

Temperature-related mortality burden and projected change in 1368 European regions: a modelling study



David García-León, Pierre Masselot, Malcolm N Mistry, Antonio Gasparrini, Corrado Motta, Luc Feyen, Juan-Carlos Ciscar



Summary

Background Excessively high and low temperatures substantially affect human health. Climate change is expected to exacerbate heat-related morbidity and mortality, presenting unprecedented challenges to public health systems. Since localised assessments of temperature-related mortality risk are essential to formulate effective public health responses and adaptation strategies, we aimed to estimate the current and future temperature-related mortality risk under four climate change scenarios across all European regions.

Methods We modelled current and future mortality due to non-optimal temperatures across 1368 European regions, considering age-specific characteristics and local socioeconomic vulnerabilities. Overseas territories were excluded from the analysis. We applied a three-stage method to estimate temperature-related risk continuously across age and spatial dimensions. Age and city-specific exposure–response functions were obtained for a comprehensive list of 854 European cities from the Urban Audit dataset of Eurostat. Regional aggregates were calculated using an aggregation and extrapolation method that incorporates the risk incidence in neighbouring cities. Mortality was projected for present conditions observed in 1991–2020 and for four different levels of global warming (1·5°C, 2°C, 3°C, and 4°C increase) by regions, and subregions using an ensemble of 11 climate models produced by the Coordinated Regional Climate Downscaling Experiment-CMIP5 over Europe, and population projection data from EUROPOP2019.

Findings Our results highlight regional disparities in temperature-related mortality across Europe. Between 1991 and 2020, the number of cold-related deaths was 2·5 times higher in eastern Europe than western Europe, and heat-related deaths were 6 times higher in southern Europe than in northern Europe. During the same time period, there were a median of 363 809 cold-related deaths (empirical 95% CI 362 493–365 310) and 43 729 heat-related deaths (39 880–45 921), with a cold-to-heat-related death ratio of 8·3:1. Under current climate policies, aligned with 3°C increase in global warming, it is estimated that temperature-related deaths could increase by 54 974 additional deaths (24 112–80 676) by 2100, driven by rising heat-related deaths and an ageing population, resulting in a cold-to-heat-related death ratio of 2·6:1. Climate change is also expected to widen disparities in regional mortality, particularly impacting southern regions of Europe as a result of a marked increase in heat-related deaths.

Interpretation This study shows that regional disparities in temperature-related mortality risk in Europe are substantial and will continue to increase due to the effects of climate change and an ageing population. The data presented can assist policy makers and health authorities in mitigating increasing health inequalities by prioritising the protection of more susceptible areas and older population groups. We identify the projected areas of heightened risk (southern Europe), where policy intervention aimed at building adaptation and enhancing resilience should be prioritised.

Funding European Commission.

Copyright © 2024 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Introduction

Climate change is associated with adverse outcomes in physical, mental, and community health and wellbeing through the increasing frequency and intensity of extreme weather events, rising cases of infectious and vector-borne diseases, declining air quality, and decreases in food and water quality and security.¹ Moreover, climate change is expected to exacerbate heat-related morbidity and mortality, presenting unprecedented challenges to public health systems.

It has been estimated that a third of heat-related deaths can be attributed to anthropogenic climate change and

increased mortality is evident on all continents.² During the summer of 2022, the hottest on record for Europe, mortality rates were unusually high, with more than 60 000 heat-related deaths estimated in Europe.³ Morbidity and mortality from climate-related hazards are projected to continue to increase across most regions of the world.¹ Multi-impact studies done in the USA and Europe have underscored the social and economic ramifications of heat-related mortality,⁴ emphasising the urgent need for targeted interventions and adaptation measures.

Despite growing recognition of the health impacts of climate change, the evidence base remains small, even for

Lancet Public Health 2024;
9: e644–53

Published Online

August 21, 2024

[https://doi.org/10.1016/S2468-2667\(24\)00179-8](https://doi.org/10.1016/S2468-2667(24)00179-8)

See [Comment](#) page e636

See [Comment](#) page e636

European Commission, Joint Research Centre, Seville, Spain

(D García-León PhD,

J-C Ciscar PhD); Environment

and Health Modelling

Laboratory, Department of

Public Health, Environments

and Society, London School of

Hygiene & Tropical Medicine,

London, UK (P Masselot PhD,

M N Mistry PhD,

Prof A Gasparrini PhD);

Department of Economics,

Ca' Foscari University of Venice,

Venice, Italy (M N Mistry);

Arcadia SIT, Vigevano, Italy

(C Motta MSc); European

Commission, Joint Research

Centre, Ispra, Italy

(L Feyen PhD)

Correspondence to:

Mr David García-León, European

Commission, Joint Research

Centre, Seville 41092, Spain

david.garcia-leon@ec.europa.eu

Research in context

Evidence before this study

We searched PubMed from database inception to April 5, 2024, to identify papers published on temperature-related mortality impact assessments in Europe without language restrictions, using the search terms “((Mortality) AND (Temperature) AND (Socioeconomic Factors) AND (Europe) AND (Region))”. We identified 117 publications, of which 70 were directly relevant to our analysis. Most published literature analysed either heat-related or cold-related risks separately, covered small areas or individual countries, and often focused on specific episodes of intense cold or heatwaves. Some studies targeted specific population groups, but age considerations were generally not taken into account. One study assessed winter mortality in Europe, but the results were only presented at the country level. We found no studies simultaneously investigating the magnitude of heat-related and cold-related mortality risks under different warming conditions across a large geographical scope.

Added value of this study

To our knowledge, this study is the first to quantitatively assess present and future temperature-driven excess mortality at the subnational level across Europe. This level of granularity enables the inherent spatial heterogeneity of this risk to be addressed. We estimated current and future mortality risk under four

different global warming scenarios to assess regional heterogeneity, while accounting for age composition and sociodemographic characteristics. Between 1991 and 2020, we estimated 363 809 cold-related deaths (empirical 95% CI 362 493–365 310) and 43 729 heat-related deaths (39 880–45 921), subject to substantial geographical heterogeneity. Temperature-related deaths are projected to increase by 41 850–96 072 additional deaths annually depending on the warming scenario, driven by rising temperatures and an ageing population, and exacerbating regional disparities.

Implications of all the available evidence

Climate change effects on health show regional differences suggesting that adaptation policies should be framed locally, considering the substantial heterogeneity in climatic and socioeconomic factors driving climate and environmental risks. Changes in demography and warming are expected to become the main drivers of disparities, which will need to be addressed with policy action to address extreme heat and susceptible populations. Data from this study should be used in combination with local-level indicators of susceptibility to prioritise public health adaptation efforts in Europe, which are crucial for mitigating the anticipated growth in health inequalities.

a relatively well-studied area such as Europe.⁵ Compared with other environmental risks, such as air pollution, which have been more extensively studied at the local level,⁶ there is a paucity of region-specific evidence on temperature-related mortality. This highlights gaps in our understanding of localised vulnerabilities and impacts. Previous assessments have focused either on large-scale analyses or were based on data with higher resolution but with little geographical scope.^{7,8} Most evidence is also limited to western European countries,⁹ with Scandinavia and eastern Europe less represented.¹⁰ Another important limitation is the absence of consideration for demographic differences, whereby the differential risks across age groups reported in the literature can lead to a substantial variation in estimated mortality effects.¹¹ Additionally, previous analyses have not considered other characteristics that can modify susceptibility to heat and cold, such as location-specific socioeconomic and environmental variables.¹² Furthermore, assessments of future mortality have mainly focused on heat-related deaths and not considered cold-related deaths. These shortcomings pose important limits on the design and implementation of effective public health and climate adaptation strategies.

