Aus dem
Helmholtz-Zentrum München
Institut für Epidemiologie (EPI)

Exposure to Air Temperature and Air Pollution and Cardio-Respiratory Health

Dissertation
zum Erwerb des Doctor of Philosophy (Ph.D.) an der Medizinischen Fakultät der Ludwig-Maximilians-Universität München

vorgelegt von
Masna Rai

aus
Okhaldhunga/Nepal

Jahr
2024

Mit Genehmigung der Medizinischen Fakultät der
Ludwig-Maximilians-Universität München

Erstes Gutachten:	Prof. Dr. Annette Peters
Zweites Gutachten:	Prof. Dr. Dennis Nowak
Drittes Gutachten:	Prof. Dr. Stefanie Heinze
Viertes Gutachten:	Prof. Dr. Thomas M. Schiele

Dekan: Prof. Dr. med. Thomas Gudermann

Tag der mündlichen Prüfung: 01.02.2024

मामु र पापाको लागि

To my mom and dad

Table of Contents

Abbreviations

CI	Confidence Interval
CMIP6	Coupled Model Intercomparison Project
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular Diseases
DALYs	Disability Adjusted Life-Years
DLNM	Distributed Lag Non-linear Model
eCI	Empirical Confidence Interval
ERF	Exposure Response Functions
EXHAUSTION	Exposure to heat and air pollution in Europe – cardiopulmonary impacts and benefits of mitigation and adaptation
GCM	Global Climate Models
GDP	Gross Domestic Product
ICD	International Classification of Diseases
I.e.	Id est (*that is*)
IPCC	Intergovernmental Panel on Climate Change
ISIMIP3b	Inter-Sectoral Impact Model Intercomparison Project
MCC	Multi-City Multi-Country Collaborative Research Network
MI	Myocardial Infarction
MMT	Minimum Mortality Temperature
NCAR	National Centre for Atmospheric Research
NO_2	Nitrogen Dioxide
O_3	Ozone
PM	Particulate Matter
PM_{10}	Particulate Matter with a diameter of 10 µm
$PM_{2.5}$	Particulate Matter with a diameter of 2.5 µm or less
RCP	Representative Concentration Pathways
RD	Respiratory Diseases
RR	Relative Risk
SSP	Shared Socioeconomic Pathway

I. Introduction summary

1. General introduction

Climate change is today a global concern, to a greater extent from a health standpoint. With the changing climate, there are changes in weather patterns, rising frequency of natural calamities, and disrupted ecology; all adversely affecting our health. With climate change, there is a rise in the number of atypical weather phenomenon like heatwaves and extreme cold periods. Similarly, increased frequency of natural events like wildfires and altered distribution of vectors has been commonly observed [1]. Recurrence of these atypical phenomenon are expected to rise even sharply in the future [2, 3], whereby, heatwaves and extreme cold periods are noted as a major and constant health risk for many regions in the world [4]. With heat, the rate of chemical reaction in the atmosphere as well as pollutant transport is altered [5]. Recurring heatwaves escalate the emission of biogenic volatile organic compounds and accelerate the photochemical reactions forming ozone (O_3) and secondary organic aerosols, all leading to a co-occurring rise in pollutant concentrations [5-7].

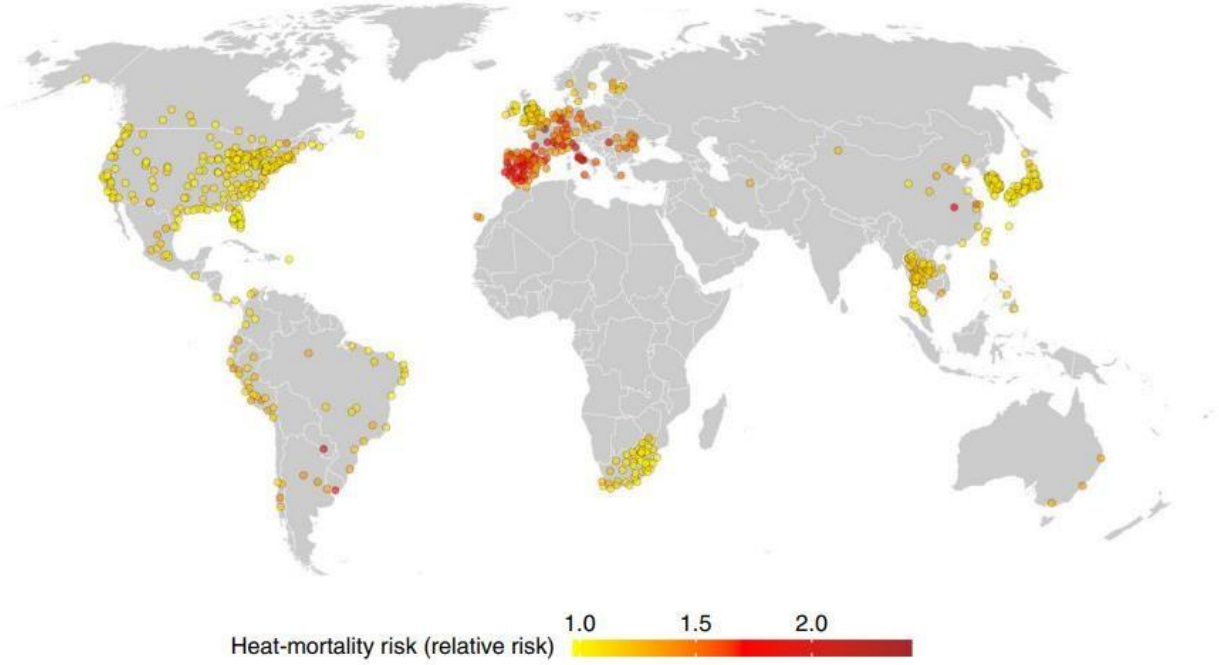

Figure 1: Heat-related total mortality in 732 locations around the world [8]. Reproduced with permission from Springer Nature on 20 Jan 2023.

Furthermore, recurring wildfires contribute to a rise in air pollution. To summarize, heatwaves, extreme cold periods, and atmospheric air pollutants are amongst the major climate threat for most regions in the world [4, 9].

As a consequence of climate change, an additional 125 million people were exposed to heatwaves between 2000 and 2016 [10]. According to a WHO report, heatwave alone was attributable to about 170 thousand global deaths during the years 1998-2017 [10]. Hotter temperature has been well-known to adversely affect health, even leading to fatality [11-13]. Research have linked atypical temperature to elevated chances of deaths due to diseases of the cardiovascular and respiratory systems [14-16]. Likewise, air pollution, amongst environmental exposures, is a leading cause of fatality. WHO 2023 report states that air pollution is associated with yearly seven million premature deaths [17]. These environmental hazards affect different organs and systems; however, the cardiovascular and respiratory systems are amongst those most affected by the changing climate. On the other hand, a recent report lists cardiovascular diseases (CVD) and respiratory diseases (RD) as the leading contributors of the global health burden [18].

Heatwave and air pollution have been observed to interact and result in amplified health effects [19-21]. Studies have found higher risk of temperature-associated fatality on days with an increased concentration of air pollutants like O_3 or particulate matter (PM) [19-21]. One of the many possible mechanisms of the effect amplification includes air pollution increasing the susceptivity of the population while being simultaneously exposed to atypical temperature [22, 23]. Results from a meta-analysis indicated that considering similar air pollution level, the risk for CVD-RD fatality was higher during hotter days in comparison to cooler days, with much elevated risk for RD fatality compared to CVD fatality [24]. In short, CVD-RD are amongst the most climate-triggered health outcomes, foreseen to rise even higher in the future because of climate change [25].

The biggest challenge of the present century is to build a climate resilient society [26]. In this regard, along with climate change alleviation programs, calculated and well-planned acclimation policies are crucial [26]. Developing acclimation plans is urgent, especially for countries like China, India, and Germany, ranking the highest in terms of heat-related fatality per year [27] and yet inadequately equipped for the forecasted health burden and challenges [28]. For this purpose, studies looking into the future and predicting the climate-associated consequences have been gaining importance as they provide a basis for planning acclimation policies [29]. However, since these studies are built on the current-day or baseline interrelation of a given climate risk and the associated health consequence [30, 31], a comprehensive investigation of the baseline interrelation is essential for reasonable estimation of the climate-associated health consequences [32, 33]. These

reasonable predictions would provide a strong basis to stakeholders and public health professionals to plan impactful acclimation policies.

Amongst the growing risk of the changing climate, acclimation programs are of prime importance to reduce the growing burden of CVD-RD hospitalizations and fatality. Planning of impactful acclimation programs are only possible with comprehensive evidence of the current-day interrelation of atmospheric temperature and CVD-RD, the variation of these interrelations in the course of time, interaction with air pollution, followed by accurate quantification of the burden of these two most climate-triggered health conditions in the future.

1.1. Exposure to temperature and cardiovascular-respiratory disease fatality

CVD-RD hospitalizations and deaths have been found to increase with atypical temperature conditions [14-16]. Existing studies associate suboptimal temperature to CVD fatality [34-36]. Although the interrelation of RD fatality and temperature have been scarcely investigated, similar results are observed [37]. However, most of the present studies on CVD fatality are focused only on the total CVD fatality [38], or a single subclass of CVD fatality [39] . In the context of studies exploring the interrelation of temperature and RD fatality, evidences are limited [37, 40], with a focus just on the heat-risk [40] or total RD fatality [37] . Thus, there exist gaps in evidence in the interrelation of suboptimal (both high and low) temperature and CVD-RD fatality. These interrelations have also not been explored for further subclasses of CVD-RD.

Several studies have found the temperature-fatality interrelations to vary with time [32, 41]. These studies found either reduction (acclimation) or elevation (susceptiveness) in the temperature-associated fatality risk with time, depending on the climatic condition of the area [32, 42] or disease outcome [41] under study. However, most of the studies investigating time trends in the temperature-associated fatality risk have only considered either all-cause [32] or only heat-associated [42] fatality. Thus, extensive research on time-associated changes in both high and low temperature-associated CVD-RD fatality risk is of prime importance. Furthermore, these interrelations are yet to be largely explored for further subclasses of fatality and across various demographic subgroups.

1.2. Exposure to temperature and air pollution and cardiovascular-respiratory disease fatality

Temperature as well as air pollution, both are seen to be adversely impacting human health. However, a probable interaction of these two high-risk environmental exposures have not been extensively studied [43]. Moving forward, such research is essential for real-life multi-exposure conditions.

Earlier studies have mostly considered air temperature and atmospheric air pollutants separately [15, 44]. Some other studies have investigated the effect of one of these exposures controlling for the other, i.e. estimating the pollution-adjusted temperature risk [15] and vice versa [44]. However, latter-day studies provide evidence of synergism of the two exposures, i.e. amplification of the health effect by one of the exposure in the presence of the other [45]. Such studies from various locations show a significant increase in the fatality risk for all-cause fatality as well as CVD-RD causes with much elevated risk during hotter months [44, 46] or hotter days [23, 24, 47], as compared to cooler months or days. Although studies on interaction exist, a large fraction of them focus on temperature altering the effect of air pollutants [24, 43, 47, 48], whereas studies on alteration of the temperature-associated risk by air pollution are still scarce [23, 49]. In addition, such studies either concentrate on all-cause fatality [49] or are limited to specific regions [23].

Thus, extensive investigation on the adverse effect of heat and its alteration by various categories of atmospheric air pollutants on climate-triggered outcomes is limited. Till date, such studies are sporadic and concentrate only on two air pollutants: PM_{10} and O_3 [23, 24, 43, 47-49]; alteration of the heat effect by other air pollutants are yet to be explored. This brings us to identify another research gap on the impact of heat on CVD-RD and its alteration by major air pollutants in the atmosphere. With the growing urgency of climate change, there is a need to assess temperature-pollution effect modification in regions with diverse climate, air quality, demography, and health-care settings.

1.3. Future prediction of temperature-associated fatality

In parallel to the current-day studies, studies looking into the future and predicting future climate-caused health consequences should be equally valued as they are the basis to impactful acclimation strategies [29]. Prediction studies have been expanding and predicting future temperature-associated fatality [50-53]. These studies have also helped us determine demographic subclasses that are most prone to climate risk.

The field of prediction research is built upon the evidence from the current-day interrelation of a given climate risk and the associated health outcome. Most prediction studies till date have considered the temperature-fatality interrelation to remain similar in the future [54], i.e. they consider the risk of fatality at that particular temperature to remain uniform and do not consider population acclimation in the future. This was noted when more studies investigating the time trends in temperature-associated fatality risk showed that this risk is not uniform but rather varies in the course of time [32, 41]. Populations of any given location might either present differing physiological acclimation or susceptiveness to temperature in the course of time [50]. Furthermore, much improved health care systems in the future may increase the capacity of the population to acclimatize to unfavorable climate [55]. This acclimation of population plays a crucial role in determining the future temperature-associated health consequences. However, despite playing a major role, future population acclimation has not been well integrated by existing studies.

To date, there exists no proposed scenarios for population acclimation in the future. Majority of the prediction studies do not integrate population acclimation [50, 51, 56], while those integrating acclimation, rather consider only heat-acclimation [57, 58]. Given that cold temperature would still persist in the future, despite the warming climate, it is evident that understanding the trends in cold-fatality relationship and its integration in studies predicting future climate-associated fatality is equally essential to produce accurate estimation [59]. Furthermore, future economic changes and its influence on population acclimation have gained attention only recently [60]. Considering all above-mentioned factors, there exists research gaps in terms of studies integrating both physiological acclimation and economic changes while quantifying the future temperature-associated fatality.

2. Objectives

Amongst the current global climate emergency, this cumulative thesis aims to address the yet to be investigated associations and discrepancies in available evidence in the current-day interrelation of temperature and CVD-RD fatality, the effects of interaction of temperature with air pollution, and the prediction of future temperature-associated CVD-RD fatality.

Specific objectives of this cumulative thesis are as follows:

i. To deeply investigate the impact of heat on CVD-RD fatality and alteration of the impact by major atmospheric air pollutants.
ii. To explore the time trends in the interrelation of temperature and fatality among subclasses of CVD-RD and among demographic subgroups.
iii. To systematically develop and propose a set of possible future acclimation conditions and methodology for predicting the future temperature-associated fatality under the developed acclimation conditions.

3. Outline of the publications

The following section provides an outline of the three publications included in this cumulative dissertation.

Publication 1: Rai M et al. and the MCC consortium. Heat-related cardiorespiratory mortality: effect modification by air pollution across 24 countries. Environment International. 2023 174:107825.

The first publication focuses on estimating the impact of heat on CVD-RD fatality and the alteration of the impact by four major atmospheric air pollutants: particulate matter with diameter ≤ 10 µm or less (PM_{10}), particulate matter with diameter ≤ 2.5 µm ($PM_{2.5}$), O_3, and nitrogen dioxide (NO_2), in 482 locations around the world. The investigation period extends up to 18 years. The publication reports an overall heat-caused fatality and the heat-caused fatality on days with varying levels of each of the air pollutant under investigation. The reporting is for each of the 482 locations separately, the pooled country-wise estimates and the pooled overall estimates.

Publication 2: Rai M, Breitner S, Zhang S, Huber V, Peters A. Temporal Variation in the Association between Temperature and Cause-Specific. Mortality in 15 German cities. Environmental Research. 2023. 174:107825.

The second publication examines the time trends in the interrelation of temperature and fatality among subclasses of CVD-RD and demographic subgroups. For this investigation, the study uses data from the 15 largest cities in Germany with a study period of 24 years. The subclasses of CVD-RD investigated by this research include ischemic heart disease (including myocardial infarction (MI) and chronic ischemic heart disease), cerebrovascular disease, heart failure, and Chronic Obstructive Pulmonary Disease (COPD). The interrelation was extensively explored among various age and sex groups.

Publication 3: **Rai M**, Breitner S, Wolf K, Peters A, Schneider A and Chen K. Future Temperature-related Mortality under Physiological Adaptation Scenarios and Socio-economic Adaptive Capacities: A Modelling Framework. Lancet Planetary Health. 2022. 6(10): e784-e792.

The third publication systematically develops and proposes a set of possible future acclimation conditions and corresponding methodology for predicting the future temperature-associated fatality under the developed acclimation conditions. The publication begins with exploring the current-day interrelation of temperature and fatality and closely studying the variation in heat- and cold-related fatality in the course of time. This evidence is then applied to systematically develop future possible acclimation conditions. This developed set of acclimation scenarios incorporates possible physiological as well as socio-economic acclimation in the future. The publication includes illustration of the methodological framework to project future all-cause and CVD fatality under a combination of all proposed acclimation conditions using an example-case dataset from five locations in southern Germany.

4. Outline of the methods

4.1. Study population and data sources

The datasets used for this cumulative thesis have been summarized in the following sections:

The multi-country dataset consisting of daily deaths with International Classification of Diseases (ICD) codes, temperature, and air pollution values was attained from the Multi-City Multi-Country (MCC) Collaborative Research Network database [63]. Furthermore, additional country-wise fatality and meteorological databases were used. The study period ranged from 2000 to 2018.

Daily death counts with ICD codes for the German cities, for the period 1993-2016, was provided by the Research Data Centre of the Federal States in Germany┼. Similarly, temperature and daily pollutant concentration data for Germany was provided by the German Weather Service* and the German Environment Agency†, respectively.

For illustration of the methodological framework of future prediction, an example-case dataset was applied. For baseline setting of the example-case, age-wise daily death counts with ICD codes for the period 1990-2006 for the southern German cities was attained from the Bavarian State Office for Statistics and Data Processing. Future temperature data was extracted from the Global Climate Models (GCMs), established for the sixth phase of the Coupled Model Intercomparison Project (CMIP6) [64]. These datasets account for bias and are with 0.5° × 0.5° spatial resolution. From these GCMs, temperature data for period 2083-2099 was derived for the locations in the example-case dataset. The future conditions considered were: Shared Socioeconomic Pathway (SSP)1-2.6 and SSP3-7.0. Future population data for the example-case locations under the corresponding population conditions were derived from spatial dataset from the National Centre for Atmospheric Research (NCAR). This spatial dataset was on 1 km × 1 km grid cell [65]. Additionally, existing extensive predictions on future death rate changes for different age groups [66] and causes of death [67] were incorporated.

┼ *Forschungsdatenzentrum der Statistischen Ämter des Bundes und der Länder*
** Deutscher Wetterdienst (DWD)*
† Umweltbundesamt (UBA)

4.2. Statistical analysis

In publication 1, the interaction between high summer temperature and air pollution, for each of the 482 locations, was analyzed by a non-parametric three-dimension dose-response model. This model predicted the outcome, i.e., fatality, based on the joint alteration of the two environmental exposures in the model, i.e. temperature and air pollution concentration. The derived estimates from the 482 cities were pooled according to countries and then also to derive an overall estimate with the application of multilevel meta-analytical method. This method of meta-analysis considers random effects among the nested groups of cities and countries.

Publication 2 utilizes time-series analysis segregated by different periods to explore changes in the interrelation of temperature and various subclasses of CVD-RD fatality. For each of the location and each of the subclasses of fatality, a quasi-Poisson regression, with Distributed Lag Nonlinear Model (DLNM), was applied. The model integrated calendar days, seasonal trends, and long-term trends. For each of the location, a dose-response curve, also termed as Exposure-Response Function (ERF), with temperature as exposure and fatality as outcome, was obtained. The analysis modelled the cumulative risk over a 14-day lag period in the derived ERF. Subsequently, the computed ERFs from different cities were pooled. Similar analysis was performed across various demographic stratums.

In publication 3, the analysis consisted of two phases: framework development and illustration of proposed methodology. For the framework development, evidence from baseline observation was applied. Initially, ERFs between temperature and fatality for the individual example-case study locations was derived with application of the methods similar to Publication 2, considering 21-day lag period. In the next step, the ERFs were extrapolated outside the temperature ranges measured during baseline. The extrapolated ERFs were used to calculate the relative risk (RR) at every value of temperature. A unique ERF was derived and applied for individual locations, considering population of any given area to behave uniquely to the same temperature exposure. The RR at temperature values above the Minimum Mortality Temperature (MMT) were classified as heat-accountable RR, and that below the MMT as cold-accountable RR. MMT is a term widely applied for the temperature value at which the least number of deaths are observed, also known as the most optimal temperature and can vary according to locations.

In parallel, a baseline time-stratified sub analysis to explore the changes in the temperature-accountable RR in the course of time, was performed separately. Results from this sub analysis were applied to define the extent of escalation or decline in the temperature-associated risk in the course of time. In addition to physiological changes, a range of possible future socio-economic

conditions, which directly impacts the ability of the population to adapt to any given weather condition, were derived, which were defined by changes in the Gross Domestic Product (GDP) per capita. A framework for future population acclimation based on combination of the derived physiological acclimation and susceptivity as well as socio-economic conditions were developed and proposed in the publication.

A methodology for prediction of future fatality and preventable cases under the set of proposed future acclimation conditions is developed by this research and illustrated in the publication. Under this methodology, heat- and cold-accountable fatality risks in the future were derived separately as a function of baseline heat- or cold-accountable RR, intercept of the respective exposure-risk regression, and log of future GDP values. Future heat- and cold-risks were derived separately for each study area and demographic subgroup, considering population of individual locations and each of age-groups to behave uniquely to the same temperature exposure. The methodology also accounts for the rate of changes in future population and fatality rate, all specific to the respective demographic subgroups. The estimate provided is termed as “adaptable fraction” and defined as the number of preventable fatalities under the respective combination of proposed future acclimation conditions.

5. Key findings

The first publication starts with providing a better understanding of the interrelationship between temperature, the major air pollutants, and CVD-RD fatality, across locations with varying climatic, geographical, and socio-economic conditions. Both the outcomes under investigation were found to increase with heat across all locations. The heat-associated risk of RD fatality was comparatively more prominent than of CVD fatality. The effect of heat was found to be escalating significantly by increased levels of the major air pollutants for both outcomes, with sharper increase in RD fatality risk. For instance, the overall result showed that on hotter days with high° levels of $PM_{2.5,}$ there were an additional 14.3 (14.1-14.5┼) RD fatalities per 100 heat-associated RD fatalities. This rate was found to be 11.3(11.2-11.3┼), and 7.7 (7.6-7.7┼) on days with medium° and low° levels of $PM_{2.5}$.

