



Temperature-related excess mortality in German cities at 2 °C and higher degrees of global warming

Veronika Huber^{a,*}, Linda Krummenauer^{b,c}, Cristina Peña-Ortiz^a, Stefan Lange^b, Antonio Gasparrini^{d,e,f}, Ana M. Vicedo-Cabrera^d, Ricardo Garcia-Herrera^{g,h}, Katja Frieler^b

^a Department of Physical, Chemical, and Natural Systems, Universidad Pablo de Olavide, Sevilla, Spain

^b Potsdam Institute for Climate Impact Research (PIK), Potsdam, Germany

^c Institute of Environmental Science and Geography, University of Potsdam, Germany

^d Department of Public Health, Environments, and Society, London School of Hygiene & Tropical Medicine, London, UK

^e Centre for Statistical Methodology, London School of Hygiene & Tropical Medicine, London, UK

^f Centre on Climate Change and Planetary Health, London School of Hygiene & Tropical Medicine, London, UK

^g Department of Earth Physics and Astrophysics, Universidad Complutense de Madrid, Spain

^h Instituto de Geociencias, IGEO (CSIC-UCM), Madrid, Spain

ARTICLE INFO

Keywords:

Temperature-related mortality
Climate change
Future projections
Germany
Global mean temperature

ABSTRACT

Background: Investigating future changes in temperature-related mortality as a function of global mean temperature (GMT) rise allows for the evaluation of policy-relevant climate change targets. So far, only few studies have taken this approach, and, in particular, no such assessments exist for Germany, the most populated country of Europe.

Methods: We assess temperature-related mortality in 12 major German cities based on daily time-series of all-cause mortality and daily mean temperatures in the period 1993–2015, using distributed-lag non-linear models in a two-stage design. Resulting risk functions are applied to estimate excess mortality in terms of GMT rise relative to pre-industrial levels, assuming no change in demographics or population vulnerability.

Results: In the observational period, cold contributes stronger to temperature-related mortality than heat, with overall attributable fractions of 5.49% (95%CI: 3.82–7.19) and 0.81% (95%CI: 0.72–0.89), respectively. Future projections indicate that this pattern could be reversed under progressing global warming, with heat-related mortality starting to exceed cold-related mortality at 3 °C or higher GMT rise. Across cities, projected net increases in total temperature-related mortality were 0.45% (95%CI: −0.02–1.06) at 3 °C, 1.53% (95%CI: 0.96–2.06) at 4 °C, and 2.88% (95%CI: 1.60–4.10) at 5 °C, compared to today's warming level of 1 °C. By contrast, no significant difference was found between projected total temperature-related mortality at 2 °C versus 1 °C of GMT rise.

Conclusions: Our results can inform current adaptation policies aimed at buffering the health risks from increased heat exposure under climate change. They also allow for the evaluation of global mitigation efforts in terms of local health benefits in some of Germany's most populated cities.

1. Introduction

Climate change is expected to alter the currently observed pattern of temperature-related excess mortality around the globe. Quantitative assessments of temperature-related mortality under climate change scenarios have often focused on heat, concluding that heat-related excess mortality is likely to increase under global warming (Huang et al.,

2011; Li et al., 2018; Sanderson et al., 2017; Wang et al., 2019). The fewer studies that investigated the entire temperature range generally estimated concomitant decreases in cold-related mortality (Martin et al., 2012; Li et al., 2013; Schwartz et al., 2015; Gasparrini et al., 2017; Weinberger et al., 2017; Martinez et al., 2018; Vicedo-Cabrera et al., 2018), albeit some of these results have been controversially discussed (Arbuthnott et al., 2018; Kinney et al., 2015).

Abbreviations: BLUPs, Best linear unbiased predictors; CI, Confidence interval; GCM, general circulation model (or global climate model); GMT, global mean temperature; MMT, minimum mortality temperature; RR, relative risk

* Corresponding author. Department of Physical, Chemical, and Natural Systems, Universidad Pablo de Olavide, Ctra. de Utrera, km. 1, 41013, Sevilla, Spain.

E-mail address: vehub@upo.es (V. Huber).

<https://doi.org/10.1016/j.envres.2020.109447>

Received 26 November 2019; Received in revised form 13 March 2020; Accepted 25 March 2020

Available online 29 March 2020

0013-9351/ © 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

The majority of projection studies has presented changes in excess mortality for different emission scenarios and future time periods. Yet, given that the international climate change policy targets, as, e.g., implemented in the Paris Agreement, are expressed as temperature limits, there is a growing need to present mortality projections as a function of global mean temperature (GMT) rise (Ebi et al., 2018). In addition, the focus on temperature magnitudes rather than on time periods facilitates the construction of damage functions to integrate health impacts in integrated assessment models (Carleton et al., 2018), and allows for the derivation of impact emulators required to quickly judge emission pledges in terms of climate impacts (Ostberg et al., 2018). So far, there are few projection studies of temperature-related mortality focussing on the magnitudes of GMT change (Chen et al., 2019; Vicedo-Cabrera et al., 2018; Wang et al., 2019; Mitchell et al., 2018; Lo et al., 2019). Most of these studies consider only the lower levels of possible GMT rise within this century (1.5 °C, 2 °C, and 3 °C above pre-industrial levels), while we also take the higher global warming levels (4 °C and 5 °C) into account.

Furthermore, we are the first to present projections of temperature-related mortality based on a newly assembled observational dataset of death counts and climate variables in 12 large cities of Germany, the most populated country of Europe. Although temperature-related excess mortality in Germany has been studied based on observational data for specific cities (Breitner et al., 2014), regions (Laschewski and Jendritzky, 2002; Muthers et al., 2017), and the entire country (Karlsson and Ziebarth, 2018), there is only a very limited number of quantitative climate change projection studies. The few existing ones are limited to specific cities or regions of Germany (Chen et al., 2019; Rai et al., 2019), neglect the effects of cold (Zacharias et al., 2015; Kendrovski et al., 2017), or use only one simplified model for the relationship between temperature and mortality for the entire country (Hübner et al., 2008).

The main objective of this study is to evaluate the policy-relevant climate change target of limiting global warming to 2 °C compared to higher warming levels in terms of changes in temperature-related mortality in Germany. In this evaluation, we focus on the potential for local benefits versus damages of climate change. To this aim, we derive temperature-mortality associations in 12 large German cities, using state-of-the-art statistical techniques developed in time-series modelling (Gasparrini et al., 2012a; 2010). Based on these associations and an ensemble of locally bias-corrected climate projections (Frieler et al., 2017), we estimate temperature-related excess mortality at different degrees of global warming (1 °C, 2 °C, 3 °C, 4 °C, and 5 °C of GMT rise above pre-industrial levels). Since we make the counterfactual assumption of no future changes in adaptation and demography, our estimates are best interpreted as exposing the current population of Germany's major cities, embedded in current infrastructures and health care systems, to different possible temperature distributions of the future.

2. Material and methods

2.1. Observational data

We obtained daily death counts of all-cause mortality in 12 major German cities (>500,000 inhabitants; see Table A1 for city coding and population data) from the Research Data Centres of the Federation and the Federal States of Germany for the period 1 January 1993 to 31 December 2015 (individual datasets are available as [https://doi.org/10.21242/23211.\[year\].00.00.1.1.0](https://doi.org/10.21242/23211.[year].00.00.1.1.0)). The cities are spread across the entire country (Fig. A1), and represent around 16% of the total German population in 2015 (Table A1). Given the susceptibility of a wide range of death causes to non-optimal temperatures (e.g., Anderson and Bell, 2009; Gasparrini et al., 2012b), it is a common approach in studies of temperature-related mortality to analyze total death counts. More specifically, it has been shown that results on temperature-mortality

associations are practically insensitive to the use of all-cause versus non-accidental mortality data across a large number of locations (Gasparrini et al., 2015).

Data of daily mean temperature (24-h averages) for the study period was derived from the Climate Data Centre of the German National Meteorological Service. If several weather stations existed within the city boundaries, stations closest to the city centre were chosen, provided that measurements were available for the whole study period (Table A2). We decided to use temperature data from a single weather station, given that more spatially refined exposure data does not generally yield different estimates of temperature-mortality associations compared to simpler one-station data (Schaeffer et al., 2016; Weinberger et al., 2019). Details on the processing of missing values are given in Appendix A.

