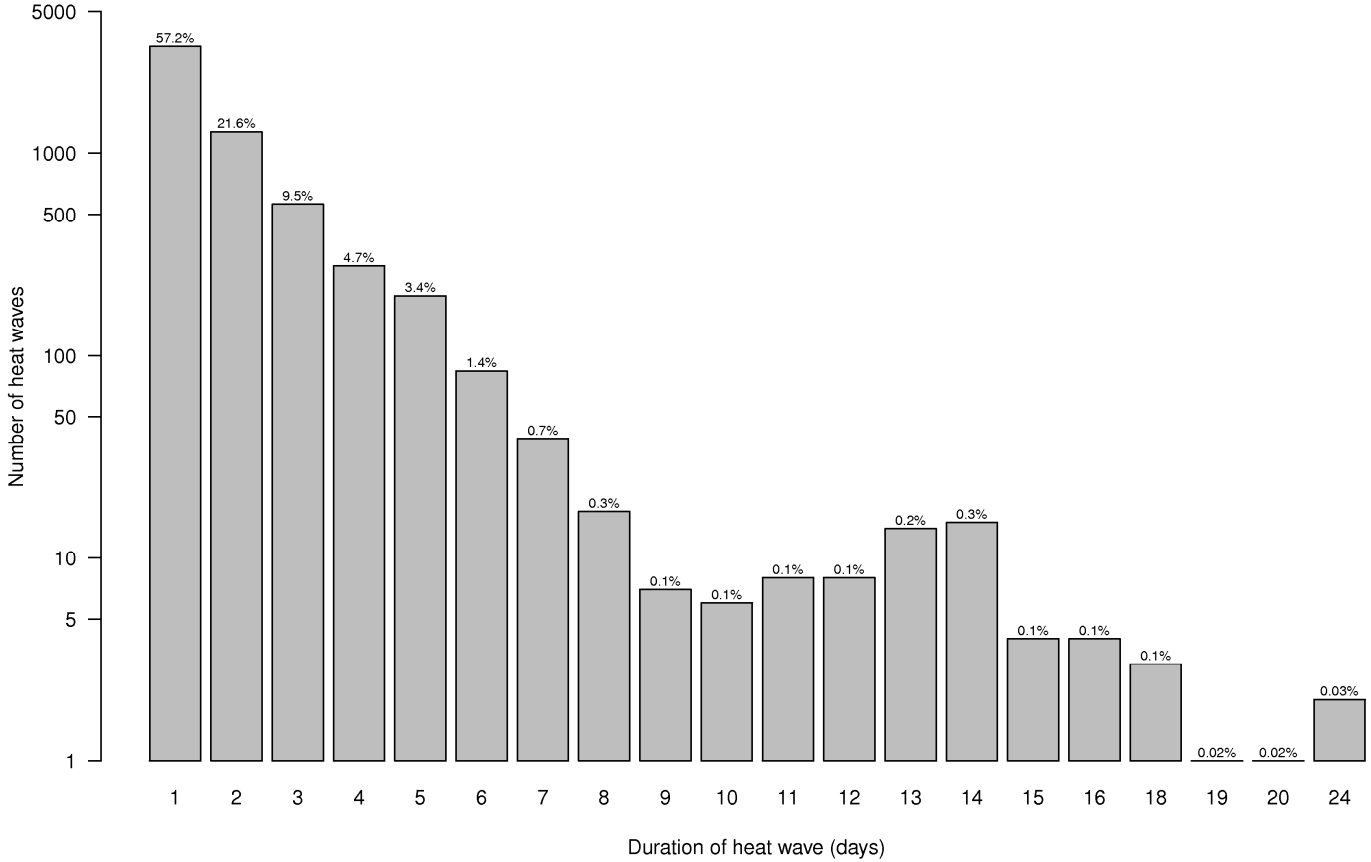
eFigure 1. Map of climatic regions, weather stations (dots) and air pollution monitors (star).