- **Key findings 1:** There is an increased risk of CVD-RD with hotter temperatures. This heat-associated risk is considerably escalated in conjunction with higher levels of air pollutants. Among the two outcomes, RD outcomes are comparatively more sensitive to these effects.

The second publication deeply investigates the changes in the interrelation of air temperature and various subclasses of CVD-RD deaths in the course of time. In the course of time, a persistent and significant elevation in the heat-associated risk of fatality was observed for most subclasses of CVD (like ischemic heart disease, cerebrovascular disease) and RD fatality. The heat-accountable RR for RD fatality increased from 1.4 (1.2-1.7┼) during 1993-2004 to 1.8 (1.6-2.0┼) during 2005-2016. Similarly, the cold-associated RR for CVD related deaths was found to escalate significantly in the course of time [from 0.9 (0.9-1.0┼) to 1.1 (1.0-1.1┼)]. Similar was the observation for cold-associated RR for RD deaths.

The results of the demographic subclass analyses showed an elevated risk of cold-attributable all-cause fatality for some of the demographic subgroups. Particularly, males and individuals of and between the age of 65 and 74 years were found most at risk. In the course of time, for females and elderly above the age of 75 years, a persistent increase in the risk of cold-attributable CVD deaths was observed. Similarly, the heat-associated risk of RD deaths escalated significantly in the course of time for both sex groups and the younger population of and below the age of 64 years.

┼95 % Confidence Interval [CI]
° low, medium, and high correspond to 5th, 50th, and 95th percentile, respectively, of the respective location-specific pollutant concentration.

- **Key findings 2:** For the cities included in the study, the risk of cold-associated risk of CVD-RD fatality escalated persistently and significantly over the course of time. Even for the younger population of and below the age of 64, usually considered less vulnerable than the elderly, heat-associated risk for RD fatality escalated significantly in the course of time. COPD, the perceived driver of heat-associated RD deaths, had a uniform heat-associated risk.

The third publication first explored the current-day interrelation of temperature and fatality and the changes in this interrelation in the course of time. Analysis of the historical dataset provided evidence for declining heat associated risk (physiological heat acclimation) and escalating cold associated (physiological cold susceptivity) in the course of time. The results of this analysis in the example-dataset showed heat-associated excess RR to reduce from 11% to 9%. Contrastingly, the cold-associated excess RR rose from 19% to 35% in the course of time.

The results of future prediction, under various possible combinations of the proposed acclimation conditions, showed that climate-associated deaths can be most avoided in the presence of socioeconomic acclimation, maximum resistance of population to heat, and minimum population susceptiveness to cold. Under this setting, for the cities in southern Germany, 14.9% (5.1-19.8*) of CVD fatality can be avoided in the future under SSP1-2.6 climate setting. With similar setting but in absence of socioeconomic acclimation, only 0·4% (12.9-7.3*) of CVD deaths can be avoided. Similarly, the largest fraction of climate-associated deaths was observed in the absence of socioeconomic acclimation, minimum resistance to heat, and maximum susceptiveness to cold. Under this combination, CVD fatality will rise in southern German cities rise by 4.0% (4.3-21*) under SSP1-2.6. For SSP3-7.0 climate setting, similar results were observed.

- **Key findings 3:** Future climate-associated health outcomes would be dependent mainly on socio-economic capacity to acclimatize to suboptimal climate. The number of preventable cold-attributable deaths is lower than the heat-associated deaths, under all future conditions. Without socio-economic acclimation, population aging would increase the proportion of temperature sensitive population, hence, largely increasing the future temperature-associated health consequences.

*empirical Confidence Interval

6. Discussion

This research work substantially fills the existing gaps in the area of the interrelation of air temperature, major air pollutants, and CVD-RD fatality. With the most extensive research till date, this thesis investigated the impact of heat on CVD-RD fatality and alteration of the impact by major atmospheric air pollutants in 482 cities across the globe. It explored the time trends in the interrelation of temperature and fatality among subclasses of CVD-RD and demographic subgroups in largest German cities. This research work addressed a major research gap in the field of climate-epidemiology and systematically developed future acclimation conditions considering both physiological climate-acclimation and climate-acclimation through increased economy.

Several physiological responses are initiated in the human body with exposure to heat. Examples of these responses include profuse sweating resulting in dehydration, hyponatremia, hyper viscosity, higher cardiac load, enhanced sympathetic reactivity resulting in the activation of the sympathetic nervous system, a systemic inflammatory response, consumptive coagulation, and microvascular thrombosis [34, 69, 70], all contributing to various CVD outcomes [69]. The physiological disturbances in the human body with exposure to heat are yet to be deeply investigated. However, it has been observed that the RD outcomes are mostly existing in conjunction with CVD outcomes [69]. Specifically, people with pre-existing respiratory conditions like COPD are in risk of hyperventilation, possibly leading to dyspnea and followed by various CVDs. In addition, increased blood coagulability or vascular events stimulates certain RDs [40, 69, 71, 72].

Apart from the cardiovascular and respiratory outcomes, exposure to extreme temperature is also associated with adverse birth outcomes [73]. Newborns, infants, ageing population, and individuals with precedent health challenges, especially with underlying CVD or neurological diseases, or mental impairments, are amongst the most vulnerable to the adverse effect of extreme temperatures. Recent studies show evidence of the impacts of atmospheric temperature on global DNA methylation in ageing population [74] and newborns [75]. In addition, telomere length was found to be shorted with exposure to extreme heat during gestation [76].

Atmospheric air pollution also negatively impacts the health and has been linked to oxidative stress and inflammation [77], mitochondrial dysfunction [78], genomic alterations [79], epigenetic alterations [80], endocrine disruption [81], altered intercellular communication [82], altered gut microbiome [83], and impaired autonomous nervous system function [84]. Air pollution affects systemic responses, as well as all of the organ-systems of the human body including the cardiovascular, respiratory, reproductive, nervous, and the digestive systems [85]. These effects

of air pollution are observed even at low concentrations (e.g., below the current European standards of annual $PM_{2.5}$ concentration: 25 mg/m^3 $PM_{2.5}$) [85].

All above facts infer that atmospheric temperatures and air pollutant impair health to a far greater extent than currently known [85]. To sum up, suboptimal temperatures and air pollutants are today the biggest climate-epidemiological risk to public health.

Comprehensive results of this cumulative dissertation have been presented and discussed in the respective publications. In the following sections, the key public health relevant inference, highlights of methodological strengths and shortcomings, as well as outlook for future research have been summarized.

6.1. Public health relevant inference

In general, this research work calls attention to climate change alleviation, air quality regulation, and public health interventions with impactful acclimation programs to lower the number of climate-caused health consequences in the future.

6.1.1. Climate change alleviation

The results of this thesis showed a higher risk of CVD-RD deaths corresponding to suboptimal temperatures. The results from the large multicounty dataset showed significant escalation in CVD-RD fatality with heat. Existing hypothesis of possible physiological acclimation of human body to heat in the course of time have been explored. Although some studies from limited regions showed reduction of heat-associated all-cause fatality with time [42], the results from this research on cause-specific fatality showed no physiological acclimation to heat in the course of time. The findings rather showed an escalation in the susceptivity to both heat and cold temperature in the course of time. Therefore, the findings of this work urge policy makers and the public to contribute to climate change alleviation or find ways to help the population to adapt to the changing climate, which is the best possible way to reduce current-day as well as future climate-associated health consequences.

6.1.2. Air quality regulation

The findings of this thesis provide strong evidence for the heat impact being significantly elevated by increased air pollution concentration. As a consequences of climate change, it is expected that both average surface temperature and air pollution levels will rise in the future [2]. The rise in the level of these two primary environmental hazards is foreseen to cause an even larger impact on human health, especially as they interact to amplify the effect of the other. In majority of 482 cities under investigation, the air pollution level strikingly exceeded the WHO Air Quality Guidelines [86]. Thus, pollution-control measures aligning with the new WHO Air Quality Guidelines, to limit the air pollution level, are crucial for public health protection.

6.1.3. Public health interventions with impactful acclimatization programs

The evidence from this dissertation aids in identifying the population most susceptible to climate-change health risk. The findings suggest the planners design impactful acclimation programs to combat the climate-change health risk. Such calculated and well-planned measures are urgent not just for countries predicted to be mostly affected by climate change but for all nations.

Furthermore, the result of this research shows high risks of temperature-associated fatality corresponding to suboptimal temperatures, i.e., both heat and cold. In this regard, it is important to note that not just heatwaves, but also cold periods are predicted in the future as a consequences of climate change [3]. Although a large proportion of existing evidence on CVD focus on heat-associated future impacts [87], the results from the future prediction in this research illustrates that susceptivity to cold would largely influence the future temperature-associated health consequences. Thus, this research illustrates that acclimation programs to combat climate change should not only focus on or be limited to heat-acclimation but should also consider cold-acclimation.

6.2. Methodological considerations: Strengths and limitations

Major strengths of this cumulative thesis include the application of elaborate multi-country dataset and the resulting estimates with substantial statistical power. The analysis in the first publication facilitates a uniform method of analysis across numerous global locations and enables valid comparison of the results from these climatically and socio-economically diverse locations. To date, this publication is the most comprehensive investigation of the interactive impact of hot summer temperature and four major air pollutants on CVD-RD fatality. Additionally, it is a pioneer study to thoroughly investigate the interaction of heat with $PM_{2.5}$ and NO_2.

The second publication studying the interrelation of temperature and fatality is a pioneer study to investigate the pattern of change in such interrelation in the course of time for subclasses of CVD-RD. This is the first study to explore the pattern of change of such association across demographic subgroups. An additional strength of this research includes meta-analysis of dose-response associations with cumulative risk.

The third publication on prediction research is the first ever work that developed a set of future acclimation settings encompassing both physiological acclimation-susceptivity and acclimation through economic capacity changes. The study systematically illustrates the importance of adjusting for population acclimation while predicting future climate-associated health consequences. The proposed methodology for prediction of future temperature-associated health burden addresses most of the existing sources of unpredictability in the field of prediction research. The methodology has been illustrated using an example-case dataset.

6.3. Outlook: Future research

In summary, the findings of this cumulative thesis indicate an increasing risk for temperature-associated health consequences in the future with increasing frequency of heatwaves and higher risks of air pollution resulting due to climate change.

The multi-country dataset used in this study with data from climatically and socio-economically diverse locations provides strong epidemiological evidence in the field. However, the dataset is not representative of all regions in the world. The availability of such data only from cities did not allow investigation of such effects in rural conditions. Further investigations in the remaining regions of the world and rural areas are required. Although the study quantifies the amplifying impact of heat and air pollution on subclasses of fatality, extensive research on physiological responses and investigation on cellular level is needed.

The results of the study on changes in pattern of temperature-fatality interrelation represent cities in Germany and may not be generalizable to other locations. Future research exploring such association in other regions are required.

The developed acclimation framework and modelling choices were proposed with German cities as baseline reference. Thus, the framework might not be directly applicable in a setting with a different climate, geography, or economy**.** Systematic investigation of the individual location followed by adaptation of the framework and methodology is recommended for future prediction studies incorporating the framework and methodology developed in this research.

6.3.1. Recommendation for future prediction studies

As we stand on the verge of global climate emergency, studies quantifying the foreseen climate-associated health consequences are essential to decision-makers to sketch and implement impactful acclimation programs. Revising the existing health policies, with evidence from prediction studies, will help evade the climate-associated health consequences. However, research in the field of climate-epidemiology is still shadowed by large unpredictability. This unpredictability arises from several ineluctable factors, existing mostly because of lack of robust findings and large research gaps.

Considering the need of reliable climate-epidemiology evidences as a public health urgency, this cumulative thesis extends to incorporate a comprehensive review on achieved accomplishments of prediction studies and the missions yet to be accomplished [88]. This narrative review, included in the appendix of this dissertation, describes the evolution of prediction methodologies in the course of time, presents the existing status of prediction research and the guiding assumptions, highlights the existing research gaps, and provides guidance and recommendation to future prediction studies. Overcoming the gaps presented in the review would enable climate-epidemiology research to move forward, allowing impactful revision of our existing health policies to safeguard public health.

7. Conclusion

Amongst global climate emergencies, impactful acclimation programs are of prime importance to reduce the growing burden of CVD-RD hospitalizations and fatality. Findings from this cumulative dissertation provide comprehensive evidence on current-day interrelation of temperature and CVD-RD outcomes, and of the interactive associations with air pollution. This research work also provides a comprehensive quantification of the future temperature-associated CVD-RD deaths.

Well-planned acclimation measures like early weather alert systems, increased green spaces, and others, are the solution to achieve resilience to climate change and promote planetary health. Furthermore, pollution-control measures aligned with the new WHO Air Quality Guidelines are crucial to safeguard public health.

8. Contribution of the PhD Candidate

The thesis encompasses three manuscripts published in *Environment International, Environmental Research, and Lancet Planetary Health*. All the listed journals are international peer-reviewed scientific journals. *Environment International* is enlisted as top 6%, *Environmental Research* as top 12%, and the *Lancet Planetary Health* as top 1% Environmental Sciences Journals according to Journal Citations Reports® 2022.

The PhD candidate is the first author of all publications included in this thesis. The candidate developed the research questions and the statistical analysis plans under the supervision of Dr. Susanne Breitner (Publication 1), Dr. Alexandra Schneider (Publication 2), or Dr. Kai Chen and Dr. Alexandra Schneider (Publication 3). For all of the three publications, the candidate prepared the datasets, developed R software [68] codes for data analysis, performed all the extensive statistical analysis, interpreted the results, and coordinated all three studies independently. The candidate presented results during the regular Thesis Advisory Committee meetings and considered advice from the committee members. The candidate drafted all three manuscripts, coordinated communication between co-authors, included the comments from co-authors, and selected journals for submission. The candidate organized the submission and publication process of all three manuscripts as the corresponding author, incorporated comments from peer-review process, revised the publications, and handled proof-reading and post-production responsibilities as the corresponding author.

Additionally, a comprehensive narrative review, published in *Frontiers Epidemiology* has been included in this thesis. The review was conceptualized by the PhD candidate. The candidate performed a literature search, drafted the review, included comments from co-authors, and organized the submission of the manuscript as a corresponding author. The candidate revised the manuscript after peer-review process and handled proof-reading and post-production responsibilities as the corresponding author.

II. Publications

1. Publication: Heat-related Cardiorespiratory Mortality: Effect Modification by Air Pollution Across 24 Countries

Title:	Heat-related cardiorespiratory mortality: effect modification by air pollution across 24 countries
Authors:	**Masna Rai**, Massimo Stafoggia, Francesca de'Donato, Matteo Scortichini, Sofia Zafeiratou, Liliana Vazquez Fernandez, Siqi Zhang, Klea Katsouyanni, Evangelia Samoli, Shilpa Rao, Eric Lavigne, Yuming Guo, Haidong Kan, Samuel Osorio, Jan Kyselý, Aleš Urban, Hans Orru, Marek Maasikmets, Jouni Jakkola, Niilo Ryti, Mathilde Pascal, Masahiro Hashizume, Chris Fook Sheng Ng, Barrak Alahmad, Magali Hurtado Diaz, César De la Cruz Valencia, Baltazar Nunes, Joana Madureira, Noah Scovronick, Rebecca M. Garland, Ho Kim, Whanhee Lee, Aurelio Tobias, Carmen Íñiguez, Bertil Forsberg, Christofer Åström, Ana Maria Vicedo-Cabrera, Martina S. Ragettli, Yue-Liang Leon Guo, Shih-Chun Pan, Shanshan Li, Antonio Gasparrini, Francesco Sera, Pierre Masselot, Joel Schwartz, Antonella Zanobetti, Michelle Bell, Alexandra Schneider, Susanne Breitner
Journal:	*Environment International*
Year:	2023
Volume:	174:107825.
DOI:	10.1016/j.envint.2023.107825
Supplements:	https://www.sciencedirect.com/science/article/pii/S0160412023000983#s0075
Impact factor:	13.35 (Journal Citations Reports® 2022)
Rank:	16/279 in Category Environmental Sciences Journals (Journal Citations Reports® 2022)
Rights declaration:	

Environment International 174 (2023) 107825

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Full length article

Heat-related cardiorespiratory mortality: Effect modification by air pollution across 482 cities from 24 countries

Masna Rai [a,b,*], Massimo Stafoggia [c], Francesca de'Donato [c], Matteo Scortichini [c], Sofia Zafeiratou [d], Liliana Vazquez Fernandez [e], Siqi Zhang [a], Klea Katsouyanni [d], Evangelia Samoli [d], Shilpa Rao [e], Eric Lavigne [f], Yuming Guo [g], Haidong Kan [h], Samuel Osorio [i], Jan Kyselý [j], Aleˇs Urban [j], Hans Orru [k], Marek Maasikmets [l], Jouni J.K. Jaakkola [m], Niilo Ryti [m], Mathilde Pascal [n], Masahiro Hashizume [o], Chris Fook Sheng Ng [p], Barrak Alahmad [q], Magali Hurtado Diaz [r], César De la Cruz Valencia [r], Baltazar Nunes [s], Joana Madureira [s], Noah Scovronick [t], Rebecca M. Garland [u], Ho Kim [v], Whanhee Lee [w], Aurelio Tobias [x], Carmen Íñiguez [y], Bertil Forsberg [z], Christofer Åström [z], Ana Maria Vicedo-Cabrera [aa], Martina S. Ragettli [ab], Yue-Liang Leon Guo [ac], Shih-Chun Pan [ad], Shanshan Li [ae], Antonio Gasparrini [af], Francesco Sera [ag], Pierre Masselot [ae], Joel Schwartz [ah], Antonella Zanobetti [ah], Michelle L. Bell [ai], Alexandra Schneider [a], Susanne Breitner [a,b]

[a] Institute of Epidemiology, Helmholtz Munich, - German Research Center for Environmental Health, Neuherberg, Germany
[b] Institute for Medical Information Processing, Biometry, and Epidemiology – IBE, Pettenkofer School of Public Health, LMU Munich, Munich, Germany
[c] Department of Epidemiology, Lazio Regional Health Service, ASL Roma 1, Rome, Italy
[d] Department of Hygiene, Epidemiology and Medical Statistics, Medical School,National and Kapodistrian University of Athens, Greece
[e] Department of Air Pollution and Noise, Norwegian Institute of Public Health, Oslo, Norway
[f] School of Epidemiology & Public Health, Faculty of Medicine, University of Ottawa, Ottawa, Canada and Environmental Health Science & Research Bureau, Health Canada, Ottawa, Canada
[g] Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia
[h] Department of Environmental Health, School of Public Health, Fudan University, Shanghai, China
[i] Department of Environmental Health, University of Sa˜o Paulo, Sa˜o Paulo, Brazil
[j] Institute of Atmospheric Physics, Czech Academy of Sciences, Prague, Czech Republic Faculty of Environmental Sciences, Czech University of Life Sciences, Prague, Czech Republic
[k] Department of Family Medicine and Public Health, University of Tartu, Tartu, Estonia
[l] Estonian Environmental Research Centre, Tallinn, Estonia
[m] Center for Environmental and Respiratory Health Research (CERH), University of Oulu, Oulu, Finland
[n] Sant´e Publique France, Department of Environmental Health, French National Public Health Agency, Saint Maurice, France
[o] Department of Global Health Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[p] School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan
[q] Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[r] Department of Environmental Health, National Institute of Public Health, Cuernavaca, Morelos, Mexico
[s] Department of Environmental Health, Instituto Nacional de Saúde Dr. Ricardo Jorge, Porto, Portugal
[t] Department of Environmental Health. Rollins School of Public Health, Emory University, Atlanta, USA
[u] Department of Geography, Geoinformatics and Meteorology, University of Pretoria, Pretoria, South Africa
[v] Graduate School of Public Health, Seoul National University, Seoul, Republic of Korea
[w] School of Biomedical Convergence Engineering, Pusan National University, Yangsan, South Korea
[x] Institute of Environmental Assessment and Water Research (IDAEA), Spanish Council for Scientific Research (CSIC), Barcelona, Spain
[y] Department of Statistics and Computational Research. Universitat de Val`encia, Val`encia, Spain
[z] Department of Public Health and Clinical Medicine, Umeå University, Sweden
[aa] Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
[ab] Swiss Tropical and Public Health Institute, Basel, Switzerland
[ac] Environmental and Occupational Medicine, and Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University (NTU) and NTU Hospital, Taipei, Taiwan
[ad] National Institute of Environmental Health Science, National Health Research Institutes, Zhunan, Taiwan

* Corresponding author at: Institute of Epidemiology, Helmholtz Munich-German Research Center for Environmental Health, Ingolst¨adter Landstraße 1, D-85764 Neuherberg, Germany.
E-mail address: masna.rai@campus.lmu.de (M. Rai).

https://doi.org/10.1016/j.envint.2023.107825
Received 31 August 2022; Received in revised form 11 January 2023; Accepted 12 February 2023
Available online 13 February 2023

[ae] Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia
[af] Department of Public Health Environments and Society, London School of Hygiene & Tropical Medicine, London, United Kingdom
[ag] Department of Statistics, Computer Science and Applications "G. Parenti", University of Florence, Florence, Italy
[ah] Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[ai] School of Forestry and Environmental Studies, Yale University, New Haven CT, USA

ARTICLE INFO

Handling Editor: Zorana Andersen

Keywords:
Heat
Air temperature
Air pollution
Cardiovascular mortality
Respiratory mortality
Effect modification

ABSTRACT

Background: Evidence on the potential interactive effects of heat and ambient air pollution on cause-specific mortality is inconclusive and limited to selected locations.
Objectives: We investigated the effects of heat on cardiovascular and respiratory mortality and its modification by air pollution during summer months (six consecutive hottest months) in 482 locations across 24 countries.
Methods: Location-specific daily death counts and exposure data (e.g., particulate matter with diameters ≤ 2.5 μm [$PM_{2.5}$]) were obtained from 2000 to 2018. We used location-specific confounder-adjusted Quasi-Poisson regression with a tensor product between air temperature and the air pollutant. We extracted heat effects at low, medium, and high levels of pollutants, defined as the 5th, 50th, and 95th percentile of the location-specific pollutant concentrations. Country-specific and overall estimates were derived using a random-effects multilevel *meta*-analytical model.
Results: Heat was associated with increased cardiorespiratory mortality. Moreover, the heat effects were modified by elevated levels of all air pollutants in most locations, with stronger effects for respiratory than cardiovascular mortality. For example, the percent increase in respiratory mortality per increase in the 2-day average summer temperature from the 75th to the 99th percentile was 7.7% (95% Confidence Interval [CI] 7.6–7.7), 11.3% (95% CI 11.2–11.3), and 14.3% (95% CI 14.1–14.5) at low, medium, and high levels of $PM_{2.5}$, respectively. Similarly, cardiovascular mortality increased by 1.6 (95%CI 1.5–1.6), 5.1 (95%CI 5.1–5.2), and 8.7 (95%CI 8.7–8.8) at low, medium, and high levels of O_3, respectively.
Discussion: We observed considerable modification of the heat effects on cardiovascular and respiratory mortality by elevated levels of air pollutants. Therefore, mitigation measures following the new WHO Air Quality Guidelines are crucial to enhance better health and promote sustainable development.