2.2. Temperature projections

Projections of daily mean temperatures for the 12 cities were derived from the second phase of the Inter-Sectoral Impact Model Intercomparison Project (ISIMIP2b) (Frieler et al., 2017), comprising gridded (0.5° × 0.5°), bias-corrected data from 4 general circulation models (GCMs) (GFDL-ESM2M, HadGEM2-ES, IPSL-CM5A-LR, MIROC5), which contributed simulations to the 5th Coupled Model Intercomparison Project (CMIP5). For each GCM, we considered the historical run in the period 1986–2005 and 4 different climate-change scenario runs (Representative Concentration Pathways (RCPs): RCP2.6, RCP4.5, RCP 6.0, RCP8.5) in the period 2006–2099 (2006–2100 for RCP8.5 simulations from IPSL-CM5A-LR). Time-series from the grid cell enclosing the respective city coordinates were extracted, and the data was additionally bias-corrected using the local weather station data from each city following the approach by Lange (2017). Through this additional bias-correction step we mapped the spatial temperature mean of the grid cell to the local scale of the city. The remaining bias in the distribution of daily mean temperatures was relatively small (Fig. A2). In addition to local projection data, we also considered annual averages of corresponding GMT series.

2.3. Defining global warming levels

To select time slices corresponding to the considered levels of global warming, we first computed a series of annual GMT differences against pre-industrial levels for each GCM and RCP (extended backwards in time using data from the historical run). In this step, given that some of the GCMs considered (especially HadGEM2-ES and IPSL-CM5A-LR) simulate historical global warming trends that deviate substantially from the observed trend, we chose 1986–2005 as a reference period and added the observed global warming of 0.6 °C between this reference period and pre-industrial levels (following Schleussner et al., 2016). Subsequently, we computed 21-year running means of GMT increases above pre-industrial levels and determined the corresponding temporal windows when the considered levels of global warming (1–5 °C) were reached for the first time (see Table A3 for selected time windows). Finally, we extracted the local temperature projections in these temporal windows (for an example of the resulting temperature distributions for Berlin based on RCP8.5, see Fig. 1). It can be noted that only HadGEM2-ES and IPSL-CM5A-LR reached 4 °C and 5 °C above pre-industrial levels in the scenarios considered (Fig. 1, Table A3). We used the lowest warming level 1 °C, which roughly corresponds to the historical global warming up to present-day, as a reference to compute relative changes in projected mortalities.

2.4. Deriving temperature-mortality associations

Temperature-mortality associations were estimated with a two-stage approach, following Gasparrini et al. (2015). The details of the methodology are extensively documented in Gasparrini et al. (2010)

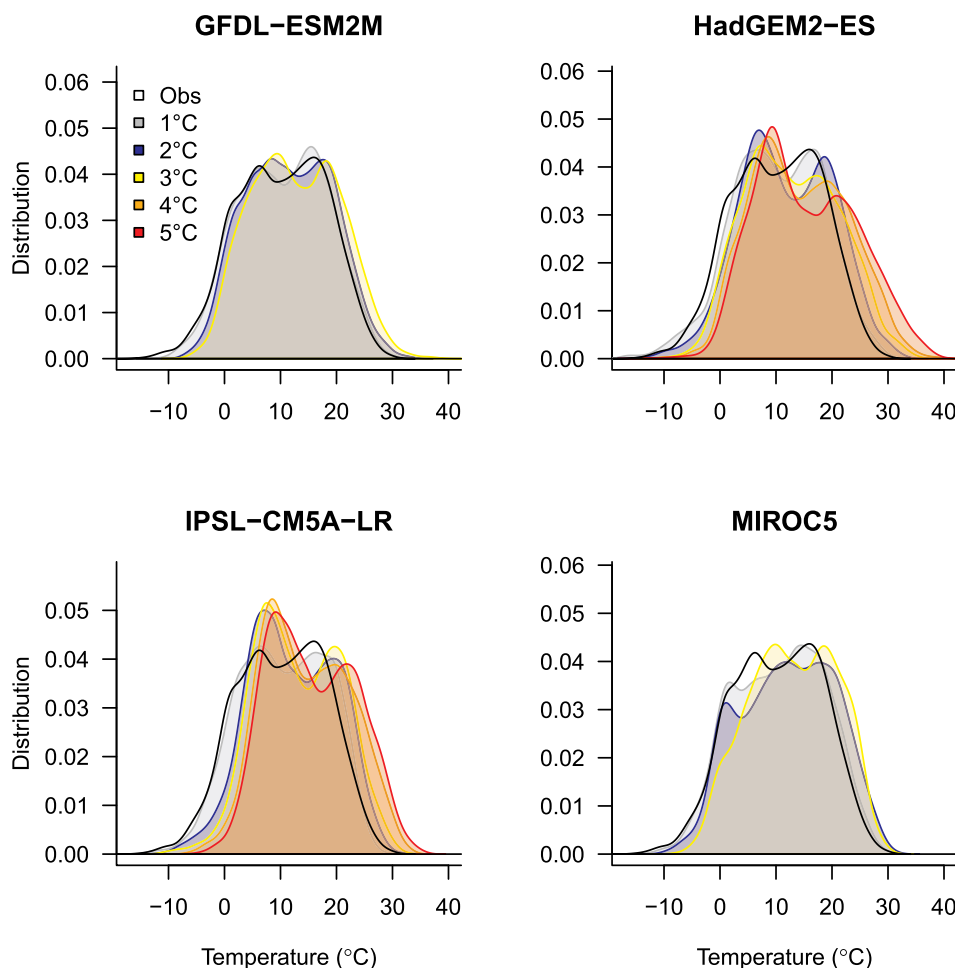


Fig. 1. Example distributions of observed (black) and projected (colours) mean daily temperatures at different levels of global warming in Berlin, by GCM. Distributions were constructed based on daily simulation data (1986–2099, historical run combined with RCP8.5), mapped to global warming levels by considering 21-year running means of annual differences in global mean temperature (GMT) above pre-industrial levels (see Table A3). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and Gasparrini et al. (2012a). In the first stage, we used time-series quasi-Poisson regression to estimate city-specific exposure-response functions. Temperature-mortality associations were modelled with distributed-lag non-linear models (DLNMs). We fitted a natural cubic spline function with three internal knots placed at the 10th, 75th, and 90th percentiles of the local temperature distribution to model the exposure-response curve. This choice assures a log-linear extrapolation of the exposure-response curve beyond the observed temperature range (Vicedo-Cabrera et al., 2019). The lag-response curve was modelled with a natural cubic spline with an intercept and three internal knots equally distributed in the log-space, accounting for up to 21 days of lag. We controlled for day of the week with an indicator, and for seasonal and long-term trends with a natural cubic spline of time with 7 degrees of freedom per year. The chosen number of degrees of freedom for control of season and long-term trends corresponded to the minimum quasi-Akaike information criterion (QAIC) summed across all cities (Fig. A3). Model choices were further tested in a sensitivity analysis (Table A4).

In the second stage, we performed a multivariate meta-regression on reduced coefficients from the first stage, which describe the overall cumulative exposure-response curve across the 21 days of lag. Long-term average temperature and temperature range (difference between maximum and minimum temperature) (Table 1) were included as meta-predictors in the model. Both meta-predictors explained part of the heterogeneity between cities (Table A5). From the meta-regression model, we derived the best linear unbiased predictors (BLUPs) for each

city, which represent a trade-off between the location-specific association provided by the first-stage regression and the pooled association, and identified the minimum mortality temperature (MMT) (Table 1).

2.5. Computation of attributable mortality

All computations of daily mortality attributable to non-optimal temperatures, in the observational period and at different levels of GMT rise (1–5 °C) followed a similar setup. We used the exposure-response curve defined by the BLUPs and centred on the MMTs, and combined these with different daily series of temperature and mortality. To derive attributable mortality in the observational period (1993–2015), we used the observed temperature series and forward moving averages of observed deaths counts across the lag period as described in Gasparrini and Leone (2014). To estimate projected attributable mortality at different levels of global warming, we built upon the approach by Gasparrini et al. (2017) and Vicedo-Cabrera et al. (2018). A series of projected daily mortality was constructed by averaging observed deaths counts per day of the year. We then replicated the annual pattern 21-times, in order to derive mortality series of the same length as the projected temperature series. We summed attributable numbers in the observational period or across each series of projected temperatures to derive total temperature-related excess mortality. We also separated components due to heat and cold by considering only days with temperatures higher or lower than the MMT. Dividing by the total number of observed deaths or the sum of projected mortality series we also

Table 1

Descriptive statistics, estimated minimum mortality temperatures (MMT), and attributable fractions in the observational period (1993–2015).