To address these limitations, we aimed to estimate the temperature-related (heat and cold) mortality in Europe, for 1368 regions across 30 countries, including the 27 EU Member States, as well as Norway, Switzerland, and the UK. The study leveraged a dataset¹³ of city-specific

exposure–response functions (ERFs) resulting from epidemiological and socioeconomic analysis of more than 854 cities across Europe with populations exceeding 50 000 inhabitants. The analysis accounted for age-specific susceptibility to temperature variations, and spatially explicit demographic projections. We present impacts for global warming levels corresponding to the Paris climate targets (increases of 1.5°C and 2°C), an upper estimate according to current climate policies in place (increase of 3°C),¹⁴ and a high-end estimate representative of no climate policies (increase of 4°C), enabling us to evaluate the future mortality burden of different levels of climate mitigation. We further disentangled the projected future temperature-mortality risk by accounting for its two main driving factors: changes in temperatures and shifts in population structure. Finally, we identified future geographical regions of heightened mortality risk where policy action should be prioritised.

Methods

Time series epidemiological analysis

We obtained data for 854 European cities included in the Urban Audit dataset of Eurostat,¹⁵ to identify patterns of vulnerability on the basis of city-specific characteristics and demographic structure. We applied a three-stage method¹³ to estimate the mortality risk of temperature continuously for different age groups (20–44, 45–64, 65–74, 75–84, and ≥85 years) within these 854 cities.

Overseas cities were excluded (Saint Denis, Fort-de-France, Mamoudzou, Cayenne, and Saint-Louis [France]; Reykjavik [Iceland]; Funchal and Ponta Delgada [Portugal]; Las Palmas, Santa Cruz de Tenerife, Telde, Ceuta, and Melilla, Arrecife, Santa Lucía de Tirajana, and Puerto de la Cruz [Spain]). The final sample included 854 cities from 30 countries (appendix p 5). These risks were then used to derive temperature thresholds of minimum mortality and related percentiles and raw and age-standardised excess mortality rates for heat and cold. Details about how the ERFs were obtained and a visual representation of the different modelling stages are provided in the appendix (pp 1–2).

Climate models

We used projections of climate variables from an ensemble of 11 bias-adjusted regional climate models produced by the Coordinated Regional Climate Downscaling Experiment-CMIP5 over Europe.¹⁶ The climate models are run under two representative concentration pathways (RCPs): RCP4.5 and RCP8.5 and climate data are bias-adjusted using a transfer function method¹⁷ based on the E-OBS daily gridded observational dataset for precipitation, temperature and sea level pressure in Europe (version 10).¹⁸ We compared four future global warming level scenarios (Paris Agreement targets [increases of 1.5°C and 2°C] and two higher warming levels [increases of 3°C and 4°C]) with the period of 1991–2020. We used the time sampling approach (appendix p 3), whereby information from different emissions scenarios were merged to estimate impacts for global warming levels. Based on many studies, the sixth assessment report of the Intergovernmental Panel on Climate Change¹⁹ concluded that the regional response patterns at given global warming levels are consistent across different scenarios for many climate variables (including temperature considered herein) and that within scenario climate model variability is comparable with the between scenario variability, which justifies the use of this approach.

Population projections

We obtained EUROPOP2019 population projections at the Nomenclature of Territorial Units for Statistics (NUTS) 3 regional level from the Eurostat database. EUROPOP2019 national and subnational projections are produced for 31 countries, of which 30 were analysed here (all 27 EU Member States, as well as Norway, Switzerland, and the UK), covering the time horizon from 2019 to 2100. These projections are so-called what-if scenarios that aim to show the hypothetical developments of the population size and its structure based on a set of assumptions about future fertility, mortality, and net migration. For all NUTS 3 level regions, data are available by single year time intervals and for 1-year age groups from 0 to 99 years, where the base population is the population of the region on Jan 1, 2019, as reported in the

annual demographic statistics data collection run by Eurostat. EUROPOP2019 adopts assumptions on future age-specific fertility rates, probabilities of dying, and net migration levels. We used these rates to obtain the age-specific number of deaths per year and then estimated the number of deaths attributed to cold and heat using the relative risks obtained in the time series analysis.

Regional aggregation and extrapolation

Using EUROPOP2019 population projections, we obtained daily time series with the number of deaths attributable to cold and heat for each age group in each of the analysed cities. These estimates were then aggregated and extrapolated from the city to the regional level (1368 NUTS 3 regions in NUTS version 2021)²⁰ using the following methodology: when data for any number of cities were available in a particular NUTS 3 region, we created a composite city from these cities. Total attributable deaths for each age group in the composite city were calculated as population-weighted averages of attributable deaths in the included cities for this region. Once we obtained the number of deaths attributable to heat and cold among different age groups in the composite city, NUTS 3 aggregates were determined by weighting the composite city age group estimates based on the distribution of age groups in the corresponding NUTS 3 regional population. The NUTS level of reference selected for each NUTS 3 region was dependent on the availability of sample cities in each region (appendix p 9). An overview of the NUTS regional coverage of the 854 cities analysed and illustrative examples of aggregation and extrapolation methods used are provided in the appendix (pp 3, 10).

Regional economic data

We used regional account data from Eurostat to explore the relationship between temperature-related mortality and other factors beyond climate and individual characteristics, for which regional income was used as a proxy. Specifically, we retrieved data on gross domestic product (GDP) per capita from Eurostat for the year 2019 at the NUTS 3 level, based on the 2016 version of NUTS.

Contribution analysis

Future excess mortality depends on regional changes in temperature due to climate change and on the size and composition of the population at risk due to demographic changes (increases in age-specific survival). Additionally, total base mortality will be affected by lower projected fertility rates. To understand the relative contribution of these drivers of future excess deaths, the mortality analysis was applied for different combinations of climate and population scenarios.²¹ The following cases were studied: case 1, present climate combined with present population; case 2, present climate combined with future population exposure as projected by the EUROPOP2019 regional population and total mortality projections;

See Online for appendix

For more on the **E-OBS dataset** see <https://cds.climate.copernicus.eu/cdsapp#!/dataset/insitu-gridded-observations-europe?tab=overview>

For **data on GDP by NUTS 3 region** see https://ec.europa.eu/eurostat/databrowser/view/nama_10r_3gdp/default/table?lang=en

For the **Eurostat database** see <https://ec.europa.eu/eurostat/web/population-demography/population-projections/database>