1. Introduction

Many epidemiological studies have documented the adverse effects of short-term exposure to high ambient temperature and heat waves on non-accidental mortality (Roye et al., 2021; Williams et al., 2018; Gasparrini and Armstrong, 2011). The WHO states that from 1998 to 2017, heatwaves caused more than 166,000 deaths worldwide (Heatwaves, 2023). As a result of climate change, population exposure to heat is increasing with the number of people exposed to heatwaves increased by around 125 million between 2000 and 2016 (Heatwaves, 2023). Similarly, low ambient air quality is a major environmental risk factor for mortality. According to the 2021 WHO report, four million annual deaths worldwide were attributable to outdoor air pollution in 2016 (Air Pollution, 2021). Studies on cause-specific mortality show an increased risk of cardiovascular [CVD] and respiratory [RD] disease mortality with both high temperature (Chen et al., 2015; Gasparrini et al., 2012; Breitner et al., 2014) and ambient air pollutant levels (Liu et al., 2019; Bowe et al., 2019; Loxham et al., 2019). In addition, CVD and RD hospitalizations have increased with high temperatures in numerous locations, increasing the heat-attributable morbidity burden (Bai et al., 2018; Bai et al., 2016; Sun et al., 2019).

Previously, air temperature and ambient air pollutants have been mostly considered separately (Stafoggia et al., 2010; Turner et al., 2012). Few of these studies investigated the effect of temperature controlling for daily air pollution levels (Turner et al., 2012), while some analyzed the effects of air pollutants adjusting for daily temperature (Stafoggia et al., 2010). However, recent research shows that temperature and air pollution might interact, possibly resulting in synergistic effects (Burkart et al., 2013). These interactive effects have been, so far, explored only by a limited number of studies (Jhun et al., 2014; Scortichini et al., 2018; Breitner et al., 2014; Li et al., 2017; Chen et al., 2017; Stafoggia M, Schwartz J, Forastiere F, Perucci CA, Group S, 2008; Anenberg et al., 2020; Pascal et al., 2021). These studies demonstrate a significant increase in the risk for total, CVD, and RD mortality, providing evidence of the synergistic association between temperature and particulate matter [PM] and ozone [O_3], with the highest interactive effects during the summer months (Stafoggia et al., 2010; Pascal et al., 2021) or hotter days (Breitner et al., 2014; Li et al., 2017; Chen et al., 2017), compared to colder periods. A *meta*-analysis on the interactive effects of PM with a diameter of 10 μm or less [PM_{10}] and temperature showed a higher risk for total, CVD, and RD mortality, especially during high-temperature days, compared to colder days, with the highest risk for RD mortality (Chen et al., 2017). The study reports the Relative Risk [RR] (95 % confidence intervals [CI]s) for respiratory death per 10 mg/m^3 increase in PM_{10} to be 1.005 (1.000,1.010), 1.008 (1.006, 1.010), and 1.02 (1.01,1.03) at low, moderate, and high temperature levels, respectively (Chen et al., 2017).

Only limited studies have explored non-linear interactive effects on mortality (Scortichini et al., 2018). Most studies have assessed the modification of the air pollutant effects by temperature (Jhun et al., 2014; Li et al., 2017; Chen et al., 2017; Stafoggia M, Schwartz J, Forastiere F, Perucci CA, Group S, 2008). In contrast, studies exploring whether air pollution modifies the temperature effects are still limited (Scortichini et al., 2018; Breitner et al., 2014) and focused mainly on non-accidental mortality (Scortichini et al., 2018) or specific regions within a country (Breitner et al., 2014). Evidence on the heat effect and its modification by air pollutants on CVD and RD mortality is scarce, with few studies focusing only on PM_{10} and O_3 (Jhun et al., 2014; Scortichini et al., 2018; Breitner et al., 2014; Li et al., 2017; Chen et al., 2017; Stafoggia M, Schwartz J, Forastiere F, Perucci CA, Group S, 2008); little is known about the effects of other air pollutants. Therefore, a research gap still exists on the modification of temperature effects on CVD and RD mortality by different key ambient air pollutants.

Furthermore, in the absence of mitigation, temperature and ambient air pollutant concentrations are expected to rise in the future due to climate change (Ipcc, 2021), potentially leading to stronger interaction effects and, therefore, a higher health burden. Thus, understanding the present-day interactive effects of temperature and air pollutants on various health endpoints is crucial to combat climate change with effective adaptation strategies.

This analysis aims to explore the effect of heat on CVD and RD mortality and its modification by air pollutants, including PM_{10}, PM

with a diameter of 2.5 μm or less [$PM_{2.5}$], O_3, and nitrogen dioxide [NO_2] in 482 locations across 24 countries. To our knowledge, this is the first analysis to explore this association on a large-scale multi-country dataset.

2. Methods

2.1. Dataset

We obtained daily time-series data from 458 locations in 20 countries or regions with available data on CVD and RD mortality, air temperature, and air pollutants (PM_{10}, $PM_{2.5}$, O_3, NO_2) from the MCC Collaborative Research Network database covering various periods ranging from 2000 to 2018 (Table 1). Furthermore, we included additional locations from Germany, Greece, Italy, and Norway within the framework of the EU project: Exposure to heat and air pollution in Europe – cardiopulmonary impacts and benefits of mitigation and adaptation [EXHAUSTION] (EXHAUSTION. EXHAUSTION, 2021). The additional locations included 14 from Germany, eight from Italy, four from Norway, and five from Greece. This resulted in a dataset of 489 locations from 24 countries.

For this study, we selected the warmer months, which we define as the six consecutive hottest months for each of the selected locations. Mortality data were collected from local health authorities in each country and included daily counts of deaths for cardiovascular (International Classification of Diseases [ICD]-10 I00-I99) and respiratory (ICD-10 J00-J99) causes. The mean daily temperature for each location was calculated from central monitoring stations, either as the average between maximum and minimum values or as the 24-hour average. Similarly, we obtained daily 24-hour average concentrations of PM_{10}, $PM_{2.5}$, and NO_2, and daily maximum 8-h average O_3 concentrations (or 24-hour average if 8-hour maximum was not available) from fixed air quality monitoring stations. We excluded seven cities from China that had short periods of data (≤3 years), resulting in 482 cities being included in the final analysis. We also excluded seasons with ≥ 50 % missing values for temperature and the respective pollutant for the pollutant-specific analysis. Country-specific information on data collection are presented in the Supplementary material, section S1.

2.2. Statistical analysis

We estimated the location-specific heat effect and the effect modification by air pollutants. To estimate the heat effect, we applied an over-dispersed Poisson regression model for each location, controlling for the day of the week and sub-seasonal trends. The day of the season was fitted with a spline with four degrees of freedom per season. Two-day moving averages of the same and the previous day (lag 0–1) for temperature were incorporated into the model. The lag windows were defined based on literature (19, 20, 28) and investigations on the dataset. The heat effect was estimated as the percent (%) change in mortality per an increase in mean temperature from the 75th to the 99th percentile of the location-specific mean temperature distribution. This approach accounts for city-specific response or adaptation to air temperature.

The interactive effect of heat and air pollutants was assessed by a two-stage approach. In the first stage, we used a non-parametric response-surface model, previously applied by Scortichini et al. (Scortichini et al., 2018), to assess the interactive effect of heat and air pollutants. The model included two-day moving averages of the same and the previous day (lag 0–1), both for temperature and air pollutants.

$$Tensor(Tmean, Poll) = \sum_{i=1} \sum_{l=1}^{n_2} a_{il}(Poll)\alpha_{il} b_i(\mathrm{Tmean})$$

where b_i is the i^{th} basis for temperature and a_l is the l^{th} basis for air pollution.

This approach was advantageous in exploring the combined effect of two risk factors on an outcome by defining a tensor smoother, where a tridimensional curve modeled the increases in mortality according to a combined variation of the values of temperature and air pollutants. Three exposure–response functions were extracted from the tridimensional surface in each location, along the values of the three air pollutant categories: low, medium, and high, defined for each location as the 5th, 50th, and 95th percentile of the location-specific summer air pollutant distributions. Heat effect as % change in mortality was extracted from the derived models. Bootstrapping was used to calculate the 95 % confidence intervals [CI]. A contour plot of the model is included in Supplementary material S2.

In the second stage, we pooled the above obtained location-specific

Table 1
Country-specific number of locations, study periods, and descriptive statistics of mortality data.

Country	No. of Locations	Study Period	Cardiovascular Mortality		Respiratory Mortality	
			Total	Daily Mean	Total	Daily Mean
Canada	24	2000–2011	410,737	3.9	100,848	0.9
China	9	2001–2015	371,402	22.5	116,961	7.0
Colombia	1	2000–2013	109,802	21.5	41,346	8.1
Czech Republic	1	2000–2015	98,307	16.8	11,118	1.9
Estonia	4	2003–2018	49,750	2.5	3,336	0.2
Finland	1	2000–2014	39,840	7.3	6,152	1.1
France	18	2007–2015	234,503	3.9	62,283	0.9
Germany	14	2000–2016	1,018,593	8.1	175,094	1.4
Greece	5	2000–2016	117,257	8.3	27,971	2.0
Italy	8	2006–2015	74,412	5.3	11,809	0.8
Japan	47	2011–2015	496,710	5.8	296,015	3.4
Kuwait	1	2000–2016	35,285	5.7	57,15	0.9
Mexico	8	2000–2014	651,988	7.5	240,187	2.7
Norway	4	2000–2018	24,287	1.7	6,971	0.5
Portugal	5	2000–2018	277,609	8.5	84,655	2.6
South Africa	6	2000–2013	228,498	7.8	190,746	6.3
South Korea	7	2000–2015	367,465	10.1	101,472	2.7
Spain	48	2000–2014	583,407	2.2	214,911	0.8
Sweden	1	2000–2010	43,295	10.8	7,602	1.9
Switzerland	8	2000–2013	62,428	1.5	11,201	0.3
Taiwan	3	2000–2014	199,305	12.1	93,464	5.7
Thailand	19	2000–2008	154,584	2.6	102,480	1.7
UK	39	2000–2016	1,031,589	4.3	461,257	1.9
USA	210	2000–2006	266,6825	5.0	847,430	1.6

effect estimates using a multilevel *meta*-analytical model that accounts for variations in risk across two nested groups (cities and countries) to obtain the country-wise and the overall pooled estimate (Sera et al., 2019). We assessed heterogeneity using the I2 statistic and Cochran's Q test. Furthermore, we carried out a significance test on heat effect modification based on the difference between the heat effect on medium and high pollution days compared to the low pollution days and reported the P-values. A two-sided P-value < 0.05 was considered statistically significant.

We performed several sensitivity analyses to examine the robustness of the results. For example, we used the three consecutive warmest months instead of six. We considered the moving averages lag 0–3 (four-day moving averages of the same and the three previous days) for both temperature and air pollution. We also used alternative definitions of air pollutant levels: 25th, 50th, and 75th percentile instead of 5th, 50th, and 95th as the low, medium, and high pollutant categories, respectively. We also estimated the heat effect as the % change in mortality when the mean location-specific temperature increased from the Minimum Mortality Temperature [MMT] to the 99th percentile.

All analyses were performed in R 4.1.0 (R Core Team, 2017) using the packages *mgcv* in the first stage and *mixmeta* in the second stage.

3. Results

3.1. Descriptives

The analysis included 9,347,514 deaths from CVD and 3,221,024 from RD causes. Table 1 shows the country-specific descriptive statistics for cause-specific mortality. Similarly, Figs. 1, S3, and Table S4 include the descriptive statistics for the different exposure variables. Country-specific averages of daily mean temperatures ranged from 6.1 °C in Estonia to 27.9 °C in Thailand. The locations within this large multi-country study encompassed various climatic zones, which can be broadly categorized as: cold (Canada, Estonia, Finland, Norway, and Sweden), temperate (Czech Republic, France, Germany, Switzerland, and the UK), Mediterranean (Greece, Italy, Portugal, and Spain), humid-subtropical and temperate (Japan, and South Korea), continental (Kuwait), and tropical and subtropical (Colombia, Mexico, South Africa, Taiwan, and Thailand) (D K. World Climate Regions, 2020). The nine locations from China included in this study were in the humid-subtropical and temperate regions. Furthermore, the USA included locations with heterogeneous climatic conditions varying largely within the same country. The locations in the study also showed varying levels of air pollutant concentrations. Countries with the highest levels of air pollution (based on the highest 95th percentile) were Kuwait for PM_{10} (539.5 μg/m^3) and China for $PM_{2.5}$ (131.0 μg/m^3), O_3 (177.1 μg/m^3), and NO_2 (84.7 μg/m^3). Similarly, countries with the lowest levels of air pollution (based on the lowest 5th percentile) were Norway and Finland for PM_{10} (4.6 and 4.7 μg/m^3, respectively), Finland for NO_2 (2.1 μg/m^3), Norway and Canada for $PM_{2.5}$ (2.0 and 2.1 μg/m^3, respectively), and Germany for O_3 (8.3 μg/m^3).

3.2. Heat effect

Our overall estimate showed an increase in CVD mortality by 6.4 % (95 % confidence interval (CI) 6.3–6.4) and RD mortality by 8.4 % (95 % CI 8.4–8.5) per an increase in the 2-day average temperature from the 75th to the 99th percentile. In general, we found the heat effects to be higher for RD when compared to CVD mortality. In particular, heat effects on RD mortality in countries like Colombia, Canada, Sweden, and Switzerland were almost six to 11 times higher than CVD mortality. Similar effects were observed in locations in the Czech Republic, France, Italy, Spain, and Kuwait, where the RD mortality was about twice to three times higher than the CVD mortality. Although less pronounced effects were seen in other countries, the estimates always showed a higher proportion of heat-related RD than CVD deaths (Figs. 2 and S5).

The highest country-specific heat effects on RD mortality were observed in the Czech Republic, where mortality increased by 37.1 % (95 % CI 18.9–55.3), followed by Sweden with an increase of 36.5 % (95 %CI 34.9–38.1) (Fig. 2 and S5).

3.3. Effect modification by air pollution

We found an overall consistent increase in the heat effects on CVD and RD mortality with elevated PM_{10}, $PM_{2.5}$, O_3, and NO_2 levels, with estimates highest on high pollution days and lowest on days with low pollution levels. We observed an overall higher effect modification for RD than CVD mortality (Table 2).

Exceedingly large modification of the heat effects on CVD mortality by high levels of PM_{10} was seen in Germany, Portugal, Spain, Switzerland, and the UK (Fig. 3 and S6). For example, heat effects on CVD mortality in Germany were found to be 1.3 % (95 % CI 1.2–1.4),

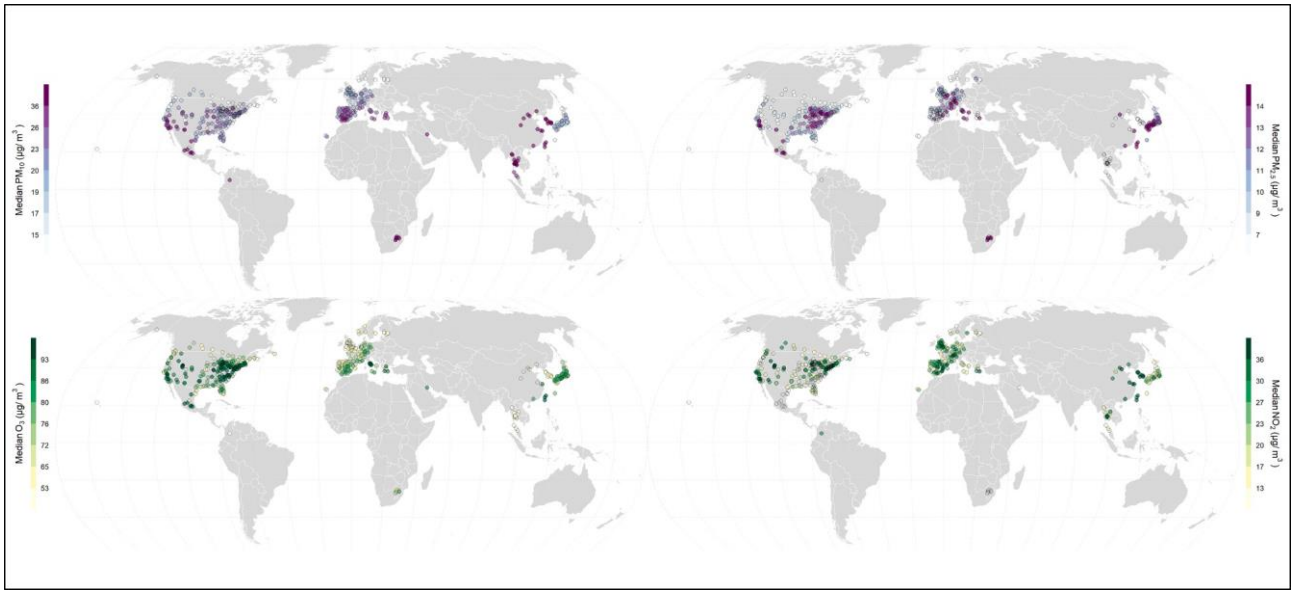

Fig. 1. Median air pollutant (particulate matter [PM] with diameter of 10 μm or less [PM_{10}], 2.5 μm or less [$PM_{2.5}$], ozone [O_3], and nitrogen dioxide [NO_2]) concentrations across study locations. [Country-specific estimates and different percentiles are inlcuded in Supplementary Material section S4].

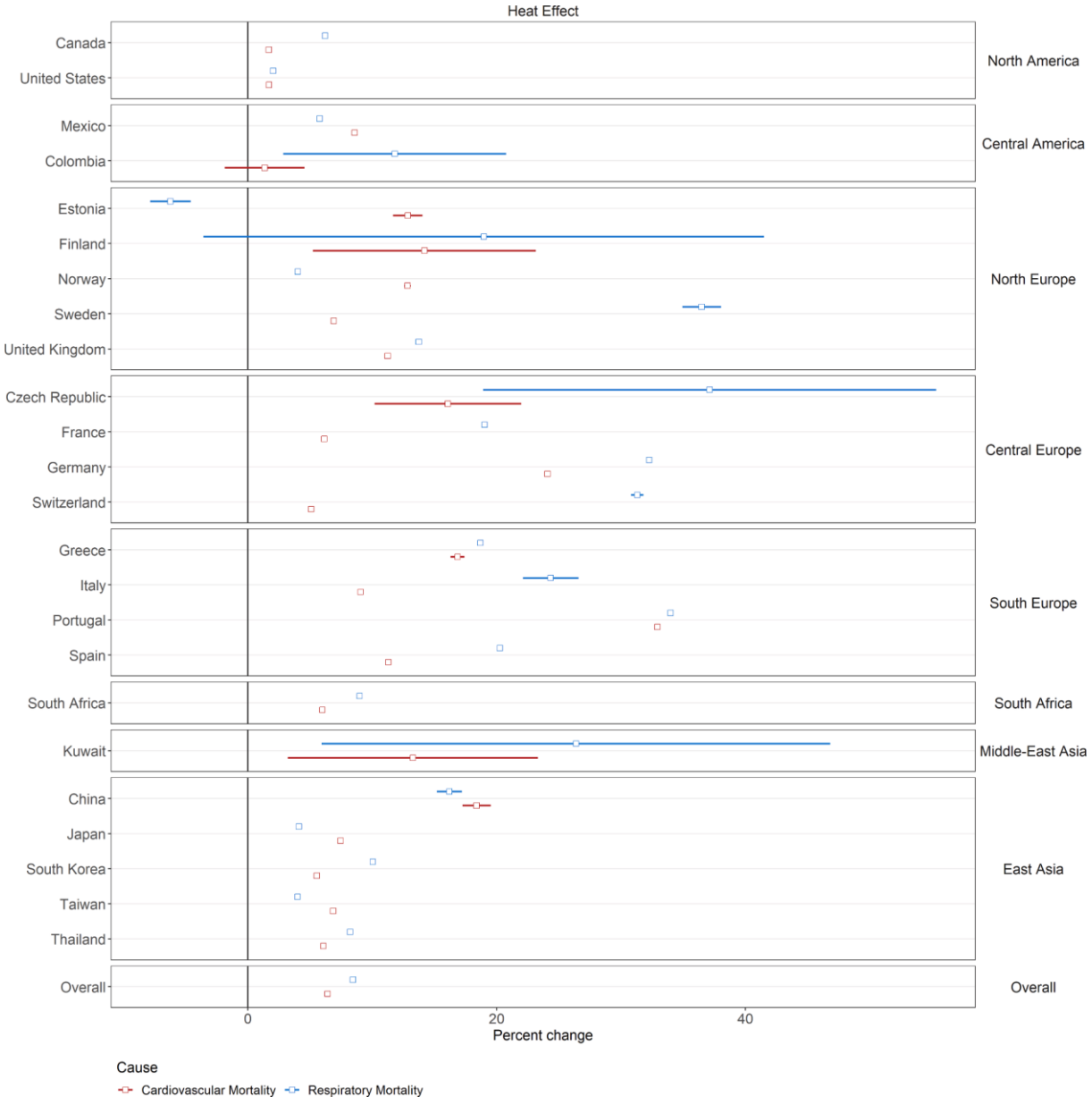

Fig. 2. Country-specific heat effects on cardiovascular and respiratory mortality. Estimates are represented as the percent change in cardiovascular and respiratory mortality (with 95% confidence intervals) per an increase in the 2-day mean temperature from the 75th to the 99th percentile of the location-specific temperature distribution. [Country-specific estimates were obtained using a multivariate multilevel *meta*-analysis of the location-specific estimates. Estimates to the figure are included in Supplementary Material section S6].