City	Total deaths	Mean daily temperature mean (min, max)	MMT °C (perc)	Attributable fractions		
				Total % (95%CI)	Cold % (95%CI)	Heat % (95%CI)
Berlin	811,051	10.2 (-15.6,30.5)	18.9 (85th)	6.95 (5.24,8.61)	5.95 (4.25,7.61)	1.00 (0.89,1.13)
Bremen	150,608	9.8 (-14.1,27.6)	17.6 (87th)	3.56 (0.23,6.81)	3.21 (-0.07,6.39)	0.36 (0.16,0.55)
Cologne	229,457	10.6 (-16.5,29.3)	17.7 (84th)	6.78 (4.84,8.79)	5.70 (3.69,7.77)	1.08 (0.93,1.24)
Dortmund	155,233	10.5 (-15.2,28.9)	17.9 (86th)	6.23 (4.21,8.23)	5.44 (3.44,7.50)	0.79 (0.68,0.91)
Dresden	125,866	9.6 (-16.3,30.4)	18.7 (86th)	5.42 (2.41,8.37)	4.72 (1.68,7.7)	0.69 (0.53,0.87)
Dusseldorf	160,069	10.9 (-14.6,30.0)	17.9 (84th)	6.84 (4.60,9.05)	5.76 (3.42,8.08)	1.08 (0.90,1.27)
Frankfurt	168,417	11.0 (-12.9,29.9)	19.8 (87th)	9.59 (5.99,12.87)	8.50 (4.97,11.73)	1.09 (0.88,1.29)
Hamburg	445,338	9.6 (-13.5,28.8)	18.5 (90th)	4.93 (1.54,8.16)	4.63 (1.37,7.75)	0.31 (0.15,0.44)
Hannover	279,125	9.9 (-16.9,29.0)	17.2 (84th)	4.62 (2.81,6.46)	3.83 (1.99,5.75)	0.79 (0.64,0.95)
Leipzig	152,861	10.0 (-17.5,29.0)	17.7 (82nd)	5.09 (3.10,7.11)	4.03 (2.00,6.11)	1.07 (0.87,1.26)
Munich	290,962	10.0 (-13.4,29.5)	19.7 (88th)	7.23 (4.77,9.57)	6.62 (4.21,8.95)	0.61 (0.47,0.74)
Stuttgart	136,878	10.7 (-13.0,30.3)	19.2 (86th)	7.98 (5.54,10.34)	7.07 (4.57,9.50)	0.91 (0.76,1.08)
All cities	3,105,865	10.3 (-17.5,30.5)	18.4 (86th) ^a	6.30 (4.60,7.98)	5.49 (3.82,7.19)	0.81 (0.72,0.89)

^a Median of city-specific estimates.

derived the corresponding attributable fractions. Overall attributable fractions, for all cities combined, were derived by summing daily attributable numbers across all cities, and dividing by the sum of deaths across cities. The ensemble mean at each level of GMT rise was calculated as the average across all GCM-specific, and RCP-specific attributable fractions. In averaging across RCPs, we assumed that it did not matter when in time a specific warming level was reached (see also Table A3), i.e., we assumed a scenario-independence of results.

2.6. Uncertainty estimation

To assess the uncertainty stemming from the fitted exposure-response functions, we conducted Monte Carlo simulations drawing 1000 times from a multivariate normal distribution defined by the BLUPs and the corresponding co-variance matrix. We determined 95% empirical confidence intervals (CI) by considering the 2.5th and 97.5th percentiles of the resulting sample. In the projections, we additionally determined the uncertainty stemming from the use of different GCMs, and RCPs. Total uncertainty, including epidemiological and climate uncertainties, was assessed by considering the 2.5th and 97.5th percentiles of mean excess mortality in each GMT bin across all Monte Carlo samples, GCMs, and RCPs.

In addition, we were interested in determining the contribution of different sources of uncertainty to the overall variability in excess mortality estimates. To assess climate uncertainty, due to differences between GCMs and RCPs, we calculated the standard deviations of mean excess mortality estimates based on central BLUPs across GCMs (SD_{gcm}), and across RCPs (SD_{rnp}), respectively. As a measure of epidemiological uncertainty, we computed the average of standard deviations resulting from Monte Carlo simulations, considering GCMs and RCPs one at a time (SD_{epi}). We normalized these standard deviations (reflecting uncertainties in GCMs, RCPs, and exposure-response functions, respectively) dividing by their sum: $SD_{gcm} + SD_{rnp} + SD_{epi}$. It can be noted that the differentiation between GCMs and RCPs in

contributing to climate uncertainty was only possible for global warming levels 1–3 °C, because results for higher warming levels were based on RCP8.5 only (cf., Table A3). Thus, for warming levels > 3 °C we only considered SD_{gcm} and SD_{epi} .

All computations were done using R (version 3.4.3) with packages *dlm* and *mymeta*. The code was partly adapted from Gasparrini et al. (2015), Gasparrini et al. (2017), and Vicedo-Cabrera et al. (2019), and is available on request from the first author.

3. Results

Our dataset of 12 major German cities included a total of 3,105,865 deaths in the period 1993–2015 (Table 1). The mean (min, max) of daily mean temperatures across cities was 10.3 °C (−17.5 °C, 30.5 °C). Overall cumulative temperature-mortality associations were relatively similar across cities (Fig. 2), showing a gradually rising RR for cold (i.e., below the MMT), and a more steeply increasing RR for heat (i.e., above the MMT). MMT estimates fell in the range 17.2 °C–19.8 °C, corresponding to the 82nd to 90th percentiles of the distribution of daily mean temperatures in the individual cities (Table 1). All cities showed a similar temporal lag structure: The effect of cold peaked a few days after the exposure and lasted up to 3 weeks, while the effect of heat was more immediate and vanished (or reversed sign, indicative of mortality displacement) after a few days (Fig. A4).

Total excess mortality attributable to non-optimal temperatures across cities was 6.30% (95%CI: 4.60–7.98) (Table 1). Out of this, 0.81% (95%CI: 0.72–0.89) were attributable to heat, and 5.49% (95%CI: 3.82–7.19) to cold. Comparing city-specific estimates, the lowest total excess mortality was observed in Bremen (3.56%; 95%CI: 0.23–6.81) and the highest in Frankfurt (9.59%; 95%CI: 5.99–12.87) (Table 1, Fig. 3). Confidence intervals of attributable fractions were significant (i.e., did not include zero) in all cities, except for cold attributable mortality in Bremen. The sensitivity analysis showed that modelling choices only marginally affected our estimates of present-day