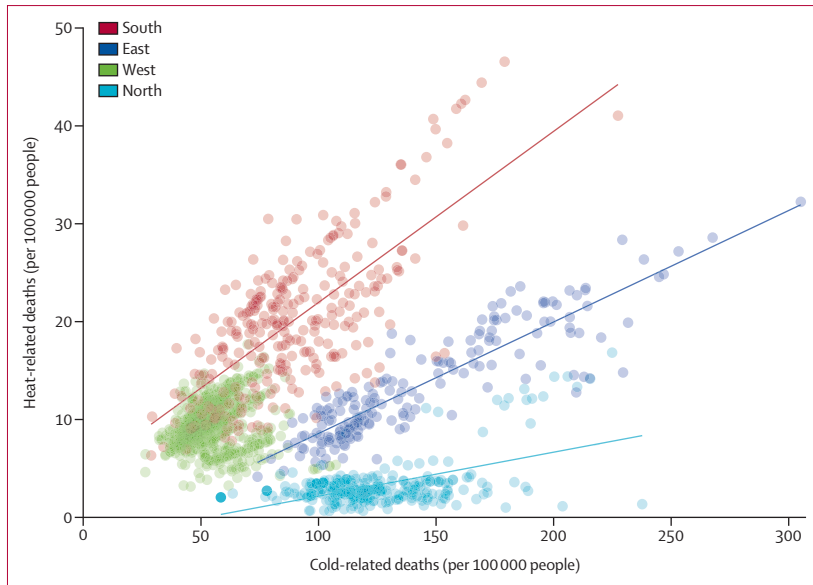


Figure 1: Patterns of temperature-related mortality in 1368 European regions (1991–2020) Cold-related and heat-related standardised death rates per 100 000 people based on 1991–2020 climate and population data for the year 2020 in the analysed regions. Each region (dot) is coloured according to the macro-region it belongs to. The UN M49 geoscheme²⁷ was used to define macroregions (south: Croatia, Cyprus, Greece, Italy, Malta, Portugal, Slovenia, and Spain; west: Austria, Belgium, France, Germany, Luxembourg, the Netherlands, and Switzerland; north: Denmark, Estonia, Finland, Ireland, Latvia, Lithuania, Norway, Sweden, and the UK; east: Bulgaria, Czechia, Hungary, Poland, Romania, and Slovakia). A visual overview of the country distribution is included in the appendix (p 11). Regression lines denote a positive relationship between cold-related and heat-related mortality in most macroregions.

case 3, future climate under different warming levels combined with future population exposure.

The combined effect of climate and demographic changes on future mortality was obtained as the difference between case 3 and case 1. The effect of demographic changes on future temperature excess mortality was isolated by calculating the difference in excess mortality between case 2 and case 1, while the contribution of climate corresponds to the residual change not explained by demographic dynamics.

All data were publicly available and de-identified, hence no ethical approval was required.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The median standardised cold and heat death rates per 100 000 people for all the 1368 NUTS 3 regions considered in the analysis (1991–2020) are shown in figure 1. Substantial spatial heterogeneity in cold-related mortality was observed across and within European countries, with rates ranging from 25 in a region in the Netherlands to 300 deaths in a region in Bulgaria per 100 000 people (appendix p 12). The lowest number of cold-related deaths were observed in regions of central Europe and

some parts of southern Europe. Higher values were mainly observed in eastern Europe and the Baltic states. The spatial variability is further emphasised by the presence of a distinct gradient from west to east (appendix p 12), with higher rates observed in western and in eastern areas (at a ratio of 2.5:1), and lower rates observed in central Europe.

Substantial spatial heterogeneity in heat-related mortality was also observed, with standardised rates ranging from 0.6 in a region in Ireland to 47 deaths in a region in Croatia per 100 000 people (appendix p 12), representing a notably smaller magnitude compared with cold-related mortality. A marked increase in heat-related deaths was observed from north to southern regions (appendix pp 12–13), with deaths 6 times more frequent in the south than in the north, indicating that heat-related mortality risk is predominantly driven by more intense heat in the south mainly during summer, while for cold-related deaths, the variability is only partly explained by more intensely cold winters. Heat-related mortality in regions of the British Isles and Scandinavian countries was low (0.6–5.0 deaths per 100 000 people), whereas the highest heat risk values (30–47 deaths per 100 000 people) were observed in Croatia and the southernmost areas.

Across Europe, for the 1991–2020 period, 407 538 deaths per year (empirical 95% CI 402 373–411 231) were attributable to hot and cold temperatures. Approximately 363 809 deaths (95% empirical CI 362 493–365 310) per year are attributable to cold (table). 43 729 deaths (empirical 95% CI 39 880–45 921) were attributed to hot temperatures. In these climate conditions, cold-related mortality significantly outnumbers heat-related mortality, with an overall median ratio of cold-related to heat-related deaths across Europe of approximately 8.3:1 (appendix p 6), with substantial regional disparities, ranging from 3.3:1 in Slovenia to 132.5:1 in Ireland. However, according to the coefficient of variation ([CV]; calculated by dividing the mean by the SD), the distribution of heat-related deaths is 20% more variable than that of cold-related deaths ($CV_{\text{cold}}=0.49$, $CV_{\text{heat}}=0.64$). Both the distributions of heat and cold-related death rates were largely positively skewed (1.19 for cold, 1.28 for heat), indicating an uneven effect of heat and cold across regions.

Joint analysis of cold-related and heat-related mortality risks highlighted regional patterns at the aggregated geographical level (figure 1). Northern regions were characterised by low heat risk and moderate-to-high cold risk. Similarly, in southern regions mortality attributed to heat was high whereas mortality attributed to cold was relatively low, although the heat to cold mortality ratio was higher than its inverse in northern regions, suggesting that the south is proportionally more affected by cold-related mortality than the north is by heat-related mortality. Western regions were characterised by moderately low values of both risks while the risk of cold-related and heat-related deaths was high in eastern