6.7 % (95 % CI 6.6–6.9), and 20.2 % (95 % CI 20.0–20.3) at low, medium, and high levels of PM_{10}, respectively (Fig. 3 and S6). Similar results were observed for high $PM_{2.5}$ levels. In contrast, few countries like China and Finland showed insignificant or no effect modification with varying levels of air pollutants. Considerable modification of the heat effects by high O_3 and NO_2 levels was seen in France, Germany, Japan, Spain, Switzerland, and the UK. CVD mortality in Germany increased up to 30.0 % (95 % CI 29.8–30.1) with high levels of O_3. High levels of NO_2 largely increased the heat effects on CVD mortality, with effects up to 18.3 % (95 %CI 17.0–19.6) in Estonia. In contrast, in certain countries like China and Thailand, the modification by high NO_2 levels tended to be reversed, however insignificantly (Fig. 3 and S6).

Substantial heat effect modifications for RD mortality were seen in various regions (Fig. 4 and S6), including Switzerland, with mortality increases of 3.9 % (95 % CI 3.1–4.8), 13.4 % (95 % CI 12.8–14.1), and 40.4 % (95 % CI 38.2–42.7) at low, medium, and high levels of PM_{10}, respectively. Substantial effect modification by elevated levels of $PM_{2.5}$ was observed in Portugal, where RD mortality increased by 13.2 % (95 % CI 11.9–14.7), 29.4 % (95 % CI 28.7–30.2), 65.1 % (95 % CI 63.4–66.9) at low, medium, and high levels of $PM_{2.5}$, respectively (Fig. 4 and S6). Considerable effect modification by elevated levels of O_3 was observed in Germany, with RD mortality increases of 3.5 % (95 % CI 3.2–3.7), 12.8 % (95 % CI 12.6–12.9), and 34.3 % (95 % CI 34.0–34.6) at low, medium, and high levels of O_3, respectively. In Switzerland, concurrent elevated NO_2 levels increased the heat effects on RD mortality, with estimates of 18.6 % (95 % CI 17.6–19.7), 25.8 % (95 % CI 25.3–26.4), and 43.5 % (95 % CI 42.2–45.0) at low, medium, and high levels of NO_2, respectively. In contrast, results from countries like Colombia and Sweden followed irregular patterns (Fig. 4 and S6).

Although the pooled estimates of countries with a large number of locations, like the US, showed no modification of the heat effects for CVD and RD mortality by varying levels of air pollutants, the location-

Table 2
Overall heat effect estimates stratified by the air pollutants.[a]

Air Pollutants		Cardiovascular Mortality				Respiratory Mortality			
		%	LCI	UCI	P-value [i]	%	LCI	UCI	P-value [i]
PM_{10}	l	**2.07**	2.04	2.10		**9.90**	9.85	9.95	
	m	**4.29**	4.26	4.32	<0.0005	**12.21**	12.15	12.27	<0.0005
	h	**7.33**	7.29	7.37	<0.0005	**14.62**	14.49	14.74	<0.0005
$PM_{2.5}$	l	**1.53**	1.48	1.58		**7.65**	7.60	7.69	
	m	**3.81**	3.77	3.85	<0.0005	**11.29**	11.21	11.38	<0.0005
	h	**7.01**	6.94	7.07	<0.0005	**14.32**	14.18	14.46	<0.0005
O_3	l	**1.60**	1.58	1.61		**4.12**	4.09	4.15	
	m	**5.16**	5.14	5.18	<0.0005	**8.34**	8.31	8.38	<0.0005
	h	**8.73**	8.69	8.76	<0.0005	**13.53**	13.42	13.65	<0.0005
NO_2	l	**6.18**	6.14	6.22		**13.12**	13.06	13.19	
	m	**7.09**	7.05	7.12	<0.0005	**14.89**	14.79	14.98	<0.0005
	h	**8.56**	8.51	8.61	<0.0005	**15.46**	15.33	15.58	<0.0005

[Estimates are represented as the percent change in heat-related cause-specific mortality with the corresponding 95% confidence interval (LCI, UCI) per an increase in the 2-day mean temperature from the 75th to the 99th percentile of the location-specific temperature distribution during low, medium, and high air pollution days for PM_{10}, $PM_{2.5}$, O_3, and NO_2. Low, medium, and high pollution days are represented as days with 2-day mean air pollutant concentration as 5th, 50th, and the 95th percentile of the location-specific air pollutant distribution. Overall estimates were obtained by multivariate multilevel *meta*-analysis of the location-specific estimates.

[a] Significance test based on the difference between the estimate at higher or medium levels of air pollution (m or h) and low level of air pollution (l).

specific estimates showed quite heterogeneous effect modifications with substantial associations for many locations. In addition, in numerous locations, we found significantly higher heat effects on RD mortality with concurrent high air pollution levels (S8).

The results of the sensitivity analysis are included in S7. In general, the results increased, for example, when reporting heat effect as % change when the temperature increases from the MMT to the 99th temperature percentile, showing that our model choices were rather conservative. Our results were robust to all other sensitivity analyses.

4. Discussion

To the best of our knowledge, this is the most extensive research investigating the modification of the effects of summer temperatures on daily CVD and RD mortality by air pollutants in 482 locations across 24 countries. Further, it is the first-ever study to deeply investigate effect modifications by air pollutants such as $PM_{2.5}$ and NO_2. Both CVD and RD mortality increased in association with high summer temperatures, with a higher risk for RD than CVD mortality. Similarly, considerable modification of the overall heat effects by elevated levels of PM_{10}, $PM_{2.5}$, O_3, and NO_2 was observed for both CVD and RD mortality, with much higher heat effect modifications for RD than CVD mortality, for all air pollutants considered. This study, thus, provides evidence for the interactive association between heat and ambient air pollutants (PM_{10}, $PM_{2.5}$, O_3, and NO_2).

The results of our study are consistent with the existing literature on the interactive effects on CVD and RD mortality, which suggests effect modification by high levels of PM_{10} and O_3 (Breitner et al., 2014; Li et al., 2014). Similarly, a study in the US population shows effect modification by O_3 for CVD mortality (Ren et al., 2008) and a study in Australia by PM_{10} for CVD and RD hospitalizations (Ren et al., 2006). When comparing the results of our study to those investigating similar associations but on total mortality, we see a similar pattern and estimates for PM_{10} and/or O_3 effect modification (Scortichini et al., 2018; Analitis, 2014). In a study investigating the effect modification by PM_{10}, in various locations in Italy, the increase in heat-related total mortality was found to increase by up to 7.5 % (95 % CI — 1.6, 17.3), 15.5 % (95 % CI 6.8–24.9), and 24.4 % (95 % CI: 17.6–31.6) on days with low, moderate, and high PM_{10} concentration, respectively (Scortichini et al., 2018). The study reported similar estimates for effect modification by O_3 (Scortichini et al., 2018). Similarly, another study in Greece reported total mortality to increase by 54 % during heat wave episodes on high O_3 days compared with low, among people aged 75–84 years and by 36 % on high PM_{10} days compared to low PM_{10} days (Analitis, 2014). Contrastingly, a study from nine US cities reported no evidence of temperature effect modifications by $PM_{2.5}$ or O_3 on total mortality (Zanobetti and Schwartz, 2008).

Our results suggest much higher heat effect modifications for RD mortality than the commonly perceived CVD mortality. Much stronger heat effects and their modification by elevated levels of air pollutants imply that heat or high temperature is a risk factor for RD in addition to the commonly observed cold effects. These findings are in line with the current limited local studies, which explore the heat effect modification by air pollutants simultaneously for CVD and RD outcomes, including mortality (Breitner et al., 2014) or hospitalizations (Analitis, 2014), which also infer a higher effect modification for RD than CVD outcomes. Thus, stronger evidence added by our study, which explores this association across a large dataset including 482 locations and diverse climatic conditions, would be beneficial for future health policy design, particularly in the context of climate change and the SARS-COV-2 pandemic affecting the respiratory system (WHO. Coronavirus disease (COVID-19), 2023).

We observed large regional differences in heat effects and interactive effects with key ambient air pollutants. Considerably higher heat effects with elevated concentrations of air pollutants were observed in countries like Portugal, Spain, the UK, Japan, Germany, Thailand, Kuwait, and Switzerland. In contrast, results from other countries like Taiwan and Colombia followed inconsistent patterns. Similarly, few results from countries like China and Thailand tended to follow insignificant reverse patterns. One contributing factor for such results might be relatively fewer locations included in the analysis or the relative completeness of the data from these locations. Similarly, the country-wide estimate for large territories like the US also showed minimal heat effects and no effect modification by elevated air pollution levels. This could be expected, as there were locations from different climatic conditions within these large territories. However, when looking at the individual location-specific estimates, we observed varying heat effects and mortality risks with elevated levels of air pollution. Higher risks were observed in most locations, whereas less to no associations in a few others. Therefore, a country-wide estimate may not represent all locations for large countries like the US, with a wide range of climatic diversity. Previous studies in the US showed similar observations with patterns of effect estimates across different locations (Zanobetti and Schwartz, 2008; Kioumourtzoglou et al., 2016).

Mechanisms of heat stress on physiology include increased sweating causing dehydration, salt depletion, increased blood circulation and cardiac work, as well as hemoconcentration, leading to various cardiovascular outcomes like myocardial infarction, heart failure, and stroke (Breitner et al., 2014; Schneider et al., 2017). For respiratory mortality, the underlying mechanisms are less clear and often occur in combination

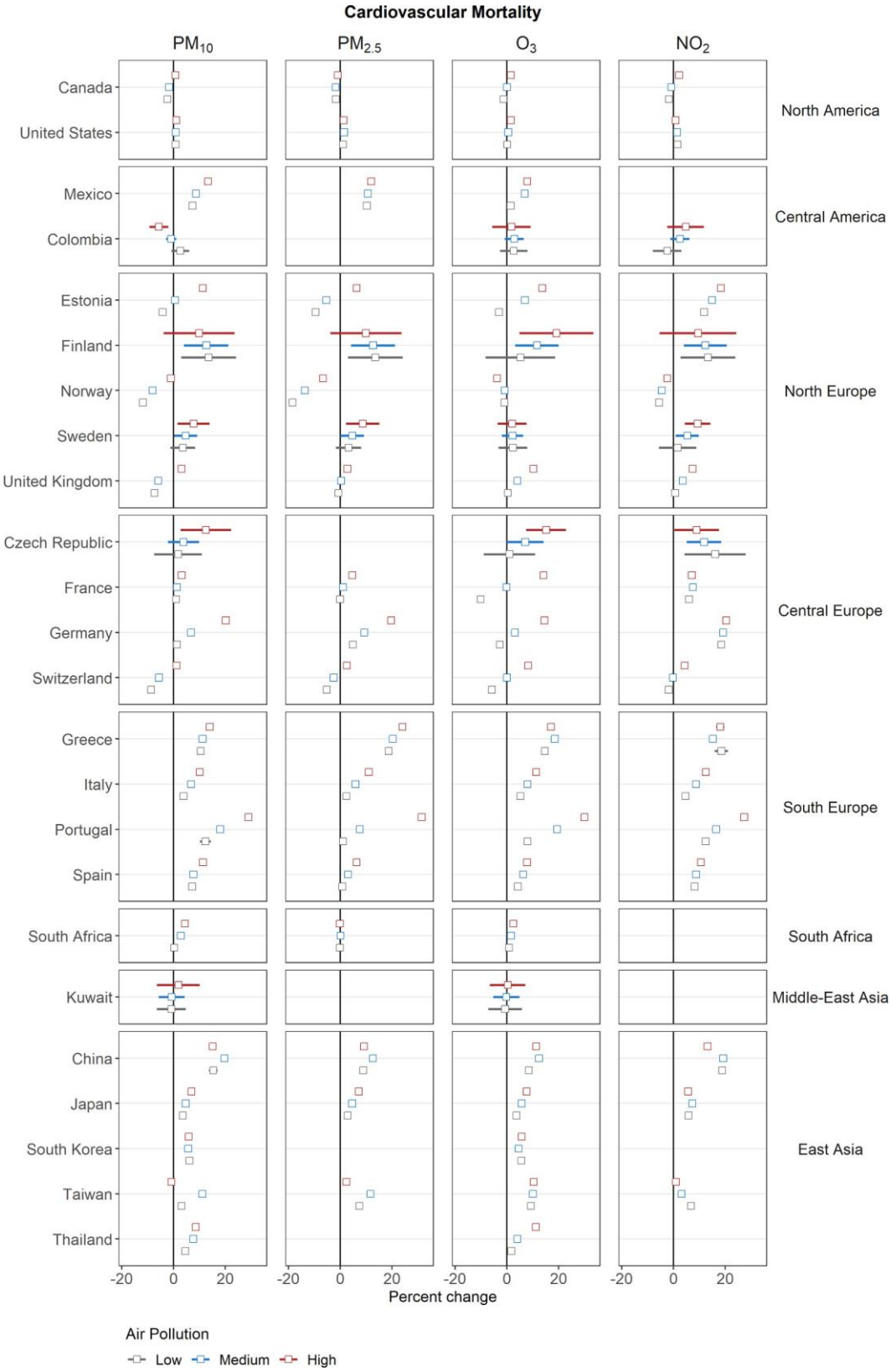

Fig. 3. Country-specific heat effects on cardiovascular mortality stratified by air pollutant levels.Estimates are presented as the percent change CVD mortality with the corresponding 95% confidence intervals per an increase in the 2-day mean temperature from the 75th to the 99th percentile of the location-specific temperature distribution by low, medium, and high levels of air pollutants represented by the 5th, 50th, and 95th percentile of city-specific respective pollutant distribution. [Country-specific estimates were obtained using a multivariate multilevel *meta*-analysis of the location-specific estimates. Estimates to the figure with **P-values** are included in Supplementary Material section S6].

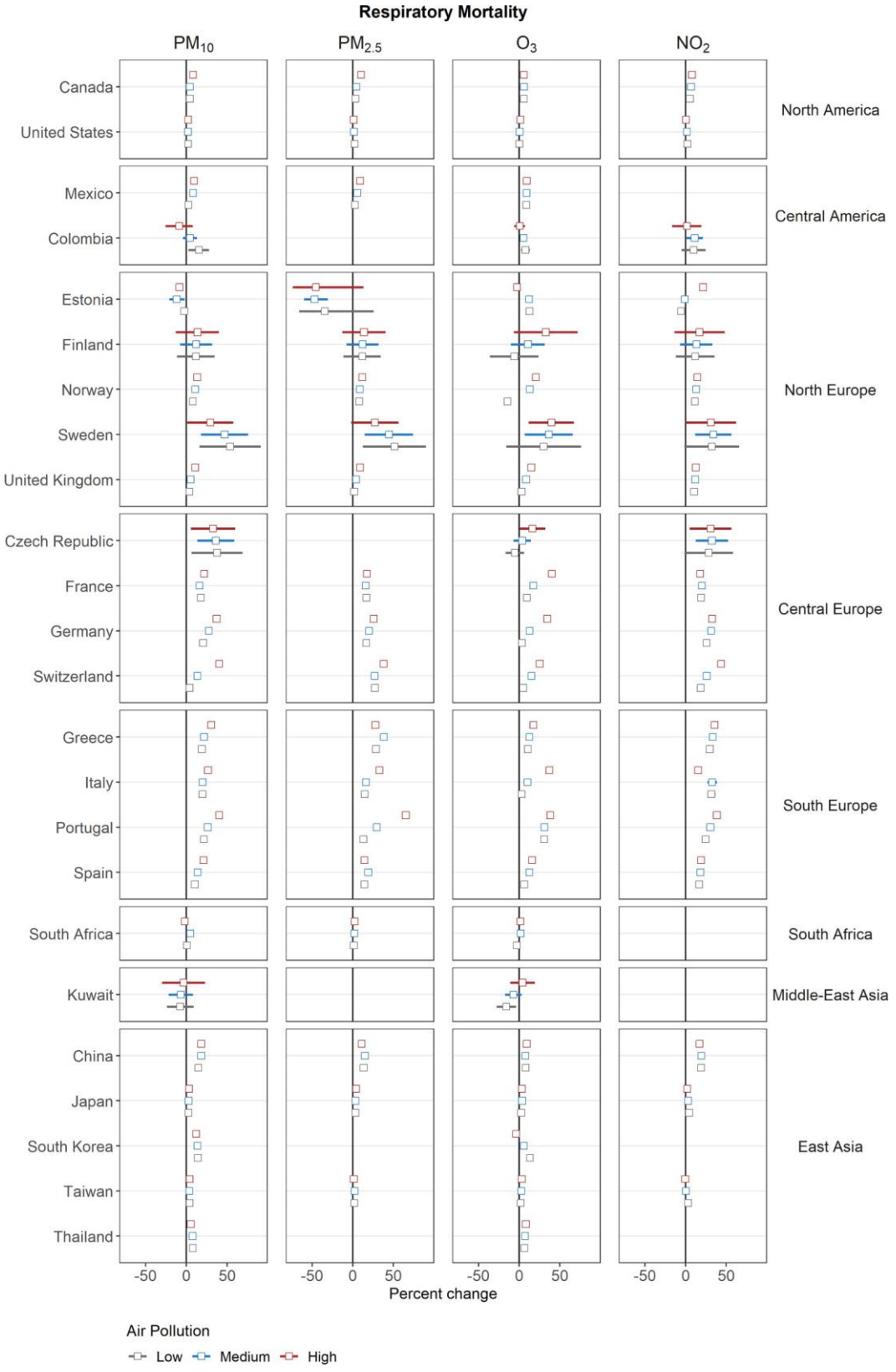

Fig. 4. Country-specific heat effects on respiratory mortality stratified by air pollutant levels. Estimates are presented as the percent change respiratory mortality with the corresponding 95% confidence intervals per an increase in the 2-day mean temperature from the 75th to the 99th percentile of the location-specific temperature distribution by low, medium, and high levels of air pollutants represented by the 5th, 50th, and 95th percentile of city-specific respective pollutant distribution. [Country-specific estimates were obtained using a multivariate multilevel *meta*-analysis of the location-specific estimates. Estimates to the figure with **P-values** are included in Supplementary Material section S6].

with cardiovascular effects (Schneider et al., 2017). It has often been noted that people with pre-existing chronic obstructive pulmonary disease [COPD] are most affected during unfavorable high ambient temperatures (Konstantinoudis et al., 2022; Zhao et al., 2019). During an (extreme) heat event, subjects with COPD may hyperventilate, which increases the possibility of dynamic hyperinflation. This, in turn, leads to dyspnea and mechanical and cardiovascular effects. Additionally, changes in blood towards a more coagulant state and other vascular changes may activate the complement system and thus trigger the respiratory distress syndrome resulting in various respiratory outcomes (Schneider et al., 2017; Michelozzi et al., 2009).

High temperatures and air pollutants might cause synergistic effects through various pathways. The first pathway includes the increase in the overall concentration of air pollutants during heat waves (Doherty et al., 2017; Horton et al., 2014); for example, the photochemical reactions during hot days, which correspond to high solar irradiance and high temperature, facilitate the formation of ground-level O_3 in the atmosphere. O_3 has been directly associated with respiratory outcomes like airway irritation and inflammation and decrements in pulmonary function (Schelegle et al., 2009). In addition, the exposure to air pollutants increases during warm months, when people spend more time outdoors, indicating better exposure assessment (Turner et al., 2012). The second pathway includes increased intake of air pollutants into the airways due to the activated thermoregulatory mechanisms, such as the increase in ventilation rate (Gordon, 2003). Another possible mechanism includes the reduced ability of the body to detoxify chemicals as a result of increased thermoregulatory responses to heat stress (Gordon, 2003). Air pollutants like PM may share common cellular pathways with high temperatures, like increased levels of markers of systemic inflammation such as C-reactive protein, which then could enhance the effects on various cardiopulmonary outcomes. Similarly, NO_2 has been known to damage the lung cells directly (Institute, 1991).

A major strength of this study is the extensive dataset and the standardized analytical approach for cities across different countries and regions, which provides evidence with considerable statistical power and allows comparison of the findings across countries and diverse climatic regions. Additionally, this is the first study to provide such extensive evidence on the effect of temperature on cause-specific CVD and RD mortality, as well as the interactive effect with various air pollutants, including $PM_{2.5}$ and NO_2, for which the evidence so far has been scarce.

We acknowledge several limitations of the study. First, our study has insufficient coverage of specific parts of the world, namely Africa, Latin America, Australia, and parts of Asia. Furthermore, our findings should be interpreted as the pooled estimates of the locations (primarily cities) within each country; thus, our estimates mainly represent the urban population and not necessarily the countries as a whole. Moreover, we only used fixed monitoring stations for temperature and ambient air pollution exposures; thus, exposure assessment error was inevitable. However, this non-differential misclassification should bias the effect estimates towards the null (Breitner et al., 2014). Although our study estimates the interactive effects of heat and air pollution on cause-specific mortality, further investigations are required to understand the possible underlying mechanisms. Furthermore, individual-level confounding or effect modifying variables could not be incorporated in this study.

In conclusion, this large-scale multi-country study observed considerable effects of heat on cardiovascular and respiratory disease mortality. We further observed effect modification by various ambient air pollutants (PM_{10}, $PM_{2.5}$, O_3, and NO_2). The interactive heat effect was higher for respiratory than cardiovascular mortality. With both temperature and air pollution concentrations foreseen to increase considering climate change, a higher health burden is to be expected in the future due to the interactive nature of these two environmental risk factors. Most locations included in the study have pollutant concentrations well above the WHO Air Quality Guidelines (AQG), which recommends limiting annual PM_{10}, $PM_{2.5}$, and NO_2 concentrations to 15, 5, and 10 μg/m^3 (World Health O, 2021 2021.), respectively, and the peak season mean 8-hour O_3 concentration to 60 μg/m^3. Therefore, targeted adaptation and mitigation measures (following the new WHO AQG) are crucial to enhance resilience and sustainable development in alignment with climate change policies.

CRediT authorship contribution statement

Conceptualization: MR, SB, AS, MS. Data curation: MR. Formal analysis: MR, Funding acquisition: AS. Investigation: MR,SB. Methodology: MR,SB, MS. Project administration: SB, MR. Resources: SB, AS. Software: MR. Supervsion: SB, Validation: SB. Visualization: MR. Writing-original draft: MR. Writing-review and editing: all co-authors.