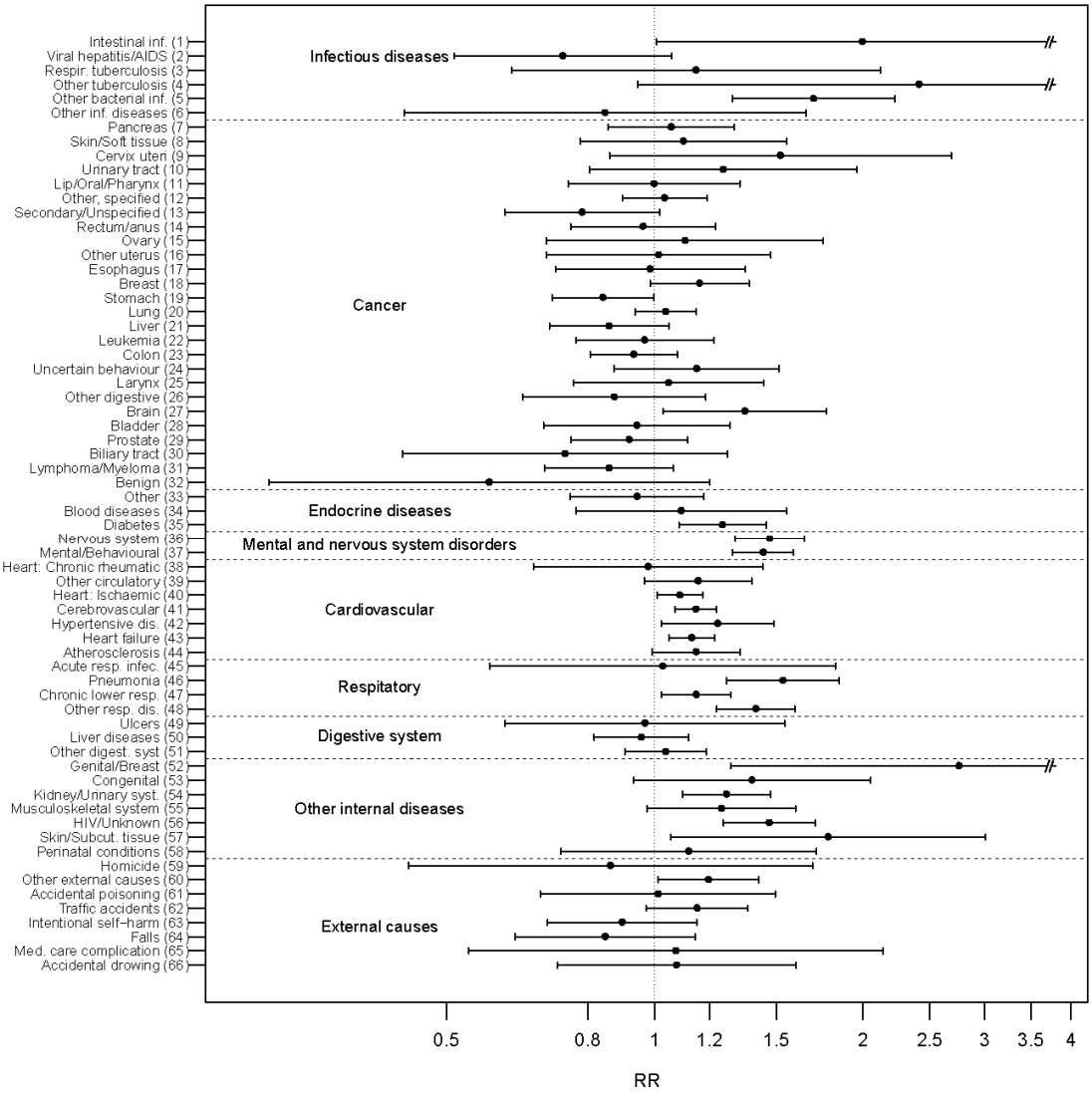
eFigure 2. Historic 95th percentile of maximum temperature by climatic region.



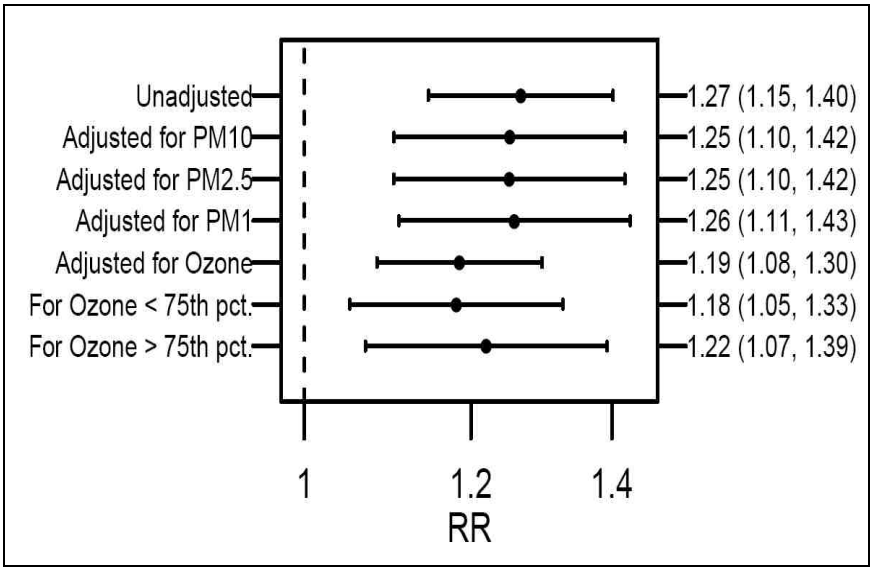
eFigure 3. Distribution of the number days in a heat wave, where a heat wave is defined as the period from the first extremely hot day to the last consecutive hot day. Extremely hot days were those that exceeded the weather station-specific 95th percentile of maximum temperature. The Y-axis is on logarithmic scale.