Heat-related deaths

Cold-related deaths

	Present conditions (1991–2020)	1.5°C increase	2°C increase	3°C increase	4°C increase	Present conditions (1991–2020)	1.5°C increase	2°C increase	3°C increase	4°C increase
Austria	3742 (3729–3757)	5018 (4876–5151)	4795 (4681–4950)	4329 (4248–4415)	3846 (3654–3988)	636 (510–701)	1081 (662–1360)	1352 (989–1963)	2148 (1596–2478)	3454 (2540–4043)
Belgium	4736 (4701–4784)	6207 (6020–6285)	5815 (5594–6175)	5204 (5018–5431)	4553 (4280–4830)	655 (572–731)	915 (648–1181)	1194 (740–1572)	1986 (1144–2473)	3092 (1775–3873)
Bulgaria	9977 (9943–10003)	5631 (5488–5874)	5426 (5274–5594)	5034 (4827–5109)	4567 (4248–4715)	1033 (951–1105)	859 (652–988)	1083 (943–1318)	1766 (1516–2180)	2944 (2669–3453)
Croatia	3922 (3916–3932)	2609 (2556–2703)	2500 (2402–2546)	2230 (2157–2300)	1948 (1872–2071)	1068 (1013–1105)	908 (805–1047)	1112 (909–1331)	1559 (1449–1722)	2285 (2114–2579)
Cyprus	522 (520–525)	864 (832–892)	807 (770–848)	697 (663–714)	593 (565–625)	82 (77–87)	193 (170–212)	254 (211–281)	423 (371–471)	640 (555–741)
Czechia	9021 (9003–9049)	8943 (8708–9234)	8567 (8316–8814)	7832 (7629–7996)	7016 (6692–7197)	700 (592–773)	930 (599–1244)	1187 (771–1705)	1923 (1284–2330)	2954 (2008–3393)
Denmark	4800 (4771–4849)	5730 (5588–5883)	5446 (5217–5630)	4940 (4816–5141)	4317 (4242–4622)	149 (134–177)	301 (190–477)	388 (237–632)	680 (472–1205)	1152 (749–2170)
Estonia	1349 (1342–1354)	1183 (1162–1226)	1138 (1104–1170)	1048 (1029–1078)	954 (922–984)	53 (48–57)	70 (56–107)	87 (68–139)	130 (101–236)	201 (149–374)
Finland	4833 (4803–4850)	5453 (5385–5641)	5268 (5114–5350)	4841 (4785–5007)	4466 (4365–4605)	142 (127–174)	266 (212–430)	349 (265–485)	573 (464–777)	948 (671–1369)
France	31316 (31115–31455)	42600 (41500–43221)	40284 (38964–41942)	36018 (35109–37034)	31946 (30046–32810)	3061 (2627–3458)	5424 (4209–6471)	7366 (4942–9851)	13564 (9439–16800)	23382 (14458–28218)
Germany	36863 (36649–37188)	37727 (36594–38493)	35642 (34524–37138)	31750 (31027–32702)	27910 (26306–28925)	6909 (6110–7646)	7894 (5467–10887)	10156 (6484–13398)	16913 (10546–19718)	26032 (15665–30098)
Greece	9404 (9360–9453)	8353 (8021–8699)	7884 (7551–8230)	6961 (6597–7120)	5890 (5470–6343)	1730 (1669–1837)	2203 (1864–2493)	2928 (2589–3261)	4767 (4177–5481)	8032 (6625–8746)
Hungary	11278 (11259–11300)	9567 (9429–9932)	9281 (8972–9434)	8502 (8306–8713)	7771 (7361–8022)	1102 (960–1194)	1243 (946–1499)	1438 (1099–1956)	2155 (1806–2242)	3251 (2788–3629)
Ireland	3974 (3961–3999)	9032 (8723–9230)	8648 (8360–9163)	7696 (7499–8470)	6817 (6491–7611)	30 (21–42)	134 (81–176)	210 (121–298)	563 (269–732)	918 (472–1413)
Italy	41340 (41225–41447)	40418 (39247–41153)	38075 (37139–39216)	33522 (32696–34268)	29192 (28119–29851)	10433 (9690–10763)	14081 (12083–16563)	18255 (14275–21895)	28285 (23951–32996)	45683 (36273–51728)
Latvia	2749 (2737–2759)	1314 (1294–1357)	1272 (1235–1302)	1182 (1167–1212)	1091 (1064–1118)	186 (181–199)	111 (96–147)	131 (111–163)	170 (164–208)	233 (211–294)
Lithuania	3949 (3929–3961)	2053 (2009–2118)	1986 (1926–2041)	1852 (1830–1906)	1713 (1658–1757)	264 (254–278)	176 (137–228)	199 (170–253)	261 (238–321)	357 (330–439)
Luxembourg	188 (187–190)	410 (401–414)	389 (374–405)	352 (344–361)	312 (298–323)	34 (27–38)	76 (49–100)	102 (67–140)	179 (114–225)	304 (181–367)
Malta	315 (314–317)	651 (614–663)	612 (577–632)	523 (501–536)	440 (415–463)	78 (73–82)	258 (208–327)	361 (273–454)	604 (513–849)	1050 (858–1351)
Netherlands	5487 (5421–5578)	7955 (7707–8218)	7397 (7048–8040)	6551 (6254–6872)	5474 (5222–5899)	1054 (947–1150)	1231 (909–1704)	1606 (1037–2163)	2800 (1593–3317)	4505 (2443–5013)
Norway	4118 (4091–4134)	7351 (7197–7493)	7079 (6809–7232)	6544 (6311–6743)	6072 (5758–6183)	94 (75–119)	269 (175–430)	328 (200–617)	682 (467–1115)	1139 (800–1998)
Poland	33308 (33211–33451)	30438 (29600–31456)	29250 (28108–29969)	26697 (26331–27664)	24149 (23044–24704)	3043 (2680–3251)	3349 (2527–4546)	4108 (2974–5619)	6039 (4708–7174)	8765 (6794–10458)
Portugal	7345 (7298–7394)	6029 (5873–6207)	5615 (5496–5842)	4682 (4520–4912)	3822 (3661–4002)	1008 (851–1061)	1038 (885–1285)	1362 (1078–1628)	2284 (2027–2486)	3448 (2961–4419)

(Table continues on next page)

	Cold-related deaths					Heat-related deaths				
	Present conditions (1991–2020)	1.5°C increase	2°C increase	3°C increase	4°C increase	Present conditions (1991–2020)	1.5°C increase	2°C increase	3°C increase	4°C increase
<i>(Continued from previous page)</i>										
Romania	26039 (25987–26103)	17428 (17053–18189)	16868 (16329–17307)	15667 (15273–16001)	14763 (13804–15143)	2574 (2373–2748)	2370 (1869–2891)	3031 (2403–3803)	4368 (4036–4909)	6926 (6260–7597)
Slovakia	4609 (4603–4623)	5129 (5018–5326)	4931 (4747–5049)	4472 (4358–4648)	4038 (3781–4205)	466 (405–512)	688 (513–876)	807 (621–1161)	1267 (1025–1396)	1918 (1584–2089)
Slovenia	1088 (1083–1090)	1161 (1131–1185)	1106 (1076–1135)	988 (964–1015)	868 (834–919)	332 (308–346)	428 (355–516)	518 (407–653)	732 (611–863)	1119 (891–1264)
Spain	22508 (22340–22646)	28705 (28301–29315)	26801 (26466–27934)	23272 (22614–23911)	19603 (19070–20373)	4414 (4172–4573)	7501 (6819–8937)	10635 (9643–12890)	20194 (18129–24401)	35928 (29213–40987)
Sweden	7803 (7761–7834)	11942 (11752–12256)	11397 (11085–11755)	10398 (10213–10755)	9427 (9252–9749)	240 (214–285)	638 (403–955)	824 (497–1209)	1316 (1061–2401)	2474 (1677–3650)
Switzerland	3052 (3024–3068)	5603 (5432–5670)	5322 (5141–5517)	4774 (4711–4954)	4229 (4017–4433)	583 (458–668)	1274 (797–1651)	1655 (1142–2331)	2907 (2197–3803)	5148 (3281–6500)
UK	64195 (63850–64452)	75781 (73397–76995)	72356 (69900–75917)	64952 (64088–69495)	57894 (55824–62940)	1258 (1093–1613)	2383 (1669–3244)	3378 (1886–4540)	7931 (4274–8833)	11755 (8166–16928)
EU-27	292399 (291554–293664)	302676 (297330–308136)	288273 (279530–295233)	256777 (251579–262360)	226907 (218719–232127)	41692 (38179–43914)	53916 (44554–66086)	70552 (55782–87637)	117249 (92575–135786)	191407 (147604–215008)
Europe	363809 (362493–365310)	391331 (383414–397531)	372857 (362140–383899)	333703 (326202–343454)	296458 (285506–305573)	43729 (39880–45921)	58057 (47498–70575)	76277 (59263–94882)	128809 (100283–148453)	207452 (156149–234455)

Data are median deaths (empirical 95% CI). Median deaths were obtained as the 50th percentile of the death distributions from the 11 climate models and two emission scenarios considered. Empirical 95% CIs were obtained as the 5th and 95th percentiles of the death distribution. We used the 2020 EUROPOP2019 population for the 1991–2020 scenario and sociodemographic estimates for year 2100 for the respective warming scenarios. EU-27=all 27 EU Member States.