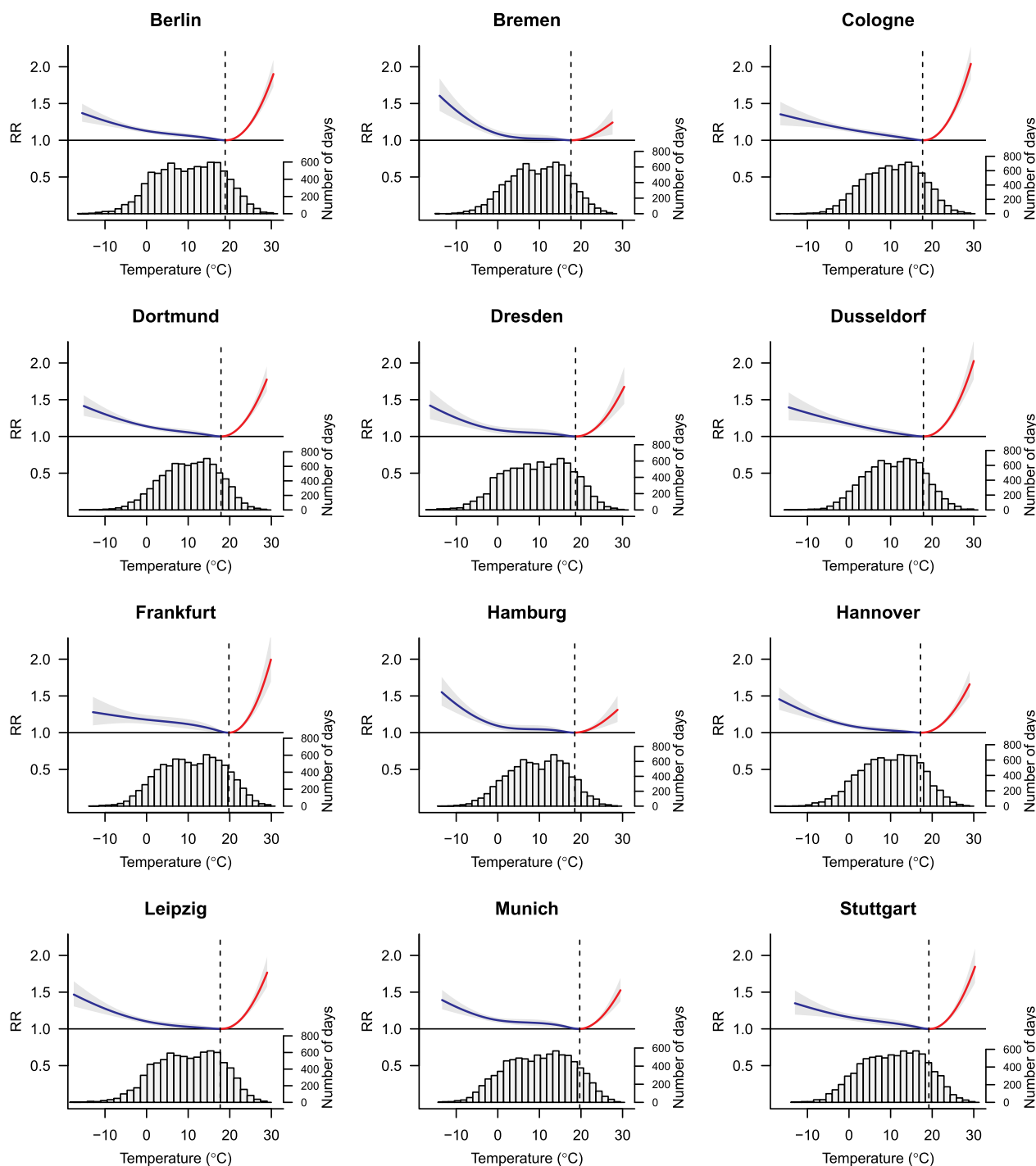


Fig. 2. Temperature-mortality associations in German cities estimated from observed deaths counts and mean daily temperatures in 1993–2015. Mortality is reported as relative risk (RR) with respect to the minimum mortality temperature (MMT) (dashed line). Cold-related RR (temperature < MMT) is shown in blue, heat-related RR (temperature > MMT) in red. Shading corresponds to empirical 95% CIs. Lower panels depict daily mean temperature distributions. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

attributable fractions (Table A4).

Projections of excess mortalities for 1 °C of GMT rise above pre-industrial levels, roughly corresponding to historical global warming up to today, were very close to the estimates based on observational data (Fig. 3). In all cities, heat excess mortality was projected to increase from today's GMT level towards higher magnitudes of global warming, while cold excess mortality was projected to decrease (Fig. 3, Table A6). Whereas at lower levels of GMT rise cold contributed considerably

stronger to total excess mortality than heat, this pattern was reversed at higher levels of GMT rise (see crossing points of blue and red curves in Fig. 3). For a 5 °C increase in GMT above pre-industrial levels total excess mortality attributable to non-optimal temperatures was projected to reach 9.02% (95%CI: 6.60–11.44) across cities, with heat contributing the larger part 5.75% (95%CI: 4.48–7.09), and cold contributing only 3.27% (95%CI: 1.93–4.60) (Table 2, Fig. 3).

In all cities, net changes in total excess mortality from today's 1 °C to

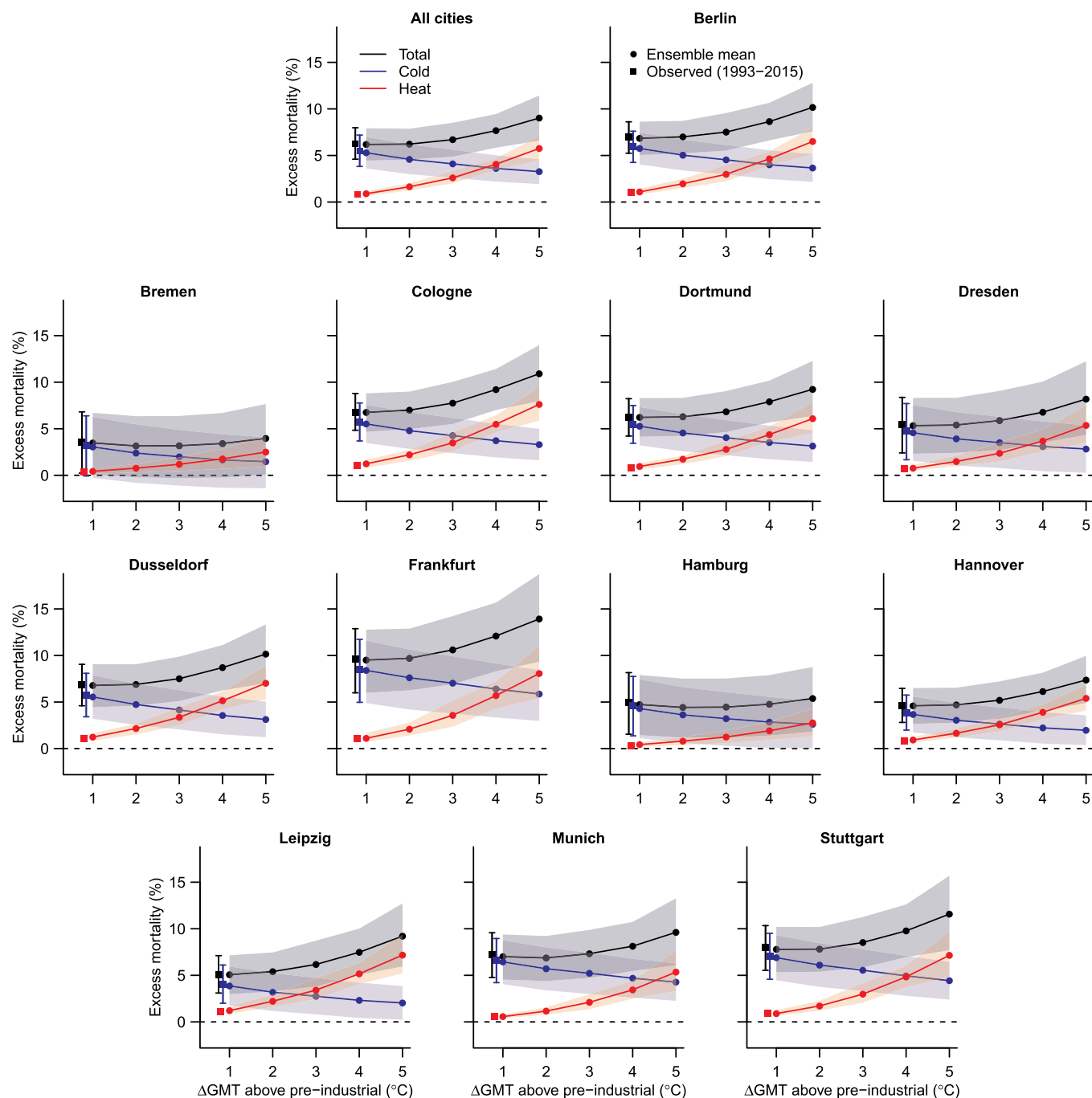


Fig. 3. Projected total (black), cold-related (blue) and heat-related (red) excess mortality at different levels of global warming, for all cities combined, and by individual city. Circles show mean excess mortality averaged across climate models (GCMs) and scenario types (RCPs) for considered increases in global mean temperature (Δ GMT) above pre-industrial levels. Squares depict excess mortality estimates based on observations (see Table 1). Shading and whiskers correspond to 95% CIs, taking into account uncertainty related to temperature-mortality associations and climate projections (GCMs and RCPs). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

a 2 °C increase in GMT above pre-industrial levels were marginal and not significant from zero (Fig. 4). At this warming level, projected increases in heat-related mortality were largely compensated for by decreases in cold-related mortality. In most cities, significant net increases in total excess mortality started to appear at 3 °C or 4 °C of GMT rise above pre-industrial levels (Fig. 4, Table A6).