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.

Data availability

The authors do not have permission to share data.

Acknowledgements

Masna Rai, Massimo Stafoggia, Francesca K. de' Donato, Sofia Zafeiratou, Liliana Vazquez Fernandez, Siqi Zhang, Klea Katsouyanni, Evangelia Samoli, Shilpa Rao, Antonio Gasparrini, Pierre Masselot, and Alexandra Schneider were supported by the European Union's Horizon 2020 Project Exhaustion (Grant ID: 820655). Joana Madureira was supported by the Fundaça˜o para a Ci^encia e a Tecnologia (FCT) (Grant SFRH/BPD/115112/2016).

Role of the funding source

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

Author Contribution

SB, AS, FD, and MS designed the study and developed the statistical methods. MR performed the statistical analysis for the MCC dataset and Germany MR. MS, SZ, and LV performed the analysis for Italy, Greece, and Norway, respectively. SB verified the analysis. MR coordinated the work and took the lead in drafting the manuscript and interpreting the results. SB, AS, FD and MS provided substantial scientific input in interpreting the results and drafting the manuscript. All other authors provided data and reviewed the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.107825.

References

WHO. Air Pollution 2021 [Available from: https://www.who.int/health-topics/air-pollution#tab=tab_1.

Analitis A MP, b Daniela D'Ippoliti,b Francesca de'Donato,b Bettina Menne,c, Franziska Matthies cRWA, d Carmen In˜iguez,e,f,g Xavier Basagan˜a,f,h,i Alexandra Schneider, Agn`es Lefranc,k Anna Paldy,l Luigi Bisanti,m and Klea Katsouyannia. Effects of Heat Waves on Mortality Effect Modification and Confounding by Air Pollutants. Epidemiology. 2014;25:15-22.

Anenberg, S.C., Haines, S., Wang, E., Nassikas, N., Kinney, P.L., 2020. Synergistic health effects of air pollution, temperature, and pollen exposure: a systematic review of epidemiological evidence. Environ Health. 19 (1), 130.

Bai, L., Li, Q., Wang, J., Lavigne, E., Gasparrini, A., Copes, R., et al., 2016. Hospitalizations from Hypertensive Diseases, Diabetes, and Arrhythmia in Relation to Low and High Temperatures: Population-Based Study. Sci. Rep. 6, 30283.
Bai, L., Li, Q., Wang, J., Lavigne, E., Gasparrini, A., Copes, R., et al., 2018. Increased coronary heart disease and stroke hospitalisations from ambient temperatures in Ontario. Heart 104 (8), 673–679.
Bowe, B., Xie, Y., Yan, Y., Al-Aly, Z., 2019. Burden of Cause-Specific Mortality Associated With PM2.5 Air Pollution in the United States. JAMA Netw Open. 2 (11), e1915834.
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. 485–486, 49–61.
Breitner, S., Wolf, K., Peters, A., Schneider, A., 2014. Short-term effects of air temperature on cause-specific cardiovascular mortality in Bavaria. Germany. Heart. 100 (16), 1272–1280.
Burkart, K., Canario, P., Breitner, S., Schneider, A., Scherber, K., Andrade, H., et al., 2013. Interactive short-term effects of equivalent temperature and air pollution on human mortality in Berlin and Lisbon. Environ. Pollut. 183, 54–63.
Chen, K., Bi, J., Chen, J., Chen, X., Huang, L., Zhou, L., 2015. Influence of heat wave definitions to the added effect of heat waves on daily mortality in Nanjing China. Sci. Total Environ. 506–507, 18–25.
Chen, F., Fan, Z., Qiao, Z., Cui, Y., Zhang, M., Zhao, X., et al., 2017. Does temperature modify the effect of PM10 on mortality? A systematic review and meta-analysis. Environ. Pollut. 224, 326–335.
D K. World Climate Regions 2020 [Available from: https://storymaps.arcgis.com/stories/61a5d4e9494f46c2b520a984b2398f3b.
Doherty, R.M., Heal, M.R., O'Connor, F.M., 2017. Climate change impacts on human health over Europe through its effect on air quality. Environ. Health. 16 (Suppl 1), 118.
EXHAUSTION. EXHAUSTION 2021 [Available from: https://www.exhaustion.eu/.
Gasparrini, A., Armstrong, B., 2011. The impact of heat waves on mortality. Epidemiology 22 (1), 68–73.
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 (1), 56–61.
Gordon, C.J., 2003. Role of environmental stress in the physiological response to chemical toxicants. Environ. Res. 92 (1), 1–7.
WHO. Heatwaves 2023 [Available from: https://www.who.int/health-topics/heatwaves#tab=tab_1.
Horton, D.E., Skinner, C.B., Singh, D., Diffenbaugh, N.S., 2014. Occurrence and persistence of future atmospheric stagnation events. Nat. Clim Chang. 4, 698–703.
Institute HE. Mechanisms of Nitrogen Dioxide Toxicity in Humans. 1991.
IPCC. Climate Change 2021: The Physical Science Basis.; 2021.
Jhun, I., Fann, N., Zanobetti, A., Hubbell, B., 2014. Effect modification of ozone-related mortality risks by temperature in 97 US cities. Environ. Int. 73, 128–134.
Kioumourtzoglou, M.A., Schwartz, J., James, P., Dominici, F., Zanobetti, A., 2016. PM2.5 and Mortality in 207 US Cities: Modification by Temperature and City Characteristics. Epidemiology 27 (2), 221–227.
Konstantinoudis, G., Minelli, C., Vicedo-Cabrera, A.M., Ballester, J., Gasparrini, A., Blangiardo, M., 2022. Ambient heat exposure and COPD hospitalisations in England: a nationwide case-crossover study during 2007–2018. Thorax 77 (11), 1098–1104.
Li, G., Jiang, L., Zhang, Y., Cai, Y., Pan, X., Zhou, M., 2014. The impact of ambient particle pollution during extreme-temperature days in Guangzhou City China. Asia Pac J Public Health. 26 (6), 614–621.
Li, J., Woodward, A., Hou, X.Y., Zhu, T., Zhang, J., Brown, H., et al., 2017. Modification of the effects of air pollutants on mortality by temperature: A systematic review and meta-analysis. Sci. Total Environ. 575, 1556–1570.
Liu, C., Chen, R., Sera, F., Vicedo-Cabrera, A.M., Guo, Y., Tong, S., et al., 2019. Ambient Particulate Air Pollution and Daily Mortality in 652 Cities. N Engl J Med. 381 (8), 705–715.
Loxham, M., Davies, D.E., Holgate, S.T., 2019. The health effects of fine particulate air pollution. BMJ 367, l6609.
Michelozzi, P., Accetta, G., De Sario, M., D'Ippoliti, D., Marino, C., Baccini, M., et al., 2009. High temperature and hospitalizations for cardiovascular and respiratory causes in 12 European cities. Am. J. Respir. Crit. Care Med. 179 (5), 383–389.
Pascal, M., Wagner, V., Alari, A., Corso, M., Le Tertre, A., 2021. Extreme heat and acute air pollution episodes: A need for joint public health warnings? Atmos. Environ. 249, 118249.
R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing Vienna, Austria2017 [Available from: http://www.R-project.org/.
Ren, C., Williams, G.M., Tong, S., 2006. Does Particulate Matter Modify the Association between Temperature and Cardiorespiratory Diseases? Environ. Health Perspect. 114 (11), 1690–1696.
Ren, C., Williams, G.M., Morawska, L., Mengersen, K., Tong, S., 2008. Ozone modifies associations between temperature and cardiovascular mortality: analysis of the NMMAPS data. Occup. Environ. Med. 65 (4), 255–260.
Roye, D., Sera, F., Tobias, A., Lowe, R., Gasparrini, A., Pascal, M., et al., 2021. Effects of hot nights on mortality in Southern Europe. Epidemiology.
Schelegle, E.S., Morales, C.A., Walby, W.F., Marion, S., Allen, R.P., 2009. 6.6-hour inhalation of ozone concentrations from 60 to 87 parts per billion in healthy humans. Am. J. Respir. Crit. Care Med. 180 (3), 265–272.
Schneider, A., Ruckerl, R., Breitner, S., Wolf, K., Peters, A., 2017. Thermal Control, Weather, and Aging. Curr. Environ. Health Rep. 4 (1), 21–29.
Scortichini, M., De Sario, M., de'Donato, F.K., Davoli, M., Michelozzi, P., Stafoggia, M., 2018. Short-Term Effects of Heat on Mortality and Effect Modification by Air Pollution in 25 Italian Cities. Int. J. Environ. Res. Public Health. 15 (8).
Sera, F., Armstrong, B., Blangiardo, M., Gasparrini, A., 2019. An extended mixed-effects framework for meta-analysis. Stat Med. 38 (29), 5429–5444.
Stafoggia M, Schwartz J, Forastiere F, Perucci CA, Group S. Does temperature modify the association between air pollution and mortality? A multicity case-crossover analysis in Italy. Am J Epidemiol. 2008;167(12):1476-85.
Stafoggia, M., Forastiere, F., Faustini, A., Biggeri, A., Bisanti, L., Cadum, E., et al., 2010. Susceptibility factors to ozone-related mortality: a population-based case-crossover analysis. Am. J. Respir. Crit. Care Med. 182 (3), 376–384.
Sun, S., Cao, W., Mason, T.G., Ran, J., Qiu, H., Li, J., et al., 2019. Increased susceptibility to heat for respiratory hospitalizations in Hong Kong. Sci. Total Environ. 666, 197–204.
Turner, L.R., Barnett, A.G., Connell, D., Tong, S., 2012. Ambient temperature and cardiorespiratory morbidity: a systematic review and meta-analysis. Epidemiology 23 (4), 594–606.
WHO. Coronavirus disease (COVID-19) 2023 [Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
Williams, S., Venugopal, K., Nitschke, M., Nairn, J., Fawcett, R., Beattie, C., et al., 2018. Regional morbidity and mortality during heatwaves in South Australia. Int. J. Biometeorol. 62 (10), 1911–1926.
World Health O. WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. Geneva: World Health Organization; 2021 2021.
Zanobetti, A., Schwartz, J., 2008. Temperature and Mortality in Nine US Cities. Epidemiology 19 (4), 563–570.
Zhao, Q., Li, S., Coelho, M., Saldiva, P.H.N., Xu, R., Huxley, R.R., et al., 2019. Ambient heat and hospitalisation for COPD in Brazil: a nationwide case-crossover study. Thorax 74 (11), 1031–1036.

2. Publication: Temporal Variation in the Association between Temperature and Cause-Specific Mortality in 15 German cities

Title:	Temporal Variation in the Association between Temperature and Cause-Specific Mortality in 15 German cities
Authors:	**Masna Rai**, Susanne Breitner, Siqi Zhang, Veronika Huber, Annette Peters, Alexandra Schneider
Journal:	*Environmental Research*
Year:	2023
Volume:	229:115668
DOI:	10.1016/j.envres.2023.115668
Supplements:	https://doi.org/10.1016/j.envres.2023.115668 (available online)
Impact factor:	8.43 (Journal Citations Reports® 2022)
Rank:	37/279 in Category Environmental Sciences Journals (Journal Citations Reports® 2022)
Rights declaration:	This is a subscription article and the author had rights to include it in the thesis or dissertation copies. The further reuse of this content requires Elsevier permission via Copyright Clearance Center's RightsLink.

Environmental Research 229 (2023) 115668

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Temporal variation in the association between temperature and cause-specific mortality in 15 German cities

Masna Rai [a,b,*], Susanne Breitner [a,b], Veronika Huber [a], Siqi Zhang [a], Annette Peters [a,b,c], Alexandra Schneider [a]

[a] Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany
[b] Institute for Medical Information Processing, Biometry, and Epidemiology –IBE, Pettenkofer School of Public Health LMU Munich, Munich, Germany
[c] German Research Center for Cardiovascular Research (DZHK), Partner-Site Munich, Munich, Germany

ARTICLE INFO

Handling Editor: Jose L Domingo

Keywords:
Temporal variation
Temperature
Cardiovascular mortality
Respiratory mortality
Cause-specific mortality
Germany

ABSTRACT

Background: There is limited evidence of temporal changes in the association between air temperature and the risk of cause-specific cardiovascular [CVD] and respiratory [RD] mortality.

Method: We explored temporal variations in the association between short-term exposures to air temperature and non-accidental and cause-specific CVD and RD mortality in the 15 largest German cities over 24 years (1993–2016) using time-stratified time series analysis. We applied location-specific confounder-adjusted Poisson regression with distributed lag non-linear models with a lag period of 14 days to estimate the temper- ature–mortality associations. We then pooled the estimates by a multivariate meta-analytical model. We analysed the whole study period and the periods 1993–2004 and 2005–16, separately. We also carried out age- and sex-stratified analysis. Cold and heat effects are reported as relative risk [RR] at the 1st and the 99th temperature percentile, relative to the 25th and the 75th percentile, respectively.

Result: We analysed a total of 3,159,292 non-accidental, 1,063,198 CVD and 183,027 RD deaths. Cold-related RR for CVD mortality was seen to rise consistently over time from 1.04 (95% confidence interval [95% CI] 1.02, 1.06) in the period 1993–2004 to 1.10 (95% CI 1.09, 1.11) in the period 2005–16. A similar increase in cold-related RR was also observed for RD mortality with risk increasing from 0.99 (95% CI 0.96, 1.03) to 1.07 (95% CI 1.03, 1.10). Cold-related ischemic, cerebrovascular, and heart failure mortality risk were seen to be increasing over time. Similarly, COPD, the commonly speculated driver of heat-related RD mortality was found to have a constant heat-related risk over time. Males were increasingly vulnerable to cold with time for all causes of death. Females showed increasing sensitivity to cold for CVD mortality. Our results indicated a significant increased cold and heat vulnerability of the youngest age-groups (<64) to non-accidental and RD mortality, respectively. Similarly, the older age group (>65) were found to have significantly increased susceptibility to cold for CVD mortality.

Conclusion: We found evidence of rising population susceptibility to both heat- and cold-related CVD and RD mortality risk from 1993 to 2016. Climate change mitigation and targeted adaptation strategies might help to reduce the number of temperature-related deaths in the future.

1. Introduction

Cardiovascular [CVD] and respiratory [RD] diseases were listed as the top causes of Disability Adjusted Life-Years in the latest Global Burden of Diseases study (Vos et al., 2020). In particular, ischemic heart disease, stroke, and Chronic Obstructive Pulmonary Disease [COPD] were among the top six causes (Vos et al., 2020). Several studies have found CVD outcomes to be influenced by ambient temperature (Bai et al., 2016, 2018; Basu, 2009; Breitner et al., 2014; Chen et al., 2018; Liu et al., 2011; Ponjoan et al., 2017; Yang et al., 2015; Yin and Wang, 2017; Zhai et al., 2020; Irmela Schlegel et al., 2020; Turner et al., 2012). Although limited, evidence on the association between temperature and RD outcomes also shows increased risks attributable to non-optimal temperature, especially heat (Basu, 2009; Chen et al., 2018; Liu et al.,

* Corresponding author. Institute of Epidemiology, Helmholtz Zentrum München-German Research Center for Environmental Health, Ingolst¨adter Landstraße 1, D-85764, Neuherberg, Germany.
E-mail address: masna.rai@campus.lmu.de (M. Rai).

https://doi.org/10.1016/j.envres.2023.115668
Received 7 November 2022; Received in revised form 27 February 2023; Accepted 9 March 2023
Available online 22 March 2023
0013-9351/

2011; Irmela Schlegel et al., 2020; Turner et al., 2012; Michelozzi et al., 2009). To sum up, CVD and RD outcomes are among the most temperature-sensitive outcomes, projected to increase even further due to climate change (Zhang et al., 2018; Rodrigues et al., 2020).

Studies projecting future health burden under climate change are mainly based on the present-day exposure-response relationship between temperature and different health outcomes (Huang et al., 2011). Therefore, a systematic in-depth understanding of the present-day association between temperature and health outcomes, as well as changes in these associations over time is crucial for effective and valid projection of future health burden (Gasparrini et al., 2015a; Chung et al., 2017) and efficient planning of adaptation strategies. To date, several single-city (Yang et al., 2015; Carson et al., 2006, Astro¨m et al., 2017; Ekamper et al., 2009; Petkova et al., 2014; Oudin Astrom et al., 2018; Chen et al., 2019; Astrom et al., 2013) as well as multi-city (Bobb et al., 2014; Coates et al., 2014; Davis et al., 2003; Guo et al., 2012; Barnett, 2007; Chung et al., 2018) and multi-country (Gasparrini et al., 2015a; Chung et al., 2017) studies have explored temporal trends of the temperature-mortality association. These studies present differing evidence of either physiological adaptation or sensitivity of the population over time, varying largely across geographical locations and climatic conditions (Gasparrini et al., 2015a; Chung et al., 2017) or even mortality causes (Chen et al., 2019). In Europe, a previous global study on temporal variation, has shown population adaptation to heat in locations from Spain. In contrast, there was no change in the temperature-mortality association in locations across the UK (Gasparrini et al., 2015a). A similar study carried out in Augsburg, Germany showed increasing population sensitivity to both heat and cold over time for myocardial infarction [MI] as a specific CVD outcome (Chen et al., 2019). The varying evidence infers that the trends of the temperature-mortality relationship are rather complex. Therefore, a systematic investigation of location- and cause-specific temperature-mortality associations over time is essential.

The majority of the studies on temporal variations have focused on total or non-accidental mortality (Gasparrini et al., 2015a, Astro¨m et al., 2017; Ekamper et al., 2009; Petkova et al., 2014; Astrom et al., 2013; Bobb et al., 2014; Coates et al., 2014; Davis et al., 2003; Guo et al., 2012; Barnett, 2007; Chung et al., 2018), and most of these studies only considered heat-related mortality (Petkova et al., 2014; Bobb et al., 2014; Coates et al., 2014; Davis et al., 2003; Guo et al., 2012). Thus, limited evidence exists on the temporal variation of both heat- and cold-related temperature-mortality associations (Yang et al., 2015; Gasparrini et al., 2015a, Astro¨m et al., 2017; Astrom et al., 2013; Barnett, 2007; Chung et al., 2018). In addition, the changes in the association between temperature and the two most climate-sensitive mortality outcomes - CVD and RD mortality - over time have not been investigated widely (Yang et al., 2015; Chung et al., 2017; Carson et al., 2006; Chen et al., 2019; Barnett, 2007). Furthermore, the variation in these cause-specific temperature-mortality associations across different age and sex groups has not been extensively studied.

Therefore, with the growing threat of climate change, it is of prime importance to extensively study the temperature-mortality association for total or non-accidental as well as cause-specific CVD and RD outcomes, also tracing the vulnerable population sub-groups. Thus, this study aims to address these gaps by exploring the temporal trends in the association between both heat and cold on cause-specific CVD and RD mortality and the effect modification by age and sex in the 15 largest German cities.

2. Methods

2.1. Data sources

We conducted this study in the 15 largest German cities (>500,000 inhabitants): Berlin, Bremen, Cologne, Dortmund, Dresden, Duisburg, Dusseldorf, Essen, Frankfurt, Hamburg, Hanover region, Leipzig, Munich, Nuremberg, and Stuttgart, spreading across the entire country (Fig. S1). These cities represent around 17.4% of the total 2019 German population and both of the two climatic regions of Germany. The coastal cities Hamburg and Bremen have a marine climate, while the other 13 cities lie in a temperate zone. Further city-specific information is included in the Supplementary material (Table S1).

We obtained daily death counts of cause-specific mortality for the 15 cities from the Research Data Centre of the Federal Statistical Office and the Statistical Offices of the Federal States (Forschungsdatenzentren der Statistischen Ämter des Bundes und der L¨ander) for the period January 1, 1993 to December 31, 2016. For the Hannover region, death counts were available only from January 1, 1995 to December 31, 2016. International Classification of Diseases 9th Revision [ICD-9] codes for the period 1993–1997 and International Statistical Classification of Diseases and Related Health Problems 10th Revision [ICD-10] codes for the period 1998–2016 were used for classifying the causes of death. We obtained daily death counts for non-accidental mortality (ICD-9:1-79/ICD-10: A00-R99), CVD mortality (ICD-9:390-459/ICD-10: I00–I99), and RD mortality (ICD-9:460-519/ICD-10: J00-J99) stratified according to sex and age. In addition, we also obtained daily counts of mortality due to ischemic heart disease (ICD-9:410-414/ICD-10:I00–I25) including MI (ICD-9:410/ICD-10:I21 and chronic ischemic heart disease (ICD-9:414/ICD-10: I25), cerebrovascular disease (ICD-9:430-438/ICD-10:I60–I69), heart failure (ICD-9:428/ICD-10: I50), and COPD (ICD-9:490-492/ICD-10:J40-J44, J47). The study was approved by the Research Data Centre of the Federal Statistical Office and the Statistical Offices of the Federal States and fulfilled all requirements according to the German Federal Data Protection Act. No other ethics approval was necessary or required in Germany for this type of study using already existing, anonymized and de-identified data on daily death counts from official agencies.

Meteorological data were obtained as daily average temperature from the Climate Data Centre of the German National Meteorological Service (Deutscher Wetterdienst). For cities with several weather stations, stations with the most complete data throughout the study period were chosen. Details on the weather stations and handling of missing observations are included in Table S2.

2.2. Statistical analysis

We applied a time-stratified time-series analysis to study the association between temperature and cause-specific mortality in each location. We stratified the overall study period into two sub-periods: 1993–2004 and 2005–16. For the twoperiods, quasi-Poisson regressions with distributed lag nonlinear models extending the lag period to 14 days were used to establish the location-specific exposure-response functions [ERFs]. The lag period was chosen to efficiently capture both heat and cold effects. The regressions also included an indicator for the day of the week and a penalized spline of the day of the study with four degrees of freedom [df] per calendar year to control the seasonal and long-term trends. For the ERFs, we used natural cubic splines with three internal knots placed at the 10th, 75th, and 90th percentiles of the location-specific mean temperature. The lag-response curves for tem- perature were modelled with a natural cubic spline with three knots placed at equally spaced values on the log scale. The location-specific associations were then reduced to overall temperature-mortality asso- ciations by cumulating the risk over the lag period. The location-specific overall cumulative ERFs were then pooled using a multivariate meta- analytical model to derive the overall temperature-mortality associa- tion in the 15 cities. This approach has been previously described (Gasparrini, 2011a; Gasparrini and Armstrong, 2011) and applied by a large international study (Gasparrini et al., 2015b). We report the cold effect as the relative risk [RR] at the 1st temperature percentile relative to the 25th and the heat effect as the RR at the 75th temperature percentile relative to the 99th percentile of the temperature distribution of the overall period: 1990–2016, for obtaining comparable estimates.