Table: Projected median cold-related and heat-related deaths in Europe under present climate conditions (1991–2020), equivalent to global warming of 1°C, and under four different warming scenarios

regions. The contribution of socioeconomic characteristics is further reinforced by a positive correlation between regional GDP per capita and mortality risks (appendix p 15).

Projections indicate a shifting landscape of temperature-related deaths in Europe, where the median ratio of cold-related to heat-related deaths is projected to decrease substantially by the end of the century, from 8·3:1 (1991–2020) to a range between 6·7:1 (1·5°C increase scenario) and 1·4:1 (4°C increase scenario; appendix p 6). The strong decline of this ratio with increasing global warming is attributed to the gradual decline of cold-related mortality and the surge in heat-related deaths as more warming unfolds. This behaviour is largely driven by the increase of heat-related deaths, especially above the +2°C temperature threshold. The number of deaths will be highest among people aged 85 years and older (figure 2). This age group, in addition to having greater vulnerability to extreme temperatures compared with other groups, will also increase in size substantially by 2100 due to the expected rise in life expectancy. The overall net effect on mortality (increase in heat-related deaths minus reduction in cold-related deaths) is expected to remain highly positive for this age group, especially in warmer climate scenarios (appendix p 8).

Under the 3°C increase scenario, compared with the present (1991–2020), the range of regional cold-related mortality rates will narrow to 29–225 deaths per 100 000 people. Maximum values will reduce by more than 25%, but the mean rate in Europe will remain largely unaffected (85·4 deaths per 100 000 people under the 3°C increase scenario vs 87·8 deaths per 100 000 under the 1991–2020 scenario). Heat-related mortality rates are projected to increase markedly ranging from 2 to 117 deaths per 100 000 people, with a north–south gradient. The projected mean heat-related mortality rate in Europe would be 30 deaths per 100 000 people, representing a three-fold increase compared with the 1991–2020 scenario. Additionally, the distribution of heat-related deaths would be projected to skew further to the right (1·46), widening the gap in mortality impacts of heat across European regions. The standardised mortality rate attributable to heat and cold in Europe would increase from 98·7 deaths per 100 000 people (1991–2020) to 113·6 deaths in 2100, representing a 15% increase, corresponding to an additional 54974 deaths (empirical 95% CI 24112–80676) annually (table).

The direction of the projected change in cold-related mortality risk is mixed depending on the area considered (figure 3A). Under the 3°C increase scenario, standardised death rates due to cold would vary from 80 fewer to 80 additional deaths per 100 000 people compared with the 1991–2020 scenario. Moderate declines in deaths would be observed in regions in eastern Europe (eg, –62·1 in Yambol Province, Bulgaria), with mild reductions in some parts of Germany (eg, –5·4 in Hannover), France, Italy, and Portugal. Moderate to high increases are

projected in Poland, Czechia, Ireland, and some Scandinavian regions. In contrast, heat-related standardised rates would univocally increase in all European regions (figure 3B), with increases ranging from 0.5 to 92 additional deaths per 100 000 people in regions of Spain. For heat-related deaths, the pattern of the projected increases follows a north–south gradient, where southern European regions will have the highest increase in excess deaths attributable to heat.

The role of climate is projected to vary depending on the considered temperature risk, showing a negative contribution to cold-related deaths and positive contribution to heat-related deaths (appendix p 14). The size of contribution of warming differs by geographical location, with net negative effects (ie, lower mortality) observed in the north and intensified positive effects (ie, higher mortality) in southern latitudes. The contribution of demographic forces was strongly driven by the ageing component and was much more pronounced for cold-related mortality, since the relative risk of cold is notably higher than that of heat for all age groups, especially for older age groups. Overall, a small negative effect (2.4 fewer deaths per 100 000 people) on the cold-related death rate would be expected in Europe (appendix p 14), since the positive impact of ageing on the risk will be outweighed by the negative contribution of climate. Notable increases in cold-related death rates by country are expected in Ireland (39.5 additional deaths per 100 000 people), Slovakia (19.0 additional deaths per 100 000 people), and Norway (17.5 additional deaths per 100 000 people), all of which have a strong ageing population. Conversely, cold-related mortality rates would decrease in Bulgaria (39.2 fewer deaths per 100 000 people) and the Baltic countries (35.8 fewer deaths per 100 000 people in Latvia and 29.7 fewer deaths per 100 000 people in Lithuania), due to a stronger decline in total mortality rates that would compensate for the ageing component.

Heat-related death rates are projected to increase by 17.3 additional deaths per 100 000 people under the 3°C increase warming scenario in Europe. Heat-related mortality will increase in all countries with a clear gradient from north to south, with a larger increase in heat-related mortality towards southern regions, thus amplifying current heat-related risk patterns. In northern Europe, the increase would be around ten additional deaths per 100 000 people, while in the most southern regions this could be 3–4 times higher. Similar to the effects seen for cold-related mortality, the relatively stronger decline in total mortality in Bulgaria, Croatia, and Baltic countries is also projected to outweigh the effect of the ageing population on mortality, resulting in a net negative demographic effect of heat-related mortality (ie, fewer deaths). For other countries, ageing will result in a slight increase in heat-related mortality, but the total change is clearly dominated by global warming. Climate and demographic changes combined

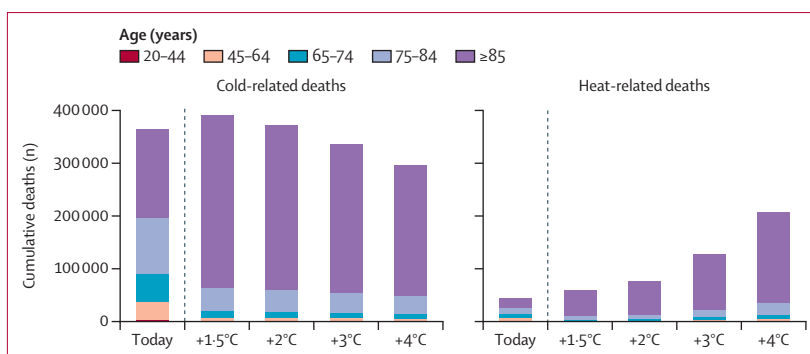


Figure 2: Age composition of temperature-related deaths in Europe by current and future warming scenarios. Cumulative number of deaths in Europe attributed to cold and heat by age group. Totals were obtained for current climate conditions (1991–2020) and four warming level scenarios. Totals for the 1991–2020 scenario are based on current (year 2020) population (EUROPOP2019) and data for the warming scenarios were obtained using year 2100 sociodemographic conditions.

are estimated to result in an additional 14.9 expected deaths per 100 000 people annually in Europe. However, this impact varies greatly between regions, ranging from a decrease of 29 deaths in Latvia to an increase of 95 deaths in Malta.