For all cities combined, total excess mortality was estimated to increase by 0.45% (95%CI: −0.02 – 1.06) towards 3 °C, 1.53% (95%CI: 0.96–2.06) towards 4 °C and 2.88% (95%CI: 1.60–4.10) towards 5 °C, compared to the current 1 °C rise in GMT (Table 2, Fig. 4). Underlying

these net changes were marked increases in heat-related mortality by 1.68% (95%CI: 1.21–2.30) at 3 °C, 3.26% (95%CI: 2.81–3.70) at 4 °C, and 4.95% (95%CI: 3.84–6.10) at 5 °C, corresponding to a 2.8-fold (95%CI: 2.3–3.4), a 5.1-fold (95%CI: 4.6–6.0) and a 7.2-fold (95%CI: 6.5–7.9) rise in heat-related excess mortality, respectively, compared to today's warming of 1 °C (Table 2, Fig. 4).

The estimated standard deviations indicated that differences in climate simulations (originating from the use of various GCMs and from considering different RCPs) were the dominant source of uncertainty in projections of heat-related excess mortality (Fig. 5). By contrast,

Table 2

Projected excess mortality (GCM-RCP-ensemble averages) at different levels of GMT rise above pre-industrial for all 12 German cities combined. Relative changes (net differences, change factor) are computed relative to 1 °C GMT rise.

GMT rise above pre-industrial	Temperature range	Attributable fractions % (95%CI)	Net differences % (95%CI)	Change factor (95%CI)
1 °C	Heat	0.89 (0.66,1.18)	–	–
	Cold	5.29 (3.61,6.99)	–	–
	Total	6.19 (4.45,7.92)	–	–
2 °C	Heat	1.64 (1.25,2.01)	0.73 (0.41,1.03)	1.8 (1.4,2.3)
	Cold	4.58 (3.00,6.18)	–0.74 (–1.03, –0.50)	0.9 (0.8,0.9)
	Total	6.22 (4.56,7.87)	–0.01 (–0.39,0.31)	1.0 (0.9,1.1)
3 °C	Heat	2.60 (2.00,3.36)	1.68 (1.21,2.30)	2.8 (2.3,3.4)
	Cold	4.10 (2.59,5.62)	–1.22 (–1.68, –0.87)	0.8 (0.7,0.8)
	Total	6.70 (4.87,8.51)	0.45 (–0.02,1.06)	1.1 (1.0,1.2)
4 °C	Heat	4.06 (3.44,4.69)	3.26 (2.81,3.70)	5.1 (4.6,6.0)
	Cold	3.61 (2.20,5.02)	–1.72 (–2.11, –1.35)	0.7 (0.6,0.7)
	Total	7.67 (5.83,9.45)	1.53 (0.96,2.06)	1.2 (1.1,1.4)
5 °C	Heat	5.75 (4.48,7.09)	4.95 (3.84,6.10)	7.2 (6.5,7.9)
	Cold	3.27 (1.93,4.60)	–2.07 (–2.56, –1.62)	0.6 (0.5,0.7)
	Total	9.02 (6.60,11.44)	2.88 (1.60,4.10)	1.5 (1.2,1.8)

uncertainties in the temperature-mortality associations were the main contributor to total uncertainty in projections of cold-related mortality. Climate uncertainty contributed increasingly to overall uncertainty in projected total excess mortality along the gradient of global warming considered. The choice of RCP was generally the least important source of uncertainty, compared to differences among GCMs and uncertainties inherent in exposure-response functions, with the exception of warming levels 1 °C and 2 °C for heat-related mortality (Fig. 5).

4. Discussion

Here, we present for the first time a comprehensive assessment of temperature-related excess mortality under current and possible future climate conditions in major German cities, taking into account both heat- and cold-related mortality. Our findings indicate that while low temperatures currently contribute stronger to overall excess mortality than high temperatures across the cities studied, this pattern could be reversed if GMTs rise more than 3 °C relative to pre-industrial levels. Higher levels of global warming on the order of 3 °C, 4 °C and 5 °C are accompanied in our projections with marked net increases in total temperature-related excess mortality compared to today. By contrast, limiting the rise in GMT to 2 °C would avoid any significant change in total temperature-related mortality compared to today. Yet, underlying increases in heat-related mortality at this warming level are still considerable on a relative scale, with a mean projected 1.8-fold rise in the attributable fraction across cities.

Our results on attributable mortality in the observational period (1993–2015) agree with [Gasparrini et al. \(2015\)](#), who found that a larger fraction of the current temperature-related excess mortality in cities around the world can be attributed to cold than to heat. The temperature-mortality associations estimated here are also in qualitative agreement with [Breitner et al. \(2014\)](#), who showed that both very low and very high ambient temperatures increase non-accidental mortality in three southern German cities. E.g., for Munich our RR estimates translate into a 8.7% and 19.9% increase in mortality between the 1st vs 10th, and 99th vs 90th percentiles of daily mean temperatures, respectively, compared to 8.5% and 6.8% estimated by [Breitner et al. \(2014\)](#). By contrast, a recent study on temperature-related mortality across all German counties ([Karlsson and Ziebarth, 2018](#)) found evidence for heat-related mortality, but remained inconclusive on the effect of cold. The difference with our findings might stem from methodological differences in modelling the lagged effects of temperature. In fact, [Gasparrini \(2017\)](#) suggested that simpler approaches such as moving averages or linear lag functions (as adopted by [Karlsson and Ziebarth, 2018](#)) tend to underestimate cold effects on mortality, compared to more sophisticated methods such as the DLNMs used in

our study.

Our findings on projected mortality qualitatively match the estimates presented recently by [Vicedo-Cabrera et al. \(2018\)](#), who found moderate increases in net excess mortality for warming levels 3 °C and 4 °C relative to 1.5 °C for cities in Central Europe (which in this analysis comprise France, Switzerland, Czech Republic, and Moldova as the countries geographically closest to Germany). Our results can also be compared to the only study that has so far presented quantitative projections on heat- and cold-related mortality for the whole of Germany ([Hübner et al., 2008](#)). Disregarding the effect of an aging population, this study found a doubling of heat-related fatalities for a scenario (SRES A1B) corresponding to approximately 3 °C global warming by the end of the century (conversion of scenario and time period into GMT level based on [Ebi et al., 2018](#)). Our aggregated results across all cities are approximately in line with these findings (Table 2: we found a mean increment factor of 2.8 [95% CI: 2.3–3.4]). Furthermore, [Hübner et al. \(2008\)](#) found that at 3 °C the effects of cold and heat only roughly balanced each other, with a slight surplus of additional deaths due to heat, which is also in accordance with our results.

Our study has several limitations. Most importantly, our projections do not take into account possible shifts in the vulnerability of the population towards non-optimal temperatures over time, which might occur due to demographic changes, alteration of health care services, physiological acclimatization, or adaptation measures. These shifts have been documented for the past, especially regarding decreasing vulnerability towards heat (e.g., [Achebak et al., 2018](#); [Barreca et al., 2016](#); [Chung et al., 2018](#)). Some recent projection studies have also explicitly accounted for demographic changes, based on age-specific exposure response functions ([Lee et al., 2019](#); [Rai et al., 2019](#)). However, our approach does not easily allow us to incorporate these changes in time. By integrating different climate scenarios (RCPs) in our definition of global warming levels we break up the temporal structure of projections and thus cannot directly integrate possible future changes in demography or adaptive behaviour. Thus, our results should by no means be misinterpreted as future predictions of temperature-related excess mortality. Instead, our approach allows us to isolate the effect of climate from other socio-economic factors known to influence mortality.