We furthermore carried out stratified analyses to investigate the temporal variations in modifications of the temperature effects by age (0–64, 65–74, and 75+) and sex on three primary mortality outcomes: non-accidental, CVD, and RD mortality.

2.2.1. Sensitivity analyses

In order to check the robustness of the main findings, we performed sensitivity analyses by changing the df (three and seven per year) for the trend spline to control for seasonal and long-term effects. Furthermore, to check the robustness of our effect estimates, we report the cold effect as the RR at the 2.5th temperature percentile relative to the Minimum Mortality Temperature [MMT] and the heat effect as the RR at the 97.5th percentile relative to the MMT, as reported by previous studies (Chen et al., 2019). We also explored the cause-specific ERFs excluding the heat wave years 2003 and 2015.

All analyses were performed using R project (version 4.0.3) (R Core Team. R, 2017) for statistical computing using the "dlnm (Gasparrini, 2011b)" and "mgcv (Wood, 2011)" packages.

3. Results

3.1. Descriptive

Table 1 shows the descriptive statistics for cause-specific as well as age- and sex-stratified mortality. The analysis included 3,159,292 non-accidental deaths, of which 54.7% were females, 18.5% were 0–64 years, and 19.2% were 65–74 years. We analysed a total of 1,063,198 CVD and 183,027 RD deaths. When comparing the deaths during the two periods, the proportion of both CVD (27.9%–39.7%) and RD (3.9%–7.8%) deaths increased in 2005–16 compared to 1993–2004. The mortality share of the younger age group (0–64 years) decreased, while that of the older age group (75+ years) increased during the later period, for all causes of mortality.

Table 2 includes the descriptive statistics for temperature. The daily average temperature overall, in summer, and in winter in the 15 German cities during 2005–16 rose by 0.3 °C, as compared to 1993–2004. City-specific descriptive statistics for temperature are included in Table S3.

Table 1
Summary statistics of mortality in the 15 German cities from 1993 to 2016.

	1993–2004	2005–2016
(A) Non-accidental mortality	1,630,443	1,528,849
Characteristics		
Male (%)	44.2	46.4
Female (%)	55.8	53.6
0–64 years (%)	20.6	16.2
65–74 years (%)	19.2	19.2
75+ years (%)	60.2	64.5
(B) Cardiovascular mortality	456,320	606,878
(% of non-accidental mortality)	(27.9)	(39.7)
Characteristics		
Male (%)	39.8	41.5
Female (%)	60.2	58.5
0–64 years (%)	12.7	8.7
65–74 years (%)	15.8	13.9
75+ years (%)	71.5	77.3
Ischemic heart disease	206,997	292,602
Myocardial Infarction	61,738	91,176
Chronic Ischemic heart disease	106,193	127,321
Cerebrovascular disease	73,811	97,413
Heart failure	64,002	83,016
(C) Respiratory mortality	64,005	119,022
(% of non-accidental mortality)	(3.9)	(7.8)
Characteristics		
Male (%)	47.1	49.6
Female (%)	52.9	50.4
0–64 years (%)	12.9	10.3
65–74 years (%)	18.9	19.4
75+ years (%)	68.2	70.3
COPD	27,135	55,478

Table 2
Summary statistics of daily average temperature (°C) in 15 German cities from 1993 to 2016.

	1993–2004	2005–2016
Mean (SD)	10.2 (7.3)	10.4 (7.2)
Minimum	−16.9	−17.5
1st percentile	−6.2	−5.8
2.5th percentile	−3.9	−3.6
25th percentile	4.7	5.1
75th percentile	15.7	16.1
97.5th percentile	23.4	23.3
99th percentile	25.0	25.1
Maximum	31.0	30.6
Summer (April–September)		
Mean (SD)	15.5 (4.9)	15.8 (4.7)
Minimum	−2.1	−1.1
Winter (October–March)		
Mean (SD)	4.8 (5.1)	5.1 (5.1)
Maximum	5.1	5.1

3.2. Overall results

During both periods, both cold and heat were associated with all death causes (Table 3 and Fig. 1). When comparing heat- and cold-related effects, the heat effects were seen to be stronger for all causes of death examined (Table 3 and Fig. 1). The temperature-mortality associations showed a consistent increasing cold effect on both CVD and RD mortality over time, with significant differences observed between the two periods (Table 3 and Fig. 2). Cold effect (RR at the 1st vs. 25th temperature percentile) on CVD mortality during 2005–16 was observed to be 1.10 (95% confidence interval [95% CI] 1.09, 1.11); the effect significantly higher than that during 1990–2004: 1.04 (95% CI: 1.02, 1.06). Moreover, the temporal analyses also showed strong evidence of increasing cold effects on cause-specific CVD mortality, including deaths due to ischemic heart, cerebrovascular diseases, and heart failure. No temporal changes in the cold effect were observed for non-accidental mortality. Similarly, we found increasing, although not significant, heat effects during 2005–16 compared to 1993–2004 for most death causes (Table 3 and Fig. 2).

The age- and sex-stratified analyses showed stronger effects of cold on non-accidental, CVD, and RD mortality in males and the age group 65–74 from 2005–16 as compared to 1993–2004. In addition, females and people aged 65 and above were seen to have significantly higher cold effect for CVD mortality during the later period (Fig. 2 and Table S4). The youngest age group (0–64) were found to have increasing susceptibility to cold for non-accidental mortality. In contrast, the trends in the heat effect showed irregular trends. A significant rise in the heat-related RR was observed for RD mortality, particularly the younger age groups <75 years (Fig. 2 and Table S4). The sex- and age-stratified ERFs have been included in the Supplement Figs. S2 and S3.

3.3. City-specific results

We observed large differences in mortality trends across the cities, especially for CVD and RD mortality. For non-accidental mortality, most cities showed no changes in the temperature-mortality association. Some cities like Hamburg and Leipzig showed slight adaptation to cold. In contrast, cities like Düsseldorf and Frankfurt showed adaptation to heat (Fig. S4). For CVD mortality, most cities showed either no changes in the heat-mortality association or adaptation to heat, but mainly an increase in cold sensitivity over time. Increasing sensitivity to cold was observed in cities like Berlin, Cologne, Dortmund, Dresden, and Frankfurt (Fig. S5). Furthermore, large regional differences were observed for RD mortality. Cities like Cologne, Dresden, Duisburg, and Hamburg showed an increased risk of heat-related RD mortality over time. The cold-mortality association varied less over time (Fig. S6).

The results of the sensitivity analysis have been included in the

Table 3
Lag-cumulative RR estimates for daily cause-specific mortality (95% confidence interval) as cold effect [RR at 1st (—6.0 °C) percentile relative to 25th percentile (4.9 °C)] and heat effect [RR at 99th (25.1 °C) percentile relative to 75th (15.9 °C) percentile].

	Period	Cold effect		Heat effect	
		RR	P-value[a]	RR	P-value[a]
A. Non-accidental Mortality	1993–2004	1.08 (1.07, 1.09)	0.5	1.28 (1.23, 1.34)	0.39
	2005–2016	1.08 (1.07, 1.08)		1.29 (1.24, 1.33)	
B. Cardiovascular Mortality	1993–2004	1.04 (1.02, 1.06)	**<0.0001***	1.31 (1.22, 1.41)	0.63
	2005–2016	1.10 (1.09, 1.11)		1.29 (1.25, 1.33)	
B.1. Ischemic Mortality	1993–2004	1.01 (0.99, 1.04)	**<0.0001***	1.18 (1.09, 1.28)	0.06
	2005–2016	1.13 (1.11, 1.15)		1.27 (1.21, 1.34)	
B.1.1. Myocardial Infarction	1993–2004	1.13 (1.08, 1.18)	0.36	1.14 (1.02, 1.28)	0.16
	2005–2016	1.14 (1.12, 1.17)		1.16 (1.02, 1.31)	
B.1.2. Chronic Ischemic mortality	1993–2004	1.14 (1.10, 1.19)	0.83	1.20 (1.09, 1.32)	0.33
	2005–2016	1.11 (1.07, 1.15)		1.21 (1.10, 1.34)	
B.2. Cerebrovascular Mortality	1993–2004	0.89 (0.87, 0.91)	**<0.0001***	1.35 (1.18, 1.54)	0.67
	2005–2016	1.11 (1.09, 1.13)		1.37 (1.19, 1.59)	
B.3. Heart Failure	1993–2004	1.23 (1.19, 1.27)	**<0.0001***	1.41 (1.31, 1.78)	0.07
	2005–2016	1.07 (1.03, 1.11)		1.56 (1.39, 1.74)	
C. Respiratory Mortality	1993–2004	0.99 (0.96, 1.03)	**0.0007***	1.72 (1.51, 1.95)	0.21
	2005–2016	1.07 (1.03, 1.10)		1.77 (1.54, 2.02)	
C.1. COPD	1993–2004	1.08 (1.03, 1.12)	0.76	1.52 (1.30, 1.78)	0.55
	2005–2016	1.06 (1.03, 1.09)		1.50 (1.35, 1.66)	

[COPD= Chronic Obstructive Pulmonary Disease; a Significance test on temporal variation, based on difference between RR estimates in 1993–2004 and 2005–2016, *significant p-value].

supplementary file (Table S5, Figs. S7 and S8). In general, our results were robust to the sensitivity analysis. Temporal trends excluding the year 2003 showed similar trends of temporal variation but a lower risk than previously estimated for the first period (Fig. S7). Similarly, the exclusion of the year 2015 showed no difference in the patterns of risk variation (Fig. S8). We observed comparable magnitude and direction of the cold- and heat-effect estimates when applying the MMT as the reference for reporting (Table S5).

4. Discussion

We explored the temporal changes in heat- and cold-related cause-specific CVD and RD mortality in 15 large German cities, also considering effect modification by age and sex. Our results showed a consistent change in the cold effect over time for most death causes with significant increases in both CVD and RD mortality risk. Similarly, we found increasing effects of heat on most causes of death, with a noticeable increase in RD mortality. The sub-group analyses showed increased sensitivity of all death causes towards cold for males and the age group 65–74. Moreover, we found an increase in cold-related CVD mortality risk over time in females and the age group 75+. A significant rise in the heat-related mortality risk was observed for non-accidental and RD mortality for both males and the age group 0–64 years. We observed interesting patterns with cause-specific analysis. Although, CVD showed stable heat effects over the two periods, ischemic heart disease,cerebrovascular disease, and heart failure mortality were significantly increased in association with cold effects over time.. In contrast, a constant heat-related risk was observed for COPD mortality.

Our results on temporal changes in heat-related non-accidental mortality were in contrast to most existing evidence from single-city studies, which showed mostly a decreasing pattern of heat-related mortality risk over time (Carson et al., 2006, Astro¨m et al., 2017; Petkova et al., 2014; Oudin Astrom et al., 2018; Astrom et al., 2013; Bobb et al., 2014; Chung et al., 2018). However, our results were consistent with existing limited evidence from large multi-city (Davis et al., 2003) and multi-country (Gasparrini et al., 2015a) studies, which found trends in heat-related non-accidental mortality to vary across geographical locations, with increasing risk over time in some cities and countries (Gasparrini et al., 2015a; Davis et al., 2003). For CVD and RD mortality, we observed a constant and an increasing heat-related risk over time, respectively. The results for overall CVD mortality were consistent with a study in China, which also showed stable heat-related RR (Yang et al., 2015). Contrastingly, studies conducted in Northeast Asia (Chung et al., 2017) and the United Kingdom (Carson et al., 2006) showed a decreasing heat-related mortality risk for CVD and RD deaths over time. A study conducted in Bavaria, Germany, found an increase in the heat-related MI risk over time (Chen et al., 2019), which was in line with our results also showing an increase in heat-related ischemic heart disease mortality, including MI. We observed similar trends for heart failure.

The results of the 15 German cities for cold-related non-accidental mortality were in line with locations like Canada and Australia, where a stable cold-related RR was observed over time. Similar studies in Sweden showed either dispersed (Astrom et al., 2013) or consistent (Oudin Astrom et al., 2018) patterns in cold-attributable non-accidental mortality over the decades. Evidence on cold-related CVD mortality from a multi-city (Barnett, 2007) as well a multi-country (Chung et al., 2017) study has shown increasing sensitivity of CVD deaths towards cold. Similar to these findings, the results of our study also demonstrated a significant increase in the cold effect over time for CVD mortality. In contrast, several single-city studies have shown decreasing trends in cold-related CVD (Yang et al., 2015; Carson et al., 2006). Our study also found a significant increase in cold-related RR for RD mortality, which was in line with a study exploring this association for overall cardiorespiratory mortality (Chung et al., 2017) but contrasting to another single-city study which shows a decreasing trend (Carson et al., 2006).

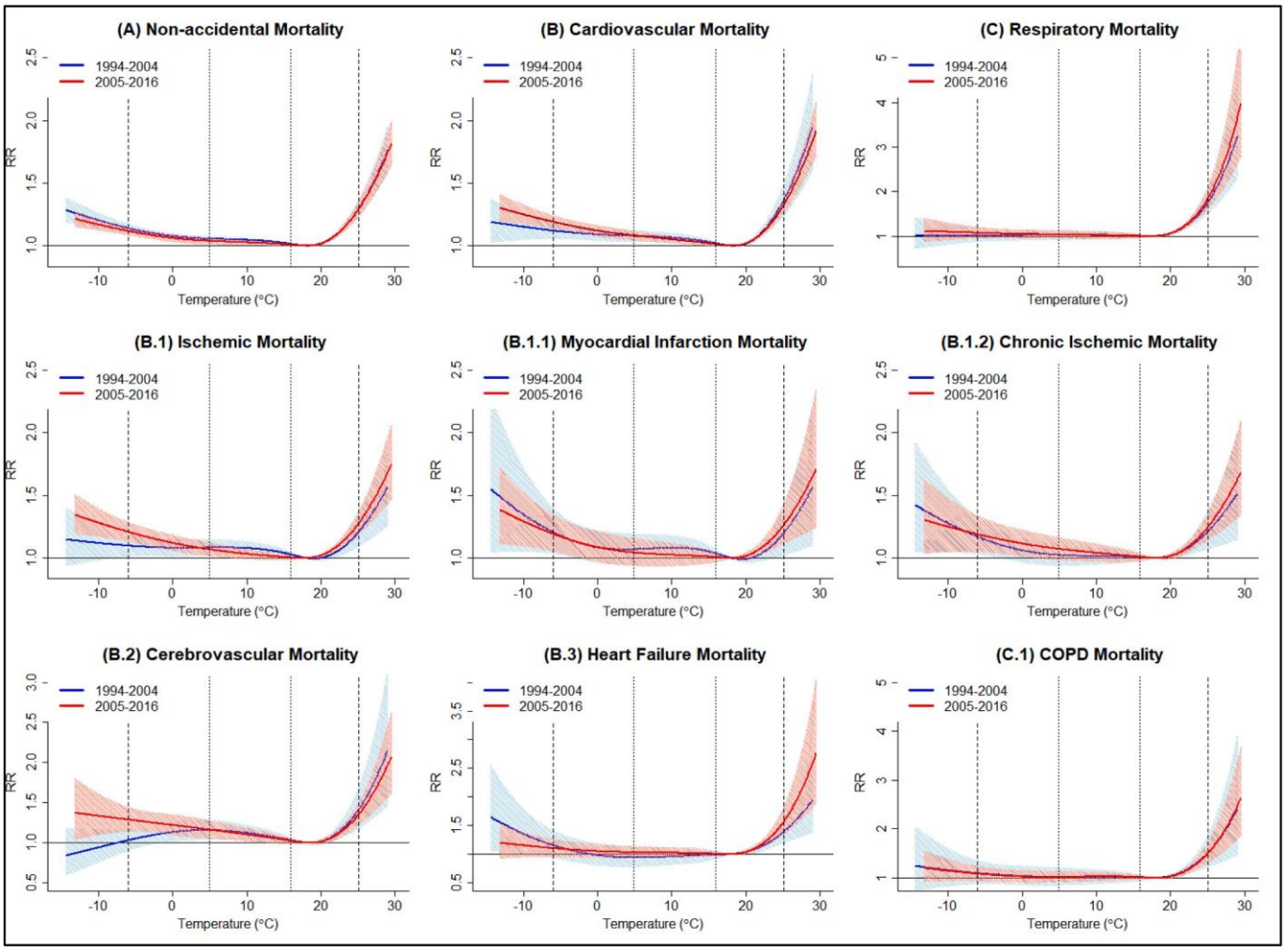

Fig. 1. Temporal variation in the lag-cumulative exposure–response relationships between air temperature and cause-specific mortality for 1993–2004 (blue) and 2004–2016 (red) with 95% confidence interval.

[Dotted lines represent the 25th(4.9 ◦C)and the 75th (15.9 ◦C) temperature percentiles; dashed lines represent the 1st (—6.0 ◦C) and the 99th (25.1 ◦C) temperature percentiles.

Several factors play a role in modifying the ERF between air temperature and health outcomes (Patz et al., 2000). Among them, improvements in infrastructures, such as housing and air conditioning, socioeconomic changes, and improved health care and services, might decrease the susceptibility to non-optimal temperature exposure. Furthermore, public health interventions that increase the awareness of the health risk associated with exposure to high temperatures might promote behavioural changes, leading to decreased heat-related mortaltiy (Ebi et al., 2006).

Our study's result show mostly an increasing trend for both cold- and heat-related mortality risk. This might infer that with a changing climate, increasing average temperatures, and the overall forward shift in the temperature distribution, the population might adapt to heat but also become more susceptible to cold. The results from our age-stratified analysis demonstrate increasing susceptibility of both the younger age group as well as the elderly to the effect of temperature. In addition, descriptive statistics also infer population aging. Therefore, the increase in population susceptibility as well the increase of susceptible population due to population aging might result in a "double -burden" of temperature related mortality in the future. Susceptibility to non-optimal temperature might be dominant during events of sharp and sudden temperature variability, anticipated to occur frequently in the future due to climate change. Similarly, the population in temperate regions like Germany, not used to prolonged extreme heat, might find it challenging to cope with the fast-changing climate, which explains the increasing heat-related mortality trend. Furthermore, many regions of the world still lack heat- and cold-adaptation actions plans and public health interventions, contributing to an overall increasing cold- and heat-related mortality burden.

Our findings have important implications for assessing the health impacts of climate change. Our results suggest that changes in the temperature-mortality associations over time can differ by cause of death, age, and sex. Furthermore, our study provides evidence that the population over time can follow both cold- and heat-sensitive pathways, rather than the commonly perceived heat-adaptation, thus, increasing the burden of both heat- and cold-related deaths in the future. The findings from our analysis, contrasting to those from other single-city studies, provide strong evidence that temperature-mortality relationships are not generalizable but rather specific to climatic regions, countries, and population composition. With these results, we urge stakeholders to consider the unique characteristics, susceptibilities, and vulnerabilities of the targeted population while designing adaptation policies. Furthermore, we also would like to draw the attention of public health professionals to design adaptation plans, considering also the younger population, who are commonly perceived to be less susceptible to temperature effects.

To our knowledge, this is the first study to extensively explore the temporal variation in temperature-mortality association for cause-

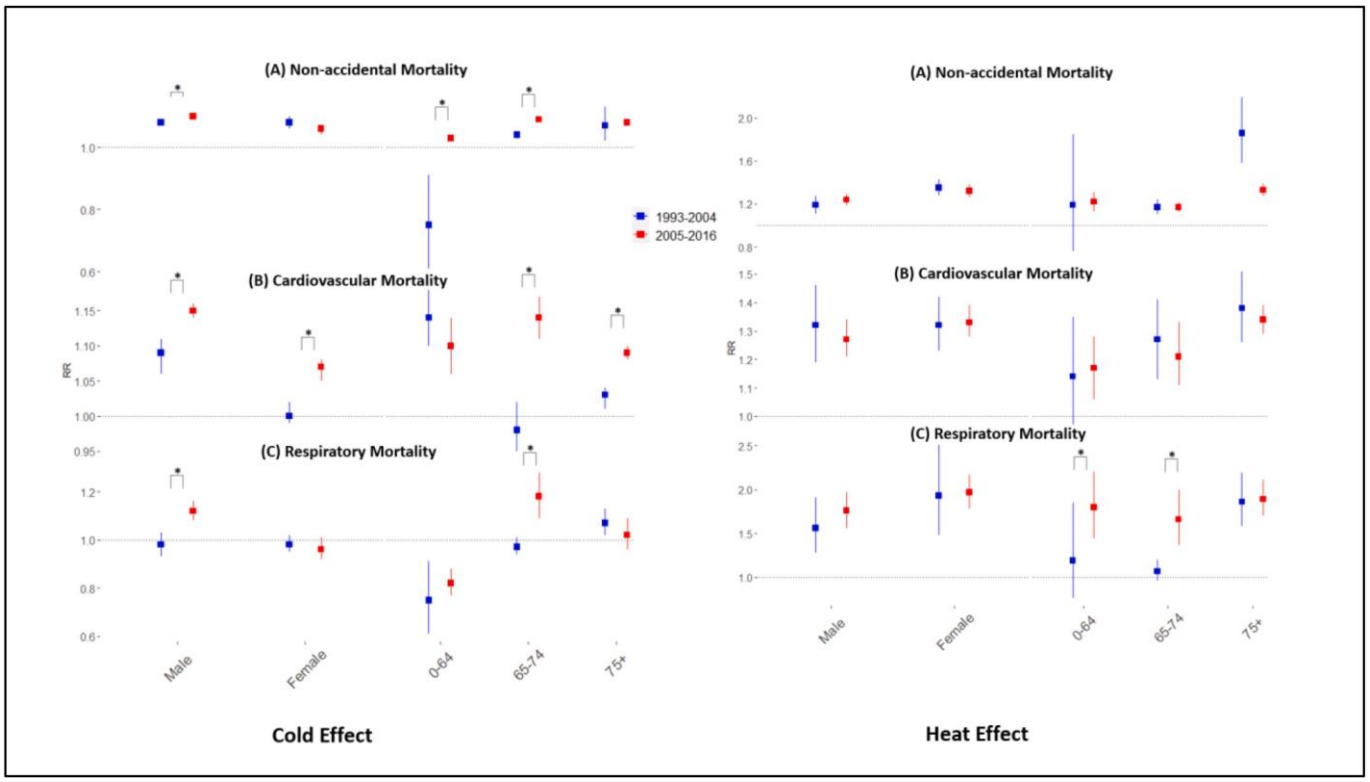

Fig. 2. Lag-cumulative RR estimates for daily cause-specific mortality (95% confidence interval) as cold effect [RR at 1st (—6.0 ◦C) percentile relative to 25th percentile (4.9 ◦C)] and heat effect [RR at 99th (25.1 ◦C) percentile relative to 75th (15.9 ◦C) percentile] for 1993–2004 (blue) and 2005–2016 (red) stratified by subgroups
[Asterisks indicate statistical significance for differences in relative risk estimates between 1993–2004 and 2005–2016.

specific CVD and RD mortality and the effect modification by age and sex using a multi-city database. Our study also had several limitations. Our exposure data were obtained from one city-specific fixed outdoor monitoring station, which led to measurement error. However, this measurement error was likely to be random and might have underestimated effect estimates. Our analysis was based on 15 German cities and may not apply to other regions with different climatic, demographic, and socioeconomic conditions. Future studies quantifying climate-related health burden as a result of population aging would further aid public health planning.