We identified areas of future heightened risk of heat-related mortality (termed hotspots) where marginally greater susceptibility (ageing), greater hazard increase (warming), or a combination of the two are expected to result in a larger increase in mortality risk by 2050. These hotspots are primarily concentrated in southern latitudes, particularly in regions of Spain, Italy, and Greece, but also extend to more northern areas, significantly impacting a substantial part of France (figure 4). The most eastern regions will be affected by an intensification of warming, but total death risk attributed to heat will be mitigated mainly by a strong decline in total mortality in these areas. In northern Europe, mean heat during summer will increase but not enough to cause additional deaths. However, the expected ageing of the population will make this area more susceptible to extreme heat episodes (figure 4).

Discussion

The risk patterns of cold-related and heat-related mortality in Europe are and will continue to remain largely heterogeneous, with marked differences between and within countries. In this study, we identified regional disparities in present risks, with risk of cold-related deaths 2.5 times higher in eastern regions than western regions and risk of heat-related deaths six times higher in southern regions than northern regions. Regional disparities were predicted to increase with warming, especially for heat-related mortality, with 9.3 times more deaths predicted in the south than in the north by 2100.

We identified clear risk discontinuities along country borders and the presence of regional clusters with a positive correlation between heat and cold mortality risks. This suggests the existence of local drivers beyond

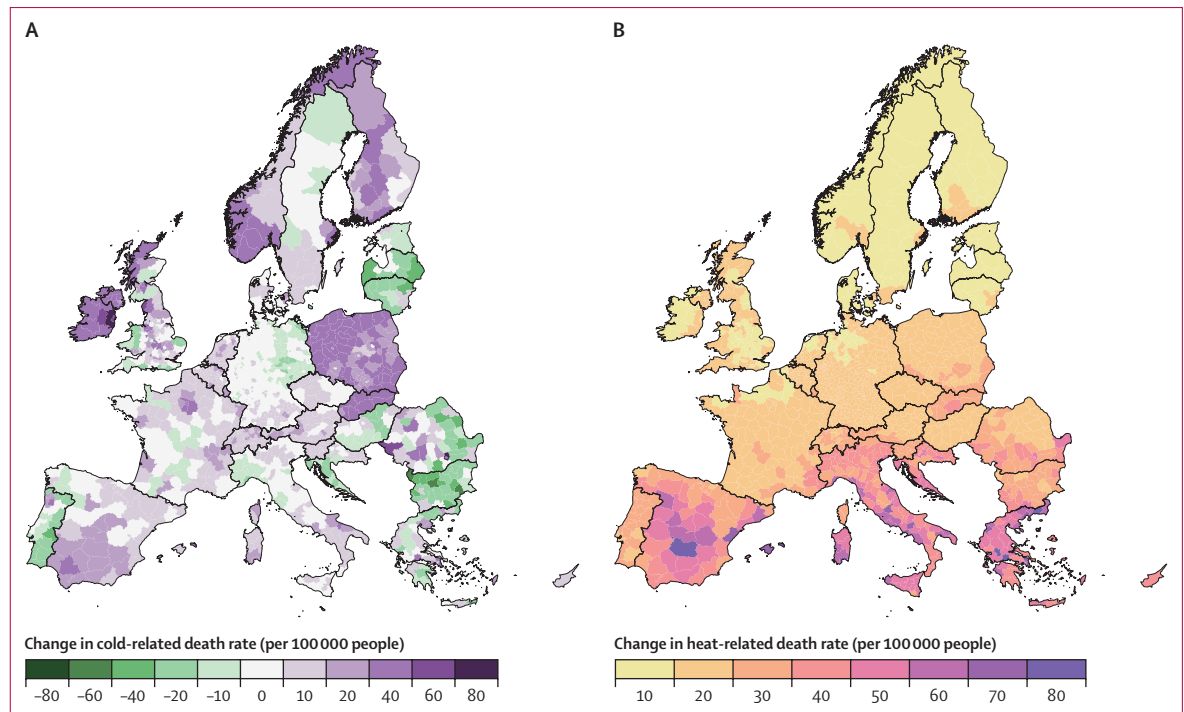


Figure 3: Projected changes in the death rate in Europe and its determinant factors by 2100

Expected change in the regional cold-related (A) and heat-related (B) standardised death rates by 2100 (for a 3°C increase in global warming scenario and projected population in 2100).

climate and individual characteristics that explain the variability of mortality attributed to temperatures in these areas. This hypothesis is further reinforced by the positive association between mortality risks and regional income (a proxy for these risk-moderating drivers), particularly evident in the case of cold mortality. A careful consideration of policy-modifiable factors, such as the quality of health infrastructure, the presence of preparedness plans,²³ the quality of insulation of buildings,²⁴ or the existence of physiological adaptation pathways¹² is crucial for effective public health planning and climate adaptation strategies aiming to moderate the effect of temperature on mortality.

Our results suggest that climate change could pose unprecedented challenges to public health systems, especially during periods of extreme heat. Projections for the end of this century indicated a rise in heat-related mortality across all regions of Europe. This increase was projected to be more pronounced as warming intensifies, particularly in a north to south direction across Europe. The evolution of cold-related mortality suggests a more complex interplay between the effect of warming and demographic shifts, which can push cold mortality risk downward or upward (eg, -20·5 expected deaths in Croatia, benefiting from lower overall mortality rates, compared with +39·5 deaths in Ireland, disadvantaged by a marked ageing of its population). The total effect for each region will depend on which of the forces dominates. For a 3°C increase in global warming scenario,

corresponding with current climate pledges in place,¹⁴ a slight change in cold-related mortality is expected for Europe, whereas heat-related deaths will increase more than proportionally, causing the cold-related to heat-related death ratio to decrease from 8·3:1 (1991–2020 scenario) to 2·6:1 in 2100. The marked increase in heat-related deaths highlights the cost of delaying climate action. Deviations from the climate target of an increase of 2°C would result in an additional 13 378 deaths annually (under the 3°C increase scenario), and 54 476 deaths annually (under the 4°C increase scenario) in 2100, indicating that the cost of inaction grows exponentially if climate targets are not met. By 2100, based on our modelling, heat-related deaths in Europe could increase to more than 234 455 deaths annually in the worst scenario, compared with around 43 729 deaths for the current scenario (1991–2020), potentially shifting the mortality peak from cold to warm seasons in certain regions.²⁵