Consistently with previous published studies we estimated large uncertainties in projected excess mortalities ([Gasparrini et al., 2017](#); [Vicedo-Cabrera et al., 2018](#)), stemming from the imprecision in estimated temperature-mortality associations, from differences among GCMs, and from sampling uncertainty related to different RCPs. Yet, even though we capture important elements of the total uncertainty, there are some limitations to our uncertainty measures. First, our approach does not account for the uncertainty in choosing the functional

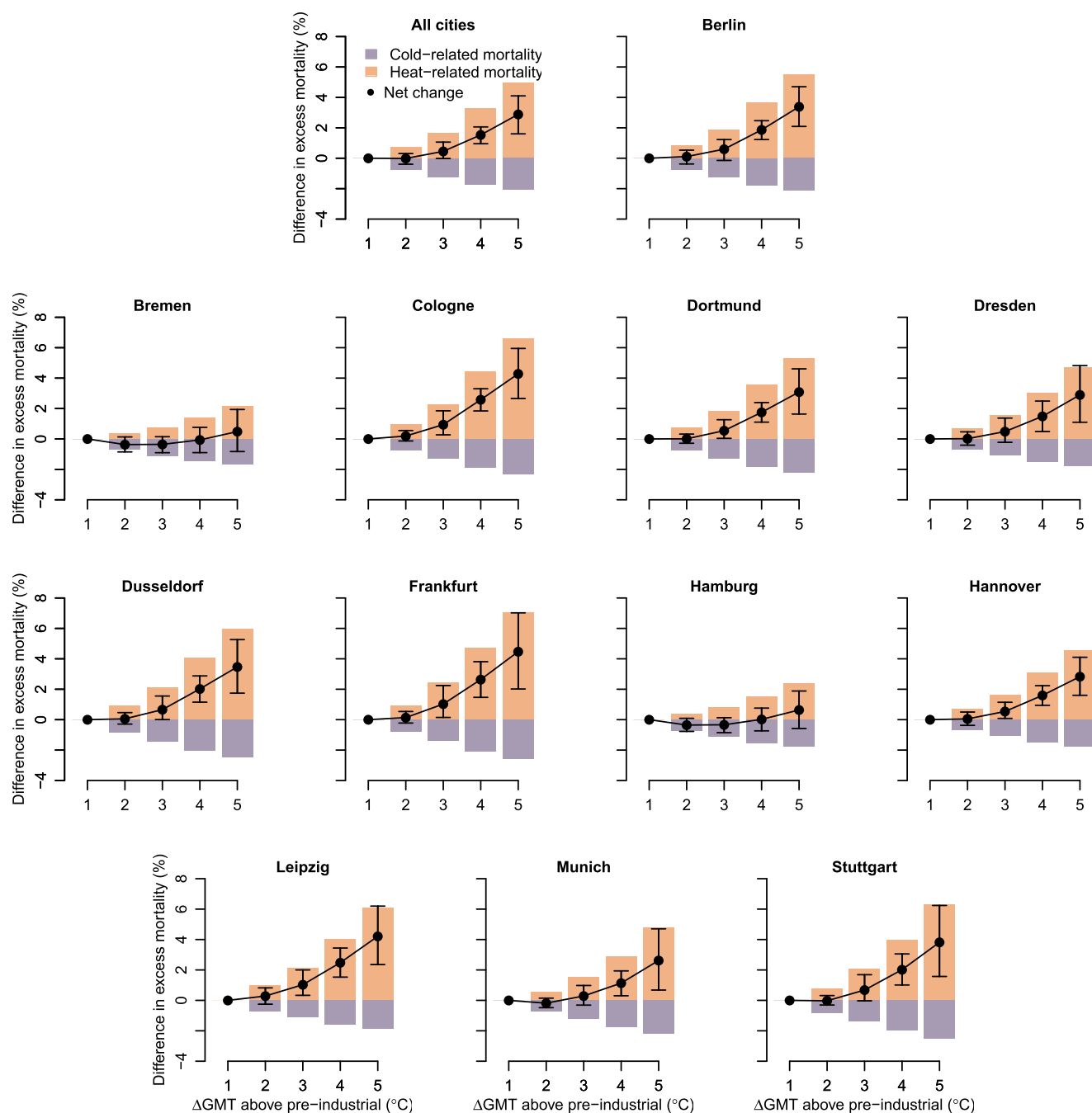


Fig. 4. Differences in excess mortality compared to today's 1 °C of global warming for all cities combined, and by individual city. Bars and circles correspond to GCM-RCP-ensemble averages (cf. Fig. 3). Whiskers show 95% CIs in net differences.

form for extrapolating exposure-response curves beyond the maximum temperatures in the observational datasets (Benmarhnia et al., 2014; Vicedo-Cabrera et al., 2018). This shortcoming would lead to an underestimation of the contribution of epidemiological uncertainty to total uncertainty in heat-related mortality projections (Fig. 5). Second, by using temperature projections derived from transient climate simulations in a limited time period we base our estimates on an incomplete sampling of the temperature distributions corresponding to the different magnitudes of global warming considered. This concerns in particular the higher warming levels (4 °C and 5 °C), where our estimates are based on RCP8.5 simulations of two GCMs only (Table A3), and, thus, the resulting bias in the estimation of climate uncertainty should be greatest.

Last but not least, our study leaves to further research the more detailed investigation of observed heterogeneity between cities. Sera et al. (2019) recently showed that some of the differences in the magnitude of attributable fractions observed among cities around the world can be related to variability in external factors such as demographic parameters, air pollution levels, socio-economic indicators, and urban infrastructure. In this regard, it is interesting to note that the two cities with the most maritime climate, and thus the comparatively coolest summers, Bremen and Hamburg, showed the lowest heat-related excess mortality (Table 1). Further analyses relating differences in exposure-response functions to local climate characteristics is a promising avenue to account for potential shifts in vulnerability to non-optimal temperature in more refined future projection studies.

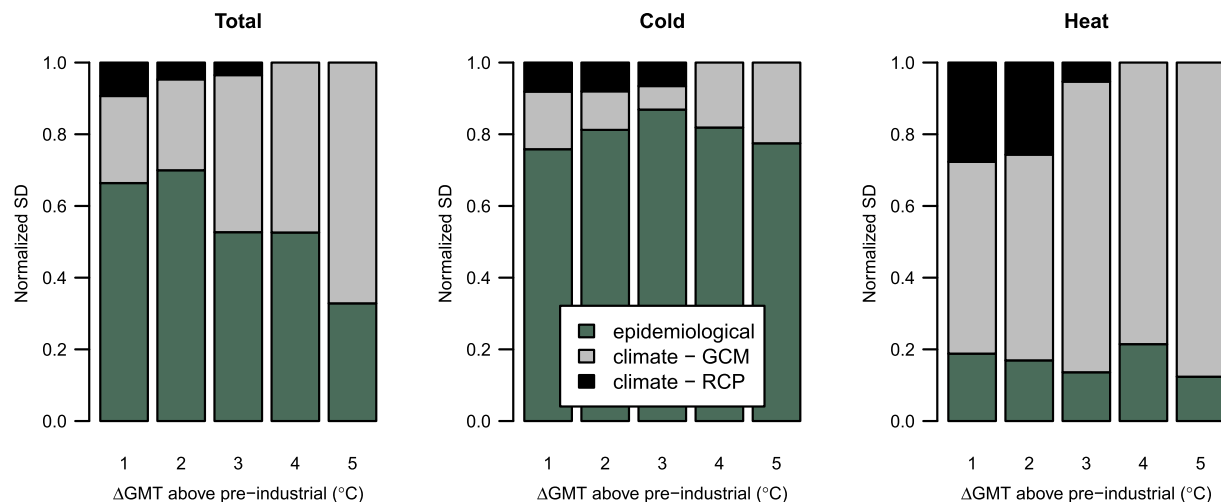


Fig. 5. Relative uncertainty expressed as normalized standard deviations (SDs) arising from GCMs and RCPs (climate uncertainty), and exposure-response functions (epidemiological uncertainty) in projections of total excess mortality (left), cold-related excess mortality (middle) and heat-related excess mortality (right), by level of global warming. Results shown are for all cities combined.

5. Conclusions

In conclusion, our findings show that keeping global warming below 2 °C above pre-industrial levels implies considerable health benefits in German cities compared to higher warming levels, especially those to be reached if global greenhouse gas emissions are not drastically reduced in the coming decades. While we found marked net increases in temperature-related excess mortality for global warming by 3 °C and more, ambitious mitigation in accordance with the Paris Agreement would avoid a net increase in overall excess mortality compared to today. At the same time, even at 2 °C of global warming, adaptation efforts would need to be implemented in order to buffer the estimated increase in heat-related mortality, which, independent of concomitant shifts in cold-related mortality, appears as a considerable future public health risk in Germany.