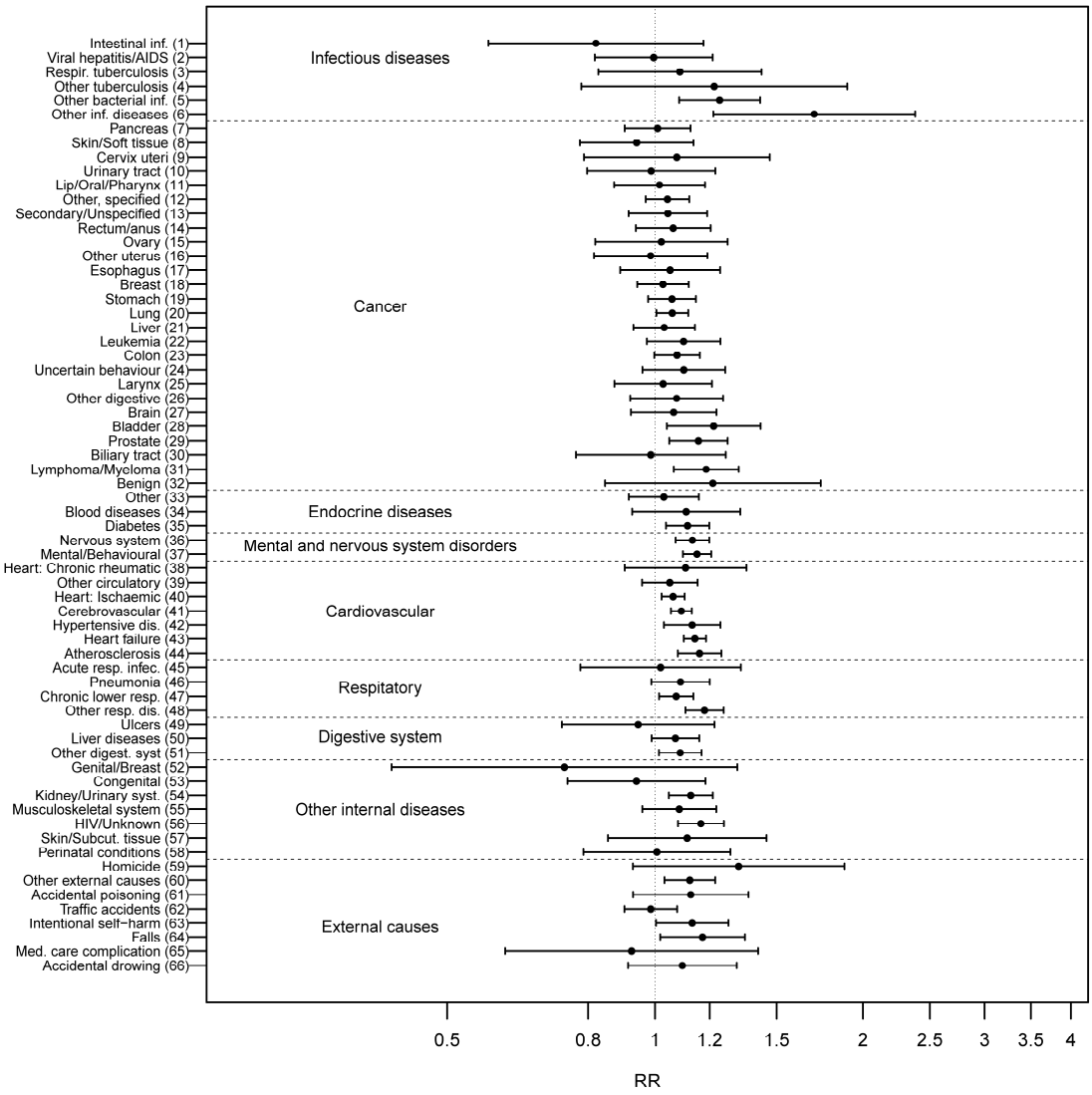
eFigure 4. Relative risk (RR) and 95% confidence intervals of mortality and heat by 66 causes of death. Estimations are cumulative lag3-6 relative risks from a distributed lag model that included lags0-6. X-axis is on logarithmic scale. Details on the 66 categories of cause of death can be found in eTable 1.