There are two main factors driving these shifts: climate and demographic changes. Climatic drivers relevant to this impact assessment include the generalised increase in average temperatures, coupled with the proliferation of longer, more intense, and more frequent extreme heat episodes.²⁶ Demographic shifts in Europe are predicted to be characterised by three processes: (1) an overall mild decrease (about -5%) in the total European population by the end of the century, subject to strong spatial variability; (2) a general and sustained population ageing process affecting all countries and regions, with the European

share of the population aged 85 years and older increasing from 2.9% (1991–2020) to 9.3% in 2100; and (3) a projected increase in life expectancy, indicated by a decrease in the total mortality rate across all age groups. Ageing and warming will be generalised and will extensively affect all the studied regions. However, these effects will be particularly pronounced in the identified hotspots, which can serve as focal points for targeted interventions and actionable adaptive measures. Other factors, such as the evolution of socioeconomic developments or other secondary consequences of climate change on demography—such as the effects of net migration—could influence total temperature-related deaths. Consequently, it should be noted that the projections presented in this study should be interpreted as conditional on current adaptation policies and socioeconomic characteristics.

Previous studies have found comparable estimates with regard to projected heat-related mortality in the UK,⁸ ratios of cold-related to heat-related deaths in Germany,²⁷ number of heat-related deaths in 2022 in Europe,²⁸ and number of cold-related deaths between 2009 and 2017 in Switzerland.⁷ Several studies found differing baseline values, such as one study using data from 2022 in 35 European countries³, heat-related deaths in 2009–17 in Switzerland,⁷ and heat-related deaths in Spain.²⁹ However, these differences could be potentially explained by the sample period considered, particularly the inclusion or exclusion of very warm years such as 2003 or 2022–23, representative of 1.5–2°C warming.^{30,31} A detailed comparison of findings with the existing literature is provided in the appendix (p 4).

Our analyses have several limitations, that need to be considered in the interpretation. First, the results presented are based on observations from a sample of the urban population living in medium to large cities. Consequently, not all regions were adequately sampled (particularly in eastern countries), and results do not cover rural populations. Urban populations typically face higher levels of temperature stress, particularly from heat.³² The presence of the urban heat island effect in cities, more evident during the night,³³ can exacerbate the impacts of heat on health. Moreover, densely populated urban areas are particularly susceptible to heatwaves, which are increasingly frequent.³⁴ Considering that the risk profiles of rural populations are not affected by these risk-amplifying factors, our total estimates might be slightly overestimated. Second, estimates of future risk did not consider possible acclimatisation³⁵ to warmer summers and the implementation of adaptation measures that can lead to the moderation of total risk. Third, we applied a double extrapolation method (cities to regions and regions to missing data regions), which propagates estimation uncertainty. Fourth, the effect of temperature on infants, a highly vulnerable population group,³⁶ could not be investigated due to too small counts of deaths in that group to include them adequately in this type of data

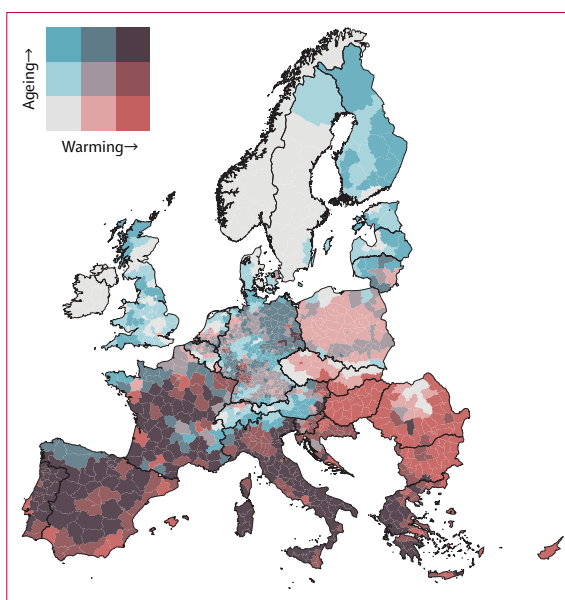


Figure 4: Projected heat-related death hotspots in Europe by 2050

This bivariate map shows the joint effect of ageing and global warming determining heat-related death risk projected for mid-century (equivalent to a +2°C world and representing a target for medium-term health policies). It combines the expected change in the average level of regional summer temperatures with the projected share of population older than 85 years (the age group showing a higher relative mortality risk) by the year 2050. A version of this map for each of the two drivers is in the appendix (p 15).

analysis. Similarly, our results do not account for gender or ethnicity. Future research should thoroughly consider of all these factors to improve precision of estimates of present and future temperature-driven mortality risk.

Finally, in a context of enhanced and greater climate policy ambition,³⁷ human health considerations, with a focus on the most susceptible population groups, should be streamlined into all relevant policies and adaptation measures. For example, spatial planning and building standards are key adaptation policy levers to reduce heat-related health risks.³⁸ Additional efforts should be focused on regions with high unemployment, poverty, structural economic changes, emigration, and ageing populations, since they have a lower capacity to adapt to the impacts of climate change while simultaneously being hotspots where heat-related death will materialise more intensely in the coming years.

Contributors

DG-L, J-CC, and LF conceptualised and designed the study. PM, MNM, and AG designed and ran the epidemiological, city-level time series exercise. LF and CM performed the contribution analysis. DG-L performed the main analysis and created the graphical output. All the authors contributed to the discussion of results. DG-L, J-CC, and LF wrote and edited the manuscript with contributions from all the coauthors. All authors had access to the data, have read and approved the final manuscript, and accept responsibility for the decision to submit for publication. DG-L, AG, and LF accessed and verified the data.

Declaration of interests

DG-L, LF, and J-CC are staff members of the European Commission. The authors alone are responsible for the views expressed here and these

do not necessarily represent the decisions or the stated policy of the European Commission. All other authors declare no competing interests.

Data sharing

The exposure–response functions used in this analysis are publicly available in a Zenodo repository (<https://doi.org/10.5281/zenodo.7672108>).

Acknowledgments

AG, PM, and MNM received funding from the European Commission under the Call for Tenders (JRC/SVQ/2020/MVP/1654). MNM was supported by the European Commission (H2020-MSCA-IF-2020; REA grant agreement 101022870). We acknowledge the use of 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>).