Funding sources

This work was supported by the Spanish Ministry of Economy, Industry and Competitiveness – State Bureau of Investigation (Grant ID: PCIN-2017-046), the German Federal Ministry of Education and Research (Grant ID: 01LS1201A2), the European Union's Seventh Framework Programme for Research, Technological Development and Demonstration (Grant ID: 603860), Medical Research Council-UK (Grant ID: MR/M022625/1), the Natural Environment Research Council UK (Grant ID: NE/R009384/1), the European Union's Horizon 2020 Project Exhaustion (Grant ID: 820655), and a scholarship from the Potsdam Graduate School.

CRediT authorship contribution statement

Veronika Huber: Conceptualization, Methodology, Software, Formal analysis, Writing - original draft. **Linda Krummenauer:** Investigation, Software, Writing - review & editing. **Cristina Peña-Ortiz:** Conceptualization, Methodology, Resources, Writing - review & editing. **Stefan Lange:** Methodology, Data curation, Writing - review & editing. **Antonio Gasparrini:** Methodology, Software, Writing - review & editing. **Ana M. Vicedo-Cabrera:** Methodology, Software, Writing - review & editing. **Ricardo Garcia-Herrera:** Supervision, Writing - review & editing. **Katja Frieler:** Funding acquisition, Writing - review & editing.

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.

Acknowledgements

We would like to thank Urban Janisch from the Research Data Centres of the Federation and the Federal States of Germany for his advice in assembling the death count statistics.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envres.2020.109447>.

References

- Achebak, H., Devolder, D., Ballester, J., 2018. Heat-related mortality trends under recent climate warming in Spain: a 36-year observational study. *PLoS Med.* 15, 1–17. <https://doi.org/10.1371/journal.pmed.1002617>.
- Anderson, B.G., Bell, M.L., 2009. Weather-related mortality: how heat, cold, and heat waves affect mortality in the United States. *Epidemiology* 20, 205–213. <https://doi.org/10.1097/EDE.0b013e318190e088>.
- Arbuthnott, K., Hajat, S., Heaviside, C., Vardoulakis, S., 2018. What is cold-related mortality? A multi-disciplinary perspective to inform climate change impact assessments. *Environ. Int.* 121, 119–129. <https://doi.org/10.1016/j.envint.2018.08.053>.
- Barreca, A., Clay, K., Deschênes, O., Greenstone, M., Shapiro, J.S., 2016. Adapting to climate change: the remarkable decline in the US temperature-mortality relationship over the 20th century. *J. Polit. Econ.* 124, 105–159. <https://doi.org/10.3386/w18692>.
- Benmarhnia, T., Sottile, M.-F., Plante, C., Brand, A., Casati, B., Fournier, M., Smargiassi, A., 2014. Variability in temperature-related mortality projections under climate change. *Environ. Health Perspect.* 122, 1293–1298. <https://doi.org/10.1289/ehp.1306954>.
- Breitner, S., Wolf, K., Devlin, R.B., Diaz-sanchez, D., Peters, A., Schneider, A., 2014. Short-term effects of air temperature on mortality and effect modification by air pollution in three cities of Bavaria, Germany: a time-series analysis. *Sci. Total Environ.* 486, 49–61. <https://doi.org/10.1016/j.scitotenv.2014.03.048>.
- Carleton, T., Delgado, M., Greenstone, M., Houser, T., Hsiang, S., Hultgren, A., Jina, A., Kopp, R., McCusker, K., Nath, I., Rising, J., Carleton, T., Delgado, M., Greenstone, M., Houser, T., Hultgren, A., Jina, A., Kopp, R., McCusker, K., Rising, J., Rode, A., Seo, S., Simcock, J., Viana, A., Yuan, J., Zhang, A., 2018. Valuing the Global Mortality Consequences of Climate Change Accounting for Adaptation Costs and Benefits. <https://doi.org/10.2139/ssrn.3224365>.
- Chen, K., Breitner, S., Wolf, K., Rai, M., Meisinger, C., Heier, M., Kuch, B., Peters, A., Schneider, A., 2019. Temperature-related myocardial infarction under and beyond Paris agreement goals in augsburg, Germany. *Dtsch Arztebl Int.* 116, 521–527. <https://doi.org/10.3238/arztebl.2019.0521>.