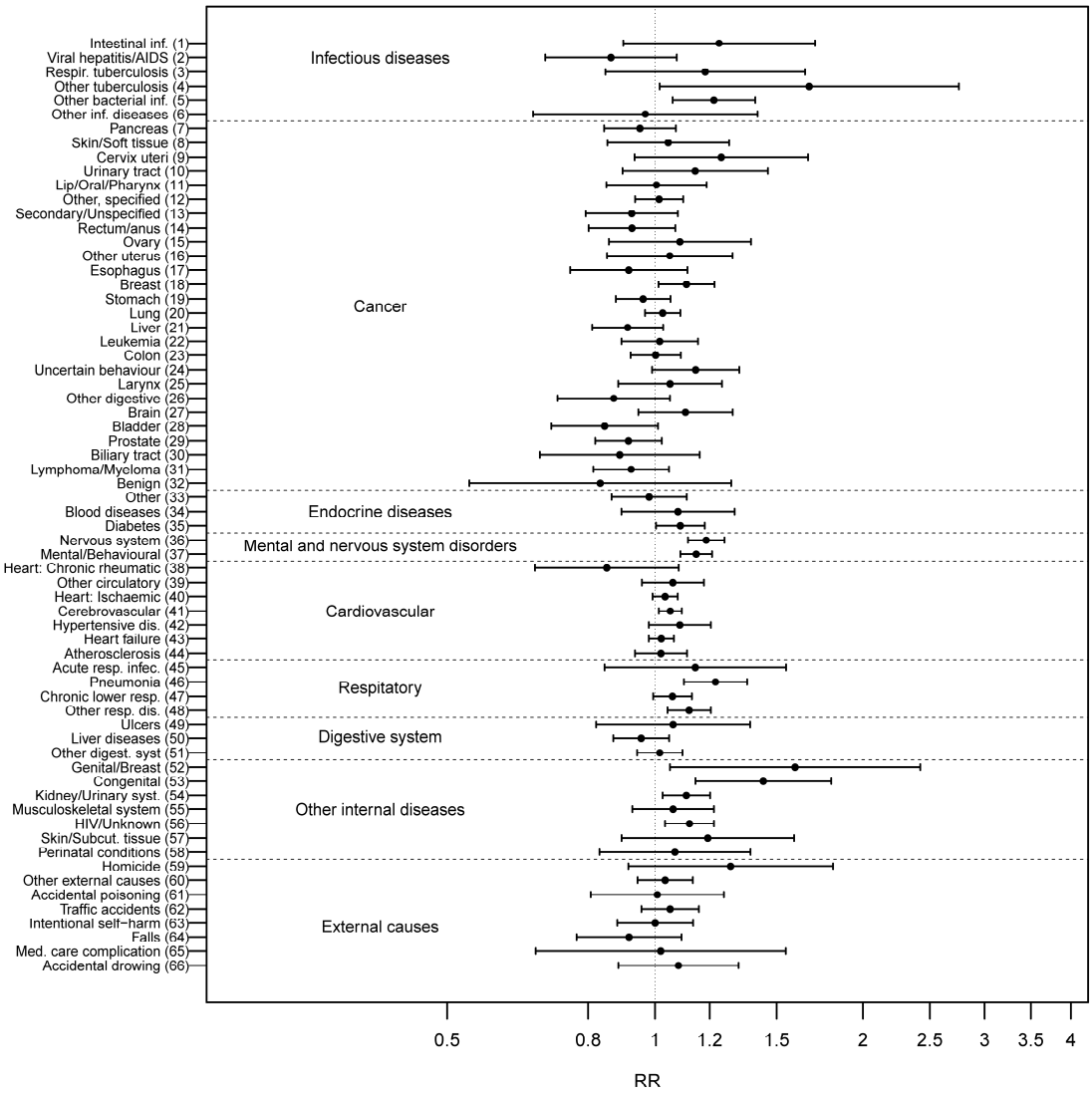
eFigure 5. Cumulative lag0-2 relative risk (RR) and 95% confidence intervals for mortality and extremely hot days defined with the maximum temperature for the period 2003-2005 in the city of Barcelona. Each estimate belongs to a different model.



eFigure 6. Relative risk (RR) and 95% confidence intervals of mortality and heat by 66 causes of death. Estimations are cumulative lag0-2 relative risks from a linear-threshold distributed lag model that included lags0-6 (described in eAppendix 2). X-axis is on logarithmic scale. Details on the 66 categories of cause of death can be found in eTable 1.



eFigure 7. Relative risk (RR) and 95% confidence intervals of mortality and heat by 66 causes of death. Estimations are cumulative lag3-6 relative risks from a linear-threshold distributed lag model that included lags0-6 (described in eAppendix 2). X-axis is on logarithmic scale. Details on the 66 categories of cause of death can be found in eTable 1.



References:

1. Armstrong B. Models for the relationship between ambient temperature and daily mortality. Epidemiology 2006;17(6):624-31.