References

- Romanello M, Napoli CD, Green C, et al. The 2023 report of the Lancet Countdown on health and climate change: the imperative for a health-centred response in a world facing irreversible harms. *Lancet* 2023; **402**: 2346–94.
- Vicedo-Cabrera AM, Scovronick N, Sera F, et al. The burden of heat-related mortality attributable to recent human-induced climate change. *Nat Clim Chang* 2021; **11**: 492–500.
- Ballester J, Quijal-Zamorano M, Méndez Turrubiates RF, et al. Heat-related mortality in Europe during the summer of 2022. *Nat Med* 2023; **29**: 1857–66.
- Carleton T, Jina A, Delgado M, et al. Valuing the global mortality consequences of climate change accounting for adaptation costs and benefits. *Q J Econ* 2022; **137**: 2037–105.
- van Daalen KR, Tonne C, Semenza JC, et al. The 2024 Europe report of the Lancet Countdown on health and climate change: unprecedented warming demands unprecedented action. *Lancet Public Health* 2024; **9**: e495–522.
- Khomenko S, Cirach M, Pereira-Barboza E, et al. Premature mortality due to air pollution in European cities: a health impact assessment. *Lancet Planet Health* 2021; **5**: e121–34.
- de Schrijver E, Sivaraj S, Raible CC, Franco OH, Chen K, Vicedo-Cabrera AM. Nationwide projections of heat- and cold-related mortality impacts under various climate change and population development scenarios in Switzerland. *Environ Res Lett* 2023; **18**: 094010.
- Jenkins K, Kennedy-Asser A, Andrews O, Lo YTE. Updated projections of UK heat-related mortality using policy-relevant global warming levels and socio-economic scenarios. *Environ Res Lett* 2022; **17**: 114036.
- Gasparrini A, Guo Y, Sera F, et al. Projections of temperature-related excess mortality under climate change scenarios. *Lancet Planet Health* 2017; **1**: e360–67.
- Orru H, Åström DO. Increases in external cause mortality due to high and low temperatures: evidence from northeastern Europe. *Int J Biometeorol* 2017; **61**: 963–66.
- Son J-Y, Liu JC, Bell ML. Temperature-related mortality: a systematic review and investigation of effect modifiers. *Environ Res Lett* 2019; **14**: 073004.
- Rai M, Bretnier S, Wolf K, Peters A, Schneider A, Chen K. Future temperature-related mortality considering physiological and socioeconomic adaptation: a modelling framework. *Lancet Planet Health* 2022; **6**: e784–92.
- Masselot P, Mistry M, Vanoli J, et al. Excess mortality attributed to heat and cold: a health impact assessment study in 854 cities in Europe. *Lancet Planet Health* 2023; **7**: e271–81.
- UN Environment Programme. Emissions gap report 2023: broken record—temperatures hit new highs, yet world fails to cut emissions (again). United Nations Environment Programme, 2023. <https://doi.org/10.59117/20.500.11822/43922> (accessed March 15, 2024).
- Eurostat. Urban Audit. 2021. <https://ec.europa.eu/eurostat/web/gisco/geodata/statistical-units/urban-audit> (accessed Dec 13, 2021).
- Jacob D, Petersen J, Eggert B, et al. EURO-CORDEX: new high-resolution climate change projections for European impact research. *Reg Environ Change* 2014; **14**: 563–78.
- Dosio A, Fischer EM. Will half a degree make a difference? Robust projections of indices of mean and extreme climate in Europe under 1.5°C, 2°C, and 3°C global warming. *Geophys Res Lett* 2018; **45**: 935–44.
- Cornes R, van der Schrier G, van den Besselaar EJM, Jones PD. 2018: an ensemble version of the E-OBS temperature and precipitation datasets. *J Geophys Res Atmos* 2018; **123**: 9391–409.
- Intergovernmental Panel on Climate Change. Climate change 2021—the physical science basis: Working Group I Contribution to the Sixth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge University Press, 2023. <https://doi.org/10.1017/9781009157896> (accessed March 18, 2024).
- Eurostat. NUTS - Nomenclature of Territorial Units for Statistics. History. <https://ec.europa.eu/eurostat/web/nuts/history> (accessed Dec 10, 2021).
- Vousdoukas MI, Mentaschi L, Voukouvalas E, Bianchi A, Dottori F, Feyen L. Climatic and socioeconomic controls of future coastal flood risk in Europe. *Nat Clim Chang* 2018; **8**: 776–80.
- UN. Methodology. Standard country or area codes for statistical use (M49). <https://unstats.un.org/unsd/methodology/m49/> (accessed Dec 10, 2023).
- Errett NA, Hartwell C, Randazza JM, et al. Survey of extreme heat public health preparedness plans and response activities in the most populous jurisdictions in the United States. *BMC Public Health* 2023; **23**: 811.
- Wang C, Wang J, Norbäck D. A systematic review of associations between energy use, fuel poverty, energy efficiency improvements and health. *Int J Environ Res Public Health* 2022; **19**: 7393.
- Madaniyazi L, Armstrong B, Tobias A, et al. Seasonality of mortality under climate change: a multicountry projection study. *Lancet Planet Health* 2024; **8**: e86–94.
- Fischer EM, Schär C. Consistent geographical patterns of changes in high-impact European heatwaves. *Nat Geosci* 2010; **3**: 398–403.
- Huber V, Krummenauer L, Peña-Ortiz C, et al. Temperature-related excess mortality in German cities at 2°C and higher degrees of global warming. *Environ Res* 2020; **186**: 109447.
- Vicedo-Cabrera AM, de Schrijver E, Schumacher DL, Ragetti MS, Fischer EM, Seneviratne SI. The footprint of human-induced climate change on heat-related deaths in the summer of 2022 in Switzerland. *Environ Res Lett* 2023; **18**: 074037.
- Tobias A, Íñiguez C, Royé D. From research to the development of an innovative application for monitoring heat-related mortality in Spain. *Environ Health* 2023; **1**: 416–19.
- World Meteorological Organization. WMO update: 50:50 chance of global temperature temporarily reaching 1.5°C threshold in next five years. World Meteorological Organization, 2022. <https://wmo.int/news/media-centre/wmo-update-5050-chance-of-global-temperature-temporarily-reaching-15degc-threshold-next-five-years> (accessed March 13, 2024).
- Hermanson L, Smith D, Seabrook M, et al. WMO global annual to decadal climate update: a prediction for 2021–25. *Bull Am Meteorol Soc* 2022; **103**: E1117–29.
- de Schrijver E, Royé D, Gasparrini A, Franco OH, Vicedo-Cabrera AM. Exploring vulnerability to heat and cold across urban and rural populations in Switzerland. *Environ Res Health* 2023; **1**: 025003.
- Mentaschi L, Duveiller G, Zulia G, et al. Global long-term mapping of surface temperature shows intensified intra-city urban heat island extremes. *Glob Environ Change* 2022; **72**: 102441.
- Vautard R, Cattiaux J, Happé T, et al. Heat extremes in Western Europe increasing faster than simulated due to atmospheric circulation trends. *Nat Commun* 2023; **14**: 6803.
- Shindell D, Zhang Y, Scott M, Ru M, Stark K, Ebi KL. The effects of heat exposure on human mortality throughout the United States. *GeoHealth* 2020; **4**: e2019GH000234.
- Schinasi LH, Bloch JR, Melly S, Zhao Y, Moore K, De Roos AJ. High ambient temperature and infant mortality in Philadelphia, Pennsylvania: a case-crossover study. *Am J Public Health* 2020; **110**: 189–95.
- European Commission. Securing our future: Europe's 2040 climate target and path to climate neutrality by 2050 building a sustainable, just and prosperous society. 2024. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM:2024:63:FIN> (accessed March 20, 2024).
- lungman T, Cirach M, Marando F, et al. Cooling cities through urban green infrastructure: a health impact assessment of European cities. *Lancet* 2023; **401**: 577–89.