- Chung, Y., Yang, D., Gasparrini, A., Vicedo-Cabrera, A.M., Ng, C.F.S., Kim, Y., Honda, Y., Hashizume, M., 2018. Changing susceptibility to non-optimum temperatures in Japan, 1972–2012: the role of climate, demographic, and socioeconomic factors. *Environ. Health Perspect.* 126 <https://doi.org/10.1289/EHP2546>. 057002–8.
- Ebi, K.L., Hasegawa, T., Hayes, K., Monaghan, A., Paz, S., Berry, P., 2018. Health risks of warming of 1.5 °C, 2 °C, and higher above pre-industrial temperatures. *Environ. Res. Lett.* 13 063007.
- Frieler, K., Lange, S., Piontek, F., Reyer, C.P.O., Schewe, J., Warszawski, L., Zhao, F., Chini, L., Denvil, S., Emanuel, K., Geiger, T., Halladay, K., Hurtt, G., Mengel, M., Murakami, D., Ostberg, S., Popp, A., Riva, R., 2017. Assessing the impacts of 1.5 °C global warming – simulation protocol of the inter-sectoral impact model Intercomparison Project (ISIMIP2b). *Geosci. Model Dev. (GMD)* 4321–4345.
- Gasparrini, A., 2017. Modelling lagged associations in environmental time series data: a simulation study. *Epidemiology* 27, 835–842. <https://doi.org/10.1097/EDE.0000000000000533>.
- Gasparrini, A., Armstrong, B., Kenward, M.G., 2010. Distributed lag non-linear models. *Stat. Med.* 29, 2224–2234. <https://doi.org/10.1002/sim.3940>.
- Gasparrini, A., Armstrong, B., Kenward, M.G., 2012. Multivariate meta-analysis for non-linear and other multi-parameter associations. *Stat. Med.* <https://doi.org/10.1002/sim.5471>.
- Gasparrini, A., Armstrong, B., Kovats, S., Wilkinson, P., 2012. The effect of high temperatures on cause-specific mortality in England and Wales. *Occup. Environ. Med.* 69, 56–61. <https://doi.org/10.1136/oem.2010.059782>.
- Gasparrini, A., Guo, Y., Hashizume, M., Lavigne, E., Zanobetti, A., Schwartz, J., Tobias, A., Tong, S., Rocklöv, J., Forsberg, B., Leone, M., De Sario, M., Bell, M.L., Guo, Y.L.L., Wu, C.F., Kan, H., Yi, S.M., De Sousa Zanotti Stagliorio Coelho, M., Saldiva, P.H.N., Honda, Y., Kim, H., Armstrong, B., 2015. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *Lancet* 386, 369–375. [https://doi.org/10.1016/S0140-6736\(14\)62114-0](https://doi.org/10.1016/S0140-6736(14)62114-0).
- Gasparrini, A., Guo, Y., Sera, F., Vicedo-cabrera, A.M., Huber, V., Tong, S., Sousa, M. De, Stagliorio, Z., Hilario, P., Saldiva, N., Lavigne, E., Correa, P.M., Ortega, N.V., Kan, H., Osorio, S., Kysely, J., Urban, A., Jaakkola, J.J.K., Rytö, N.R.I., Pascal, M., Goodman, P.G., Zeka, A., Michelozzi, P., Scortichini, M., Hashizume, M., 2017. Projections of temperature-related excess mortality under climate change scenarios. *Lancet Planet. Health* 360–367. [https://doi.org/10.1016/S2542-5196\(17\)30156-0](https://doi.org/10.1016/S2542-5196(17)30156-0).
- Gasparrini, A., Leone, M., 2014. Attributable risk from distributed lag models. *BMC Med. Res. Methodol.* 14, 55. <https://doi.org/10.1186/1471-2288-14-55>.
- Huang, C., Barnett, A.G., Wang, X., Vaneckova, P., Fitzgerald, G., Tong, S., 2011. Projecting Future heat-related mortality under climate change scenarios: a systematic review. *Environ. Health Perspect.* 119, 1681–1690. <https://doi.org/10.1289/ehp.1103456>.
- Hübner, M., Klepper, G., Peterson, S., 2008. Costs of climate change: the effects of rising temperatures on health and productivity in Germany. *Ecol. Econ.* 68, 381–393.
- Karlsson, M., Ziebarth, N.R., 2018. Population health effects and health-related costs of extreme temperatures: comprehensive evidence from Germany. *J. Environ. Econ. Manag.* 91, 93–117. <https://doi.org/10.1016/j.jeem.2018.06.004>.
- Kendrovski, V., Baccini, M., Martinez, G.S., Wolf, T., Paunovic, E., Menne, B., 2017. Quantifying projected heat mortality impacts under 21st-Century warming conditions for selected European countries. *Int. J. Environ. Res. Publ. Health* 14. <https://doi.org/10.3390/ijerph14070729>.
- Kinney, P.L., Schwartz, J., Pascal, M., Petkova, E., Tertre, A. Le, Medina, S., Vautard, R., 2015. Winter season mortality: will climate warming bring benefits? *Environ. Res. Lett.* 10 <https://doi.org/10.1088/1748-9326/10/6/064016>. 064016.
- Lange, S., 2017. ISIMIP2b Bias-Correction Code. Zenodo. doi: 10.5281/zenodo.1069050.
- Laschewski, G., Jendritzky, G., 2002. Effects of the thermal environment on human health: an investigation of 30 years of daily mortality data from SW Germany. *Clim. Res.* 21, 91–103.
- Lee, J.Y., Lee, W.S., Ebi, K.L., Kim, H., 2019. Temperature-related summer mortality under multiple climate, population, and adaptation scenarios. *Int. J. Environ. Res. Publ. Health* 16. <https://doi.org/10.3390/ijerph16061026>.
- Li, T., Horton, R.M., Kinney, P.L., 2013. Projections of seasonal patterns in temperature-related deaths for Manhattan, New York. *Nat. Clim. Change* 3, 717–721. <https://doi.org/10.1038/nclimate1902>.
- Li, Y., Ren, T., Kinney, P.L., Joyner, A., Zhang, W., 2018. Projecting future climate change impacts on heat-related mortality in large urban areas in China. *Environ. Res.* <https://doi.org/10.1016/j.envres.2018.01.047>.
- Lo, E.Y.T., Mitchell, D.M., Gasparrini, A., Vicedo-Cabrera, A.M., Ebi, K.L., Frumhoff, P.C., Millar, R.J., Roberts, W., Sera, F., Sparrow, S., Uhe, P., Williams, G., 2019. Increasing mitigation ambition to meet the Paris Agreement's temperature goal avoids substantial heat-related mortality in U.S. Cities. *Sci. Adv.* 5, 1–10. <https://doi.org/10.1126/sciadv.aau4373>.
- Martin, S.L., Cakmak, S., Hebborn, C.A., Avramescu, M.L., Tremblay, N., 2012. Climate change and future temperature-related mortality in 15 Canadian cities. *Int. J. Biometeorol.* 56, 605–619. <https://doi.org/10.1007/s00484-011-0449-y>.
- Martinez, G.S., Diaz, J., Hooyberghs, H., Lauwaet, D., De Ridder, K., Linares, C., Carmona, R., Ortiz, C., Kendrovski, V., Adamonyte, D., 2018. Cold-related mortality vs heat-related mortality in a changing climate: a case study in Vilnius (Lithuania). *Environ. Res.* 166, 384–393. <https://doi.org/10.1016/j.envres.2018.06.001>.
- Mitchell, D., Heaviside, C., Schaller, N., Allen, M., Ebi, K.L., Fischer, E.M., Gasparrini, A., Harrington, L., Kharin, V., Shioyama, H., Sillmann, J., 2018. Extreme heat-related mortality avoided under Paris Agreement goals. *Nat. Clim. Change* 5–7. <https://doi.org/10.1038/s41558-018-0210-1>.
- Muthers, S., Laschewski, G., Matzarakis, A., 2017. The summers 2003 and 2015 in south-west Germany: heat waves and heat-related mortality in the context of climate change. *Atmosphere* 8. <https://doi.org/10.3390/atmos8110224>.
- Ostberg, S., Schewe, J., Childers, K., Frieler, K., 2018. Changes in crop yields and their variability at different levels of global warming. *Earth Syst. Dyn.* 479–496.
- Rai, M., Breiter, S., Wolf, K., Peters, A., Schneider, A., Chen, K., 2019. Impact of climate and population change on temperature-related mortality burden in Bavaria, Germany. *Environ. Res. Lett.* 14, 124080. <https://doi.org/10.1088/1748-9326/ab5ca6>.
- Sanderson, M., Arbutnot, K., Kovats, S., Hajat, S., Falloon, P., 2017. The use of climate information to estimate future mortality from high ambient temperature: a systematic literature review. *PLoS One* 1–34.
- Schaeffer, L., de Crouy-Chanel, P., Wagner, V., Desplat, J., Pascal, M., 2016. How to estimate exposure when studying the temperature-mortality relationship? A case study of the Paris area. *Int. J. Biometeorol.* 60, 73–83. <https://doi.org/10.1007/s00484-015-1006-x>.
- Schleussner, C.F., Lissner, T.K., Fischer, E.M., Wohland, J., Perrette, M., Golly, A., Rogelj, J., Childers, K., Schewe, J., Frieler, K., Mengel, M., Hare, W., Schaeffer, M., 2016. Differential climate impacts for policy-relevant limits to global warming: the case of 1.5 °C and 2 °C. *Earth Syst. Dyn.* 7, 327–351. <https://doi.org/10.5194/esd-7-327-2016>.
- Schwartz, J.D., Lee, M., Kinney, P.L., Yang, S., Mills, D., Sarofim, M.C., Jones, R., Streeter, R., Juliana, A.S., Peers, J., Horton, R.M., 2015. Projections of temperature-attributable premature deaths in 209 U.S. cities using a cluster-based Poisson approach. *Environ. Health* 14, 85. <https://doi.org/10.1186/s12940-015-0071-2>.
- Sera, F., Armstrong, B., Tobias, A., Vicedo-Cabrera, A.M., 2019. How urban characteristics affect vulnerability to heat and cold: a multi-country analysis. *Int. J. Epidemiol.* 48 (4), 1101–1112. <https://doi.org/10.1093/ije/dyz008>.
- Vicedo-Cabrera, A.M., Guo, Y., Sera, F., Huber, V., Schleussner, C.-F., Mitchell, D., Tong, S., Sousa, M. de, Coelho, Z.S., Saldiva, P.H.N., Lavigne, E.O., Correa, P.M., Ortega, N.V., Al, E., 2018. Temperature-related mortality impacts under and beyond Paris Agreement climate change scenarios. *Climatic Change* 150, 391–402. <https://doi.org/10.1007/s10584-018-2274-3>.
- Vicedo-Cabrera, A.M., Sera, F., Gasparrini, A., 2019. Hands-on tutorial on a modeling framework for projections of climate change impacts on health. *Epidemiology* 30, 321–329. <https://doi.org/10.1097/EDE.0000000000000982>.
- Wang, Y., Wang, A., Zhai, J., Tao, H., Jiang, T., Su, B., Yang, J., Wang, G., Liu, Q., Gao, C., Kundzewicz, Z.W., Zhan, M., Feng, Z., Fischer, T., 2019. Tens of thousands additional deaths annually in cities of China between 1.5 °C and 2.0 °C warming. *Nat. Commun.* 10. <https://doi.org/10.1038/s41467-019-11283-w>.
- Weinberger, K.R., Haykin, L., Eliot, M.N., Schwartz, J.D., Gasparrini, A., Wellenius, G.A., 2017. Projected temperature-related deaths in ten large U.S. metropolitan areas under different climate change scenarios. *Environ. Int.* 107, 196–204. <https://doi.org/10.1016/j.envint.2017.07.006>.
- Weinberger, K.R., Spangler, K.R., Zanobetti, A., Schwartz, J.D., Wellenius, G.A., 2019. Comparison of temperature-mortality associations estimated with different exposure metrics. *Environ. Epidemiol.* 1. <https://doi.org/10.1097/ee9.0000000000000072>.
- Zacharias, S., Koppe, C., Mücke, H., 2015. Climate change effects on heat waves and future heat wave-associated IHD mortality in Germany. *Climate* 100–117. <https://doi.org/10.3390/cli3010100>.