5. Conclusion

In conclusion, our study provides evidence of rising population susceptibility for cold-related CVD and RD mortality and heat-related RD mortality. Our results highlight the increasing cold-related susceptibility to ischemic, cerebrovascular disease, and heart failure mortality. Our findings suggest increased heat susceptibility, even to the younger age group, which is commonly expected to be less vulnerable. Similarly, COPD, the commonly speculated driver of heat-related RD mortality, was found to have a constant heat-related risk over time. Thus, with the growing threat of climate change, our results on temporal variations of the temperature-mortality association for the most temperature-sensitive outcomes might aid in providing background for the design of targeted adaptation measures to protect the population from the adverse effects of climate change.

Credit author statement

MR: Conceptualization, Methodology, Data curation, Formal analysis, Project administration, Software, Visualization, Writing - original draft, Writing - review & editing. SB: Conceptualization, Methodology, Resources, Validation, Writing - review & editing. SZ and VH: Methodology, Writing - review & editing. AP, AS: Conceptualization, Methodology, Funding acquisition, Supervision, Writing - review & editing.

Funding

This study has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 820655 (EXHAUSTION).

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.

Data availability

The authors do not have permission to share data.

Acknowledgement

Source of mortality data: Research Data Centre of the Federal Statistical Office and Statistical Offices of the Federal States, DOI: 10.21242/23111.1993.00.00.1.1.0 to 10.21242/23111.2016.00.00.1.1.0. Source of temperature data: Climate Data Centre of the German National Meteorological Service.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.115668.

References

Astrom, D.O., Forsberg, B., Edvinsson, S., Rocklov, J., 2013. Acute fatal effects of short-lasting extreme temperatures in Stockholm, Sweden: evidence across a century of change. Epidemiology 24 (6), 820–829.

Åstro¨m, C., Åstro¨m, D.O., Andersson, C., Ebi, K.L., Forsberg, B., 2017. Vulnerability reduction needed to maintain current burdens of heat-related mortality in a changing climate-magnitude and determinants. Int. J. Environ. Res. Publ. Health 14 (7).

Bai, L., Li, Q., Wang, J., Lavigne, E., Gasparrini, A., Copes, R., et al., 2016. Hospitalizations from hypertensive diseases, diabetes, and arrhythmia in relation to low and high temperatures: population-based study. Sci. Rep. 6, 30283.

Bai, L., Li, Q., Wang, J., Lavigne, E., Gasparrini, A., Copes, R., et al., 2018. Increased coronary heart disease and stroke hospitalisations from ambient temperatures in Ontario. Heart 104 (8), 673–679.

Barnett, A.G., 2007. Temperature and cardiovascular deaths in the US elderly: changes over time. Epidemiology 18 (3), 369–372.

Basu, R., 2009. High ambient temperature and mortality: a review of epidemiologic studies from 2001 to 2008. Environ. Health 8, 40.

Bobb, J.F., Peng, R.D., Bell, M.L., Dominici, F., 2014. Heat-related mortality and adaptation to heat in the United States. Environ. Health Perspect. 122 (8), 811–816.

Breitner, S., Wolf, K., Peters, A., Schneider, A., 2014. Short-term effects of air temperature on cause-specific cardiovascular mortality in Bavaria, Germany. Heart 100 (16), 1272–1280.

Carson, C., Hajat, S., Armstrong, B., Wilkinson, P., 2006. Declining vulnerability to temperature-related mortality in London over the 20th century. Am. J. Epidemiol. 164 (1), 77–84.

Chen, R., Yin, P., Wang, L., Liu, C., Niu, Y., Wang, W., et al., 2018. Association between ambient temperature and mortality risk and burden: time series study in 272 main Chinese cities. BMJ 363, k4306.

Chen, K., Breitner, S., Wolf, K., Hampel, R., Meisinger, C., Heier, M., et al., 2019. Temporal variations in the triggering of myocardial infarction by air temperature in Augsburg, Germany, 1987-2014. Eur. Heart J. 40 (20), 1600–1608.

Chung, Y., Noh, H., Honda, Y., Hashizume, M., Bell, M.L., Guo, Y.L., et al., 2017. Temporal changes in mortality related to extreme temperatures for 15 cities in Northeast Asia: adaptation to heat and maladaptation to cold. Am. J. Epidemiol. 185 (10), 907–913.

Chung, Y., Yang, D., Gasparrini, A., Vicedo-Cabrera, A.M., Fook Sheng Ng, C., Kim, Y., et al., 2018. Changing susceptibility to non-optimum temperatures in Japan, 1972-2012: the role of climate, demographic, and socioeconomic factors. Environ. Health Perspect. 126 (5), 057002.

Coates, L., Haynes, K., O'Brien, J., McAneney, J., de Oliveira, F.D., 2014. Exploring 167 years of vulnerability: an examination of extreme heat events in Australia 1844–2010. Environ. Sci. Pol. 42, 33–44.

Davis, R.E., Knappenberger, P.C., Michaels, P.J., Novicoff, W.M., 2003. Changing heat-related mortality in the United States. Environ. Health Perspect. 111 (14), 1712–1718.

Ebi, K.L., Kovats, R.S., Menne, B., 2006. An approach for assessing human health vulnerability and public health interventions to adapt to climate change. Environ. Health Perspect. 114 (12), 1930–1934.

Ekamper, P., Van Poppel, F., Van Duin, C., Garssen, J., 2009. 150 Years of temperature-related excess mortality in The Netherlands. Demogr. Res. 21, 385–426.

Gasparrini, A., 2011a. Distributed lag linear and non-linear models in R: the package dlnm. J. Stat. Software 43 (8), 1–20.

Gasparrini, A., 2011b. Distributed lag linear and non-linear models in R: the package dlnm. J. Stat. Software 48 (8), 1–20.

Gasparrini, A., Armstrong, B., 2011. Multivariate meta-analysis: a method to summarize non-linear associations. Stat. Med. 30 (20), 2504–2506.

Gasparrini, A., Guo, Y., Hashizume, M., Kinney, P.L., Petkova, E.P., Lavigne, E., et al., 2015a. Temporal variation in heat-mortality associations: a multicountry study. Environ. Health Perspect. 123 (11), 1200–1207.

Gasparrini, A., Guo, Y., Hashizume, M., Lavigne, E., Zanobetti, A., Schwartz, J., et al., 2015b. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. Lancet 386 (9991), 369–375.

Guo, Y., Barnett, A.G., Tong, S., 2012. High temperatures-related elderly mortality varied greatly from year to year: important information for heat-warning systems. Sci. Rep. 2, 830.

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 (12), 1681–1690.

Irmela Schlegel, S.M., Mucke, Hans-Guido, Matzarakis, Andreas, 2020. Comparison of Respiratory and Ischemic Heart Mortality and its Relationship to Thermal Environment.

Liu, L., Breitner, S., Pan, X., Franck, U., Leitte, A.M., Wiedensohler, A., et al., 2011. Associations between air temperature and cardio-respiratory mortality in the urban area of Beijing, China: a time-series analysis. Environ. Health 10, 51.

Michelozzi, P., Accetta, G., De Sario, M., D'Ippoliti, D., Marino, C., Baccini, M., et al., 2009. High temperature and hospitalizations for cardiovascular and respiratory causes in 12 European cities. Am. J. Respir. Crit. Care Med. 179 (5), 383–389.

Oudin Astrom, D., Ebi, K.L., Vicedo-Cabrera, A.M., Gasparrini, A., 2018. Investigating changes in mortality attributable to heat and cold in Stockholm, Sweden. Int. J. Biometeorol. 62 (9), 1777–1780.

Patz, J.A.M.M., Bernard, S.M., Ebi, K.L., Epstein, P.R., Grambsch, A., et al., 2000. The potential health impacts of climate variability and change for the United States: executive summary of the report of the health sector of the U.S. National assessment. Environ. Health Perspect. 108, 367–378.

Petkova, E.P., Gasparrini, A., Kinney, P.L., 2014. Heat and mortality in New York City since the beginning of the 20th century. Epidemiology 25 (4), 554–560.

Ponjoan, A., Blanch, J., Alves-Cabratosa, L., Marti-Lluch, R., Comas-Cufi, M., Parramon, D., et al., 2017. Effects of extreme temperatures on cardiovascular emergency hospitalizations in a Mediterranean region: a self-controlled case series study. Environ. Health 16 (1), 32.

R Core Team. R, 2017. A Language and Environment for Statistical Computing. R Foundation for Statistical Computing Vienna, Austria.

Rodrigues, M., Santana, P., Rocha, A., 2020. Statistical modelling of temperature-attributable deaths in Portuguese metropolitan areas under climate change: who is at risk? Atmosphere 11 (2).

Turner, L.R., Barnett, A.G., Connell, D., Tong, S., 2012. Ambient temperature and cardiorespiratory morbidity: a systematic review and meta-analysis. Epidemiology 23 (4), 594–606.

Vos, T., Lim, S.S., Abbafati, C., Abbas, K.M., Abbasi, M., Abbasifard, M., et al., 2020. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 396 (10258), 1204–1222.

Wood, S.N., 2011. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. J. Roy. Stat. Soc. 73 (1), 3–36.

Yang, C., Meng, X., Chen, R., Cai, J., Zhao, Z., Wan, Y., et al., 2015. Long-term variations in the association between ambient temperature and daily cardiovascular mortality in Shanghai, China. Sci. Total Environ. 538, 524–530.

Yin, Q., Wang, J., 2017. The association between consecutive days' heat wave and cardiovascular disease mortality in Beijing, China. BMC Publ. Health 17 (1), 223.

Zhai, L., Ma, X., Wang, J., Luan, G., Zhang, H., 2020. Effects of ambient temperature on cardiovascular disease: a time-series analysis of 229288 deaths during 2009-2017 in Qingdao, China. Int. J. Environ. Health Res. 1–10.

Zhang, B., Li, G., Ma, Y., Pan, X., 2018. Projection of temperature-related mortality due to cardiovascular disease in beijing under different climate change, population, and adaptation scenarios. Environ. Res. 162, 152–159.

3. Publication: Future Temperature-related Mortality under Physiological Adaptation Scenarios and Socio-economic Adaptive Capacities: A Modelling Framework

Title:	Future Temperature-related Mortality under Physiological Adaptation Scenarios and Socio-economic Adaptive Capacities: A Modelling Framework
Authors:	**Masna Rai**, Susanne Breitner, Kathrin Wolf, Annette Peters, Alexandra Schneider and Kai Chen
Journal:	*Lancet Planetary Health*
Year:	2022
Volume:	6 (10): e784–92
DOI:	10.1016/S2542-5196(22)00195-4
Supplements:	https://www.thelancet.com/cms/10.1016/S2542-5196(22)00195-4/attachment/5b2c4051-64c2-4060-b690-891b3fa263cc/mmc1.pdf
Impact factor:	28.75 (Journal Citations Reports® 2022)
Rank:	3/279 in Category Environmental Sciences Journals (Journal Citations Reports® 2022)
Rights declaration:	This is an open-access article distributed under the terms of the Creative Commons License.

Future temperature-related mortality considering physiological and socioeconomic adaptation: a modelling framework

Masna Rai, Susanne Breitner, Kathrin Wolf, Annette Peters, Alexandra Schneider, Kai Chen**

Summary

Background As the climate changes, it is crucial to focus not only on mitigation measures but also on building climate change resilience by developing efficient adaptation strategies. Although population adaptation is a major determinant of future climate-related health burden, it is not well accounted for in studies that project the health impact of climate change. We propose a methodological framework for temperature-related mortality that incorporates two simultaneous adaptation-sensitivity pathways: the physiological pathway, considering both heat adaptation and cold sensitivity, and the socioeconomic pathway, which is influenced by changes in future adaptive capacities. To demonstrate its utility we apply the framework to a case study mortality time-series dataset from Bavaria, Germany.

Methods In this modelling framework, we used extrapolated location-specific and age-specific baseline exposure–response functions and propose different future scenarios of cold sensitivity and heat adaptation on the basis of varying slopes of these exposure–response functions. We also incorporated future socioeconomic adaptation in the exposure–response functions using projections of gross domestic product under the respective shared socioeconomic pathways. Future adaptable fractions, representing the deaths avoided under each of the future scenarios, are projected under combinations of two climate change scenarios (shared socioeconomic pathway [SSP]1–2.6 and SSP3–7.0) and the respective plausible population projection scenarios (SSP1 and SSP3), also incorporating the future changes in demographic age structure and mortality. The case study for this framework was done for five districts in Bavaria, for both total non-accidental mortality and cardiovascular disease mortality. The baseline data was obtained for the period 1990–2006, and the future period was defined as 2083–99.

Findings In our Bavaria case study, average temperature was projected to increase by 2099 by an average of 1·1°C under SSP1–2.6 and by 4·1°C under SSP3–7.0. We observed the adaptable fraction to be largely influenced by socioeconomic adaptation for both total mortality and cardiovascular disease mortality, and for both climate change scenarios. For example, for total mortality, the highest adaptable fraction of 18·56% (95% empirical CI 10·77–23·67) was observed under the SSP1–2.6 future scenario, in the presence of socioeconomic adaptation and under the highest heat adaptation (10%) provided the cold sensitivity remains 0%. The cold adaptable fraction is lower than the heat adaptable fraction under all scenarios. In the absence of socioeconomic adaptation, population ageing will lead to higher temperature-related mortality.

Interpretation Our developed framework helps to systematically understand the effectiveness of adaptation mechanisms. In the future, socioeconomic adaptation is estimated to play a major role in determining temperature-related excess mortality. Furthermore, cold sensitivity might outweigh heat adaptation in the majority of locations worldwide. Similarly, population ageing is projected to continue to determine future temperature-related mortality.

Funding EU Horizon 2020 (EXHAUSTION).

Lancet Planet Health 2022; 6: e784–92

This online publication has been corrected. The corrected version first appeared at thelancet.com/planetary-health on November 9, 2022

*Senior authors and contributed equally

Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany (M Rai MSc, S Breitner PhD, K Wolf PhD, Prof A Peters PhD, A Schneider PhD)**; Institute for Medical Information Processing, Biometry, and Epidemiology, Pettenkofer School of Public Health, LMU Munich, Munich, Germany** (M Rai, S Breitner, Prof A Peters)**; German Research Center for Cardiovascular Research (DZHK), Partner-Site Munich, Munich, Germany** (Prof A Peters)**; Department of Environmental Health Sciences and Yale Center on Climate Change and Health, Yale School of Public Health, New Haven, CT, USA** (K Chen PhD)

Correspondence to:
Ms Masna Rai, Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, D-85764 Neuherberg, Germany
masna.rai@helmholtz-muenchen.de

Introduction

The most recent report from the Intergovernmental Panel on Climate Change stresses that unless there are immediate large-scale mitigation measures to reduce greenhouse gas emissions, we will be unable to limit global warming to 1·5°C or even 2°C.[1] Therefore, it is crucial to focus not only on mitigation measures but also on building climate change resilience by developing efficient adaptation strategies. Studies projecting climate change-attributable future health burdens can aid in planning these adaptation strategies. Research in the field is growing, with numerous projections on temperature-related total and cause-specific mortality under the different ranges of future climate and population change scenarios,[2–6] which allow us to identify population subgroups that are vulnerable (ie, at risk due to external factors, such as outdoor workers) and susceptible (ie, at risk due to internal factors, such as people with pre-existing health conditions) to climate change-related impacts. However, most projection studies so far do not

Research in context

Evidence before this study

We searched PubMed without any language restrictions for articles published from inception to Nov 28, 2021, using the following search terms: "temperature", "mortality" or "death*", "climate change", and "projection" or "projecting" or "projected" or "future". After screening abstracts and full texts, our literature review showed that most studies on the future projection of climate change-attributable mortality did not account for possible future population adaptation. Moreover, the few studies accounting for population adaptation either focused only on future heat-related acclimatisation or socioeconomic adaptation through changes in future adaptive capacities. Therefore, there are no projection studies accounting for all aspects of future adaptation scenarios, including both heat-related and cold-related physiological as well as socioeconomic adaptation scenarios.

Added value of this study

Future population adaptation is a crucial factor that is not well accounted for in studies that project the health impacts of temperature under climate change. Most studies incorporating population adaptation for projections of the future temperature-related health burden either accounted only for heat adaptation of the population or only for socioeconomic adaptation through changes in adaptive capacities. This study proposes a methodological framework incorporating two simultaneous adaptation-sensitivity pathways: the physiological pathway, considering both heat adaptation and cold sensitivity, and the socioeconomic pathway, which is influenced by changes in future adaptive capacities. We also demonstrate the framework using a mortality time-series dataset from Bavaria, Germany.

Implications of all the available evidence

Concerning the present climate crisis, it is crucial to not only focus on mitigation measures but also to develop efficient adaptation strategies to protect population subgroups that are vulnerable (ie, at risk due to external factors) and susceptible (ie, at risk due to internal factors) to climate change-related impacts. Our developed framework supports a more systematic understanding of the potential effectiveness of adaptation mechanisms. This helps to better estimate the future temperature-related mortality burden under climate change scenarios. We found that socioeconomic adaptation plays a major role in determining the future adaptable fraction, representing the deaths avoided under each of the future scenarios. This evidence is crucial for the evidence-based planning of health policies and adaptation measures.

account for future population adaptation, which means that they potentially overestimate temperature-related health impacts and also miss an opportunity to develop a systematic understanding of the effectiveness of adaptation mechanisms.

Future populations are expected to undergo multiple simultaneous adaptation pathways, including the physiological pathway and the socioeconomic pathway, which are influenced by changes in future adaptive capacities. Physiological pathways include changes in the body's response to heat or cold, which might lead to adaptation or increased sensitivity at the same temperature. Similarly, changes in socioeconomic conditions directly influence factors such as purchasing capacities and health-care facilities, which determine our capacity to better adapt during hot days as well as during cold spells.Only a few studies have considered population adaptation when estimating the future temperature-related health burden.[7–15] However, most of these studies only considered physiological adaptive mechanisms,[7–14] whereas only one study accounted for the changes in socioeconomic adaptive capacities.[15]

Studies accounting for physiological adaptive mechanisms have applied various approaches. Earlier approaches include using analogous summers or cities to assume the changes in the future exposure–response associations between temperature and mortality outcomes.[10,11] However, these approaches are based mainly on untestable assumptions, which might result in large uncertainties—for example, assuming the population of one city will react to temperature in the same way as the population from a reference city might not hold true. More recent studies used different methodologies to account for physiological adaptation, which comprises assumptions of population acclimatisation over a few degrees[12,13] or a shift in the exposure–response function (ERF) between temperature and health outcomes.[1G] Petkova and colleagues in 2017[8] extensively studied the temperature–mortality association over a period of more than a century (1900–200G) and used the observed shifts in patterns of the temperature–mortality association to account for future adaptation. However, this approach might be challenging in regions where meteorological observations and health records have only been collected for a short period. Furthermore, all the studies mentioned focused on adaptation to heat.[8,13,14] However, cold-related mortality is mostly attributable to moderate cold, which will persist in the future under climate change. Therefore, projection studies are more complete when future changes in the cold–mortality association are included.[17] Existing evidence suggests that cold weather effects will not decrease[18,19] or may even increase[20] under climate change so that both heat and cold effects require investigation.[17]

In addition, future infrastructure changes and socioeconomic challenges might play an important role in influencing adaptation by changing adaptive capacities. A study by Wang and colleagues in 2019[15] defined future adaptive capacity as a factor of future gross domestic product (GDP). However, their study focused only on

socioeconomic adaptive capacity without incorporating physiological adaptive mechanisms.

Putting everything together, we concluded that there are gaps in future projections, especially in terms of considering physiological pathway changes, including both heat adaptation (corresponding to a reduced heat-related risk) and cold sensitivity (corresponding to an increased cold-related risk), and changes in socioeconomic adaptive capacities. Therefore, the objective of this study was to develop a framework for different physiological adaptation-sensitivity and socioeconomic adaptation scenarios, including adaptive capacities, and to introduce a methodological approach for future projections considering all these factors. This is followed by a demonstration of the proposed framework using time-series data over 17 years on temperature and mortality in Bavaria, Germany, as a case study.

Methods

Proposed framework of future adaptation scenarios

Physiological adaptation-sensitivity pathway

It is difficult to assess the physiological limit of population adaptation to extreme temperatures; however, the historical changes in ERF between temperature and the related health outcomes can provide useful information on the potential range of physiological adaptation. In this framework, we use changes in the present-day ERF to represent the future physiological adaptation-sensitivity pathway. Considering changes in ERF can be decomposed into two approaches: (1) the change in the slope of the ERF and (2) the shift in the mortality temperature. These approaches are based on the observed temporal variation in the temperature–mortality association during baseline. Using the first approach for the proposed framework, future physiological scenarios are expected to follow adaptation (represented by a decrease in the slope of present-day ERF) or sensitivity (represented by an increase in the present-day ERF). Similar approaches for heat adaptation have been applied by previous studies and proposed methodologies.[16,21] Because the temperature–mortality association is unique to every location,[22] analysis of temporal variation of the temperature–mortality association from the available baseline data is recommended while defining the percentage increase or decrease in ERF as well as deriving shifts in the mortality temperature, which are to be incorporated accordingly for the respective locations under investigation.

Socioeconomic adaptation pathway scenarios

The socioeconomic adaptation pathway scenarios incorporate changes in future adaptive capacities. Although there are many factors that can be used to represent adaptive capacities, in order to have broad applicability, such factors should be available in both the historical and future periods and be generalisable globally, including in low-income and middle-income countries with sparse data availability. Thus, we selected GDP projection under the respective shared socioeconomic pathways (SSPs) as a measure of future adaptive capacity. The change in future GDP under each SSP is considered to influence the adaptive capacities, resulting in socioeconomic adaptation. Changes in future infrastructure due to increasing GDP would affect adaptive capacities (which could determine the adaptable fraction—eg, investments in urban green space projects, stakeholder capacity to design adaptation measures such as heat warning systems, and the ability of the population to heat or cool their environment).

By incorporating both physiological and socioeconomic adaptation pathways and by considering both adaptation to heat and sensitivity to cold, this framework unifies and further expands the current research attempts to quantify the potential impact of future population adaptations on temperature-related health impacts under climate change (figure 1).

Application of the adaptation framework in a use-case analysis

The case study application of this framework was done in five districts within the state of Bavaria, Germany (appendix p 2) for two mortality causes separately (ie, total non-accidental mortality and cardiovascular disease mortality).

See **Online** for appendix

Data sources

Baseline temperature and mortality

The baseline data was obtained for the period 1990–2006. We obtained daily mean temperature for the baseline period from the German Weather Service and the Bavarian Environment Agency. Daily age-specific death counts for both total non-accidental mortality and cardiovascular disease mortality were obtained from the Bavarian State Office for Statistics and Data Processing.

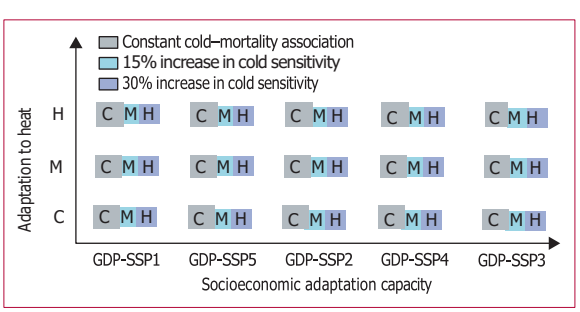

Figure 1: **Combination of the physiological adaptation pathway and socioeconomic adaptive capacity under the proposed framework**
Socioeconomic adaptation capacity on the x-axis is represented by GDP changes under each SSP scenario. The scenarios GDP-SSP1–5 represent GDP changes under the respective SSP1–5 scenarios and are placed in the order of increasing challenges for adaptation. Adaptation to heat on the y-axis is represented by the scenarios C, M, and H, corresponding to a constant, 5% decrease, and 10% decrease in the present-day heat–mortality association. Cold sensitivity is added as a third layer and represented by the scenarios C (grey), M (light blue), and H (dark blue), corresponding to a constant, 15% increase, and 30% increase in the present-day cold–mortality association. GDP=gross domestic product. SSP=shared socioeconomic pathway.

International Classification of Diseases, ninth revision (ICD-9) codes for the period 1990–97 and ICD-10 codes for the period 1998–200G were used for classifying the causes of death. The dataset we use here (1990–200G), including both mortality and temperature data, has been used in previous publications.[4,23]

Future temperature projection

In our use-case scenario, we defined the future period as 2083–99. The time frame was chosen to make it consistent with the 17-year baseline period and to capture future mortality until the end of the century. The daily mean temperature for the future period was obtained from the bias-adjusted and downscaled spatial dataset of the five global climate models (GCMs) from phase 3b of the Inter-Sectoral Impact Model Intercomparison Project (ISIMIP3b) based on phase G of the Coupled Model Intercomparison Project (CMIPG). This spatial dataset includes downscaled daily climate projections on a horizontal grid with 0·5° × 0·5° resolution from five GCMs (GFDL-ESM4, IPSL-CMGA, MPI-ESM1, MRI-ESM2, and UKESM1). We obtained location-specific daily temperature series for the future period under all the five GCMs for each of the two climate change scenarios (ie, for SSP1–2.G and SSP3–7.0), by extracting the weighted mean of the grid cells covering the location. We calibrated the extracted temperature series with location-specific observed data using the calibration method of Hempel and colleagues,[24] and observed temperature from the German Weather Service.

For more on **ISIMIP3b** see https://www.isimip.org/

Population projections, mortality rate projections, and future mortality series

The future mortality series was obtained in two stages, considering changes in both the future population and mortality rate. Initially, we applied the method of Vicedo-Cabrera and colleagues[1G] and computed annual series of mortality counts (total and cardiovascular disease) as the average for each day of the year from the baseline daily mortality data to control for the seasonal trends of the observed mortality series.

In the first stage, we obtained population projections for each of the five locations under the two SSPs (SSP1 and SSP3) for the future period from a high-resolution global spatial population projection downscaled from a 1/8-degree to a 1-km grid cell from the National Centre for Atmospheric Research.[25] We corrected them for bias using the observations from the German census authority as reference. From the population projections, we then derived age-specific population growth factors under different SSP scenarios, calculated as the future population divided by the baseline population. In the second stage, we incorporated age-specific future changes in mortality rates for both total non-accidental mortality, using the mortality projections from KC and Lutz in 2017,[2G] and cardiovascular disease mortality, using the mortality projections from Sellers in 2020,[27] to derive the mortality rate change factor of the two causes compared with the baseline. The formerly derived age-specific annual mortality series at baseline was then multiplied with the respective age-specific population growth factor and age-specific mortality rate change factor to obtain the final future annual mortality series for total non-accidental and cardiovascular disease mortality.

For the **Federal Statistical Office of Germany** see https://www.destatis.de/EN/Home/_node.html

Statistical analysis

The following statistical analysis would be applied in the proposed framework; however, the detailed parameter selection was based on the case study analysis in Bavaria, Germany.

Baseline ERF

We applied distributed lag, non-linear models with a quasi-Poisson distribution extending the lag period to 21 days to establish the age-specific ERFs for the baseline temperature–mortality association for each of the five locations. Two age categories were defined: younger than 75 years and 75 years or older. We used natural cubic splines centred on the location-specific minimum mortality temperature with three internal knots placed at 10th, 75th, and 90th percentiles of the location-specific mean temperature. The lag–response curve for temperature was modelled with a natural cubic spline with three knots placed at equally spaced values on the logarithmic scale. The regression also included an indicator for the day of the week and a natural cubic spline with seven degrees of freedom per calendar year to control the seasonal and long-term trends. The ERFs were extrapolated for future temperature observations beyond the baseline observations. The relative risk (RR) at each temperature point was obtained from the derived ERF. The RR for temperatures higher than the mortality temperature was defined as heat-RR, and for temperatures less than the mortality temperature as cold-RR.

We studied the temporal variation in the heat-RR and cold-RR during the baseline study period to determine the percentage change in excess RR over time (appendix p 3). Based on this analysis, we assumed that heat adaptation includes three scenarios: constant or no heat adaptation (a decrease in the excess RR by 0%), medium adaptation (a decrease in the excess RR by 5%), and high adaptation (a decrease in the excess RR by 10%). Similarly, cold sensitivity includes three scenarios: constant or no sensitivity (an increase in the excess RR by 0%), medium sensitivity (an increase in the excess RR by 15%), and high sensitivity (an increase in the excess RR by 30%). Details of the temporal variation analysis are presented in the appendix (p 3). Shifts in the mortality temperature were not incorporated because we observed inconsistent temporal patterns with large uncertainty from the baseline temporal analysis (appendix p 3).

Derivation of future RR

Under each of the future scenarios, future cold-RR and heat-RR were calculated separately (appendix p 5). Cold-RR incorporated the physiological sensitivity to cold and socioeconomic adaptation. Heat-RR incorporated the physiological adaptation to heat and socioeconomic adaptation. Socioeconomic adaptation was defined as the factor change in the future GDP per capita in relation to the baseline GDP per capita. The incorporation of GDP to determine the change in ERF is based on the log-linear association between RR and GDP. This log-linear association, which has been used in a previous study,[28] was also observed in the case study dataset (appendix p 4). We also investigated the log-linear association in this case study dataset (appendix p 4). We calculated the future cold-RR and heat-RR at each temperature point as:

$$\text{Future cold-RR } (RR_c) := \frac{\ln(\text{physiological sensitivity factor} \times (RR_{bc}-1)+1) + \ln[(RR_{bc}-a)\times x] + a}{\ln(RR_c)} \Big/ 2$$

$$\text{Future heat-RR } (RR_h) := \frac{\ln(\text{physiological adaptation factor} \times (RR_{bh}-1)+1) + \ln\left(\frac{RR_{bh}-b}{x}\right) + b}{\ln(RR_h)} \Big/ 2$$

where c=cold, h=heat, bc=baseline cold-RR, bh=baseline heat-RR, a=intercept of the cold-RR and log($GDP_{per\ capita}$) model, b=intercept of the heat-RR and log($GDP_{per\ capita}$) model, x=log($GDP_{per\ capita}$ future)/log($GDP_{per\ capita}$ baseline).

Projection of future mortality

Age-specific future heat-related and cold-related mortality were calculated and added to derive the net future temperature-related mortality (appendix p 5), as follows:

$$\text{Future heat-related deaths} = Y_{hl} \times P_l \times RR_{hl} \times M_l$$

$$\text{Future cold-related deaths} = Y_{cl} \times P_l \times RR_{cl} \times M_l$$

where l represents the different locations, h=heat, c=cold, Y_{hl} and Y_{cl} are the age-specific baseline mortality series, P_l is the age-specific population change rate, M_l is the age-specific mortality change rate, RR_{hl} is the future heat-related RR, and RR_{cl} is the future cold-related RR.

Calculation of the adaptable fraction

Finally, we calculated the adaptable fraction, which is the number of deaths that can be avoided through adaptation, as:

$$\text{Adaptable fraction} = \frac{\text{Net mortality without adaptation} - \text{net mortality with adaptation}}{\text{Net mortality without adaptation}} \times 100$$

Under each representative concentration pathway (RCP; which are scenarios developed by the Intergovernmental Panel on Climate Change for application in studies to explore uncertainty about future atmospheric levels of CO_2), we incorporated the five GCMs and derived five projections of future adaptable fractions (appendix p 5). The average of estimates under these five projections was considered as the adaptable fractions under each RCP.

To account for uncertainty in both the ERF and the projections of future climate and population models, we used Monte Carlo simulations to obtain 95% empirical CIs (95% empirical CIs). For the derivation of 95% empirical CIs for an estimate under one of the climate scenarios for a single location, we first obtained the empirical distribution across 5000 samples of random parameter sets describing the ERF in the distributed lag, non-linear model under the specific climate scenarios for each of the five GCMs.[2,29] This was done separately for the heat and cold adaptable fractions and for the two age groups, giving us 100 000 simulations for each location. We thus obtained 500 000 Monte Carlo simulations for the five locations that were used in deriving the 95% empirical CIs for the estimate under the corresponding climate scenario for Bavaria.

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

Climate, population, and mortality projections

The average temperature during the baseline period was 9·8°C, which was seen to increase during the future period by an average of 1·1°C under the SSP1–2.G climate change scenario and by 4·1°C under the SSP3–7.0 climate change scenario (figure 2). Both population and GDP increments are higher under the SSP1 scenario than under the SSP3 scenario (figure 3A, B). With changes in

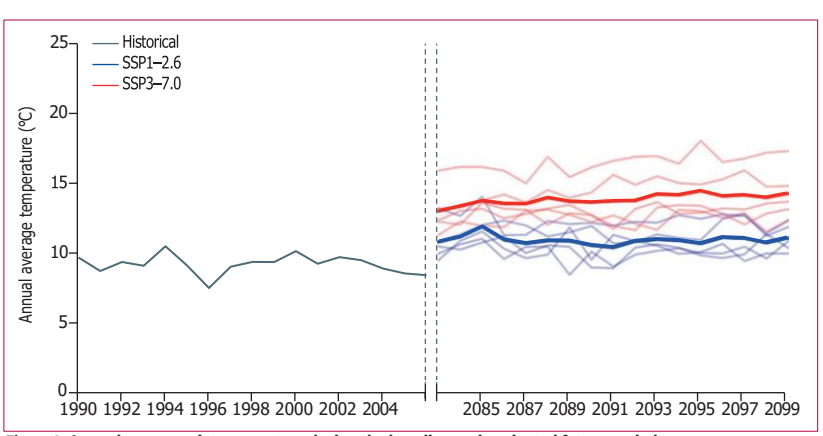

Figure 2: **Annual average air temperature during the baseline and projected future periods**
Temperature during the baseline period is the station-measured temperature, and temperature during the future period is projected by the five GCMs from ISIMIP3b based on CMIP6. Each darker line represents the average of the GCMs; faint lines represent the temperature under the six climate models (CMIP6); the dark line is the average of these six models. CMIP6=phase 6 of the Coupled Model Intercomparison Project. GCM=global climate model. ISIMIP3b=phase 3b of the Inter-Sectoral Impact Model Intercomparison Project. SSP=shared socioeconomic pathway.

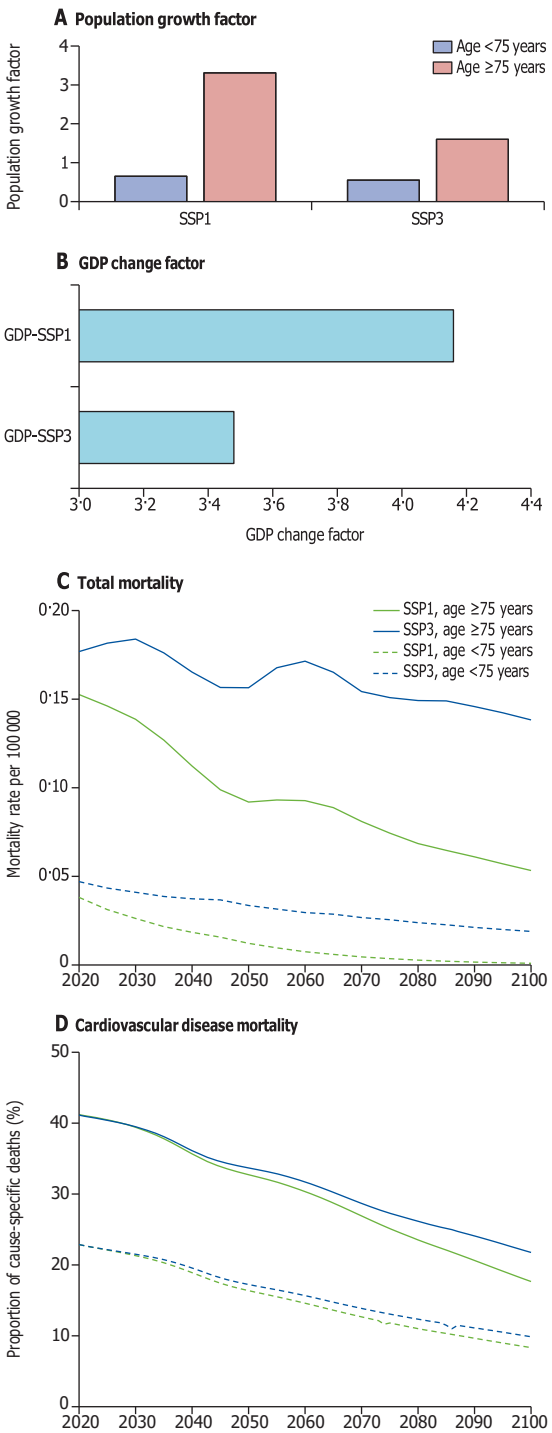

Figure 3: **Changes in future population, GDP, and mortality rates**
(A) Comparison of projected population growth factor under different SSPs; the factor is calculated as the fraction of future population divided by the baseline population. (B) Projected GDP change factor under different SSPs; the factor is calculated as the fraction of future GDP divided by present-day GDP. (C) Projected trends in total mortality per 100 000, as projected by KC and Lutz,[26] by age group and by SSP. (D) Projected trends in proportion of cardiovascular disease mortality to total mortality as projected by Sellers,[27] by age group and by SSP. GDP=gross domestic product. SSP=shared socioeconomic pathway.

future infrastructure and health-system improvement, the mortality rate for total and cardiovascular disease mortality is expected to decrease under both SSP1 and SSP3 (figures 3C, D).

Adaptable fractions under future adaptation scenarios

We projected future heat-related and cold-related adaptable fractions separately and derived the net adaptable fraction under all combinations of the proposed physiological and socioeconomic adaptation scenario pathways for total mortality (figure 4) and cardiovascular disease mortality (figure 5). Under both SSP1–2.G and SSP3–7.0, we observed that socioeconomic adaptation largely influenced the adaptable fraction for both causes. No significant net adaptable fraction is expected in the absence of socioeconomic adaptation for total mortality. Furthermore, under all scenarios, the cold adaptable fraction is less than the heat adaptable fraction. The proportion of older people is much higher under SSP1–2.G than under SSP3–7.0 and, in the absence of socioeconomic adaptation, the net adaptable fraction under SSP1–2.G is lower than it is under SSP3–7.0. In addition, we found that the adaptable fraction for cardiovascular disease mortality was not significant even when considering socioeconomic adaptation.

Total mortality

The highest adaptable fraction for SSP1–2.G was observed under socioeconomic adaptation, 10% heat adaptation, and 0% cold sensitivity, for which the adaptable fraction was 18·5G% (95% empirical CI 10·77 to 23·G7). Under the same adaptation scenario combination, the adaptable fraction was only 0·25% (–G·23 to 4·43) in the absence of socioeconomic adaptation. Similarly, the adaptation scenario associated with the highest excess mortality consists of 0% heat adaptation and 30% cold sensitivity in the absence of socioeconomic adaptation, under which there was a negative adaptable fraction of –2·55% (–10·72 to 2·81; figure 4; appendix p G).

The direction of estimates was similar but with smaller magnitude for SSP3–7.0. Under the previous scenario of highest adaptable fraction, the adaptable fraction was 15·9G% (95% empirical CI G·83 to 19·83). Similarly, under the previous adaptation scenario associated with the highest excess mortality, a negative adaptable fraction of –1·91% (–10·51 to 3·23) was observed (figure 4; appendix p G).

Cardiovascular disease mortality

The patterns of adaptable fractions for cardiovascular disease mortality were similar to those for total mortality but with a smaller magnitude. Under the highest adaptable scenario for SSP1–2.G observed for total mortality (ie, socioeconomic adaptation, 10% heat adaptation, 0% cold sensitivity), the cardiovascular disease adaptable fraction was 14·88% (95% empirical CI –5·05 to 19·78). Under the same adaptation scenario

combination, the adaptable fraction was only 0·35% (–12·90 to 7·30) in the absence of socioeconomic adaptation. Similarly, under the lowest adaptation combination of SSP1–2.G observed for total mortality, a negative adaptable fraction of –3·93% (–20·58 to 4·28) is to be expected (figure 5; appendix p 7). The direction of estimates was similar but with smaller magnitude for SSP3–7.0. Under the scenario with the highest adaptation fraction for SSP3–7.0, the adaptable fraction was 12·31% (95% empirical CI –14·95 to 1G·45). A negative adaptable fraction (–3·21% [–29·82 to 11·21]) was observed under the scenario with the highest adaptable fraction for SSP3–7.0 (figure 5; appendix p 7).

Discussion

In this Article, we propose a framework of future scenarios incorporating measures of both physiological adaptation-sensitivity and socioeconomic adaptation. Based on the proposed framework, we estimated the future net changes, including changes in the impact of both heat and cold, in the burden of total and cardiovascular disease mortality under all framework combinations, taking Bavaria, Germany, as a case study. Under all future scenarios, we found that socioeconomic adaptation played a major role in determining the future adaptable fraction. However, even with increased socioeconomic adaptive capacity, physiological adaptation-sensitivity could also influence the net adaptable fraction. Under all scenarios, the cold adaptable fraction was found to be lower than the heat adaptable fraction. Therefore, in the absence of socioeconomic adaptation, cold sensitivity might outweigh heat adaptation, thereby leading to increased excess deaths in the future. No significant adaptable fraction was observed for cardiovascular disease mortality even when considering socioeconomic adaptation.

Comparing the results from the two climate change scenarios (SSP1–2.G and SSP3–7.0) in the presence of socioeconomic adaptation, the net adaptable fraction is higher under SSP1–2.G than it is under SSP3–7.0. This difference is because of the higher GDP per capita under the socioeconomic scenario SSP1 than under SSP3, which would result in a higher adaptive capacity. However, in the absence of socioeconomic adaptation and considering only physiological adaptation sensitivity, the adaptable fraction under the climate change scenario SSP3–7.0 is seen to be slightly higher than that under SSP1–2.G, which is due to a much higher proportion of older people in the population under SSP1 than under the SSP3 scenario. A higher proportion of older people directly increases the proportion of susceptible people, leading to excess temperature-related mortality. Similarly, our results show that climate-sensitive outcomes, such as cardiovascular disease mortality, will continue to increase in the future, even with better adaptive capacities.

Heat-related impacts of climate change on cardiovascular disease are being discussed as an emerging important threat.[30] However, our analysis including physiological adaptation showed that cold sensitivity could be the major determining factor for future projections regarding the physiological adaptation-sensitivity scenario. Studies exploring the effect of temperature over time throughout the whole temperature range are sparse,[18–20] with results suggesting either that the cold–mortality association will be constant[18,19] or that susceptibility to cold will increase in the future.[20] Nevertheless, with studies estimating the present-day cold-attributable burden to be generally higher than the heat-attributable burden,[22] we can expect the future temperature-attributable health burden to be largely influenced by changes in the cold ERF rather than the heat ERF, especially in countries with temperate to cold climatic conditions.

By contrast, a previously proposed modelling framework[1G] suggests that the future population will adapt to increased heat. Nevertheless, some large studies suggest varying temporal trends (ie, decrease, constant, or increase) in the heat ERF across different locations.[31] For example, a constant heat ERF across time was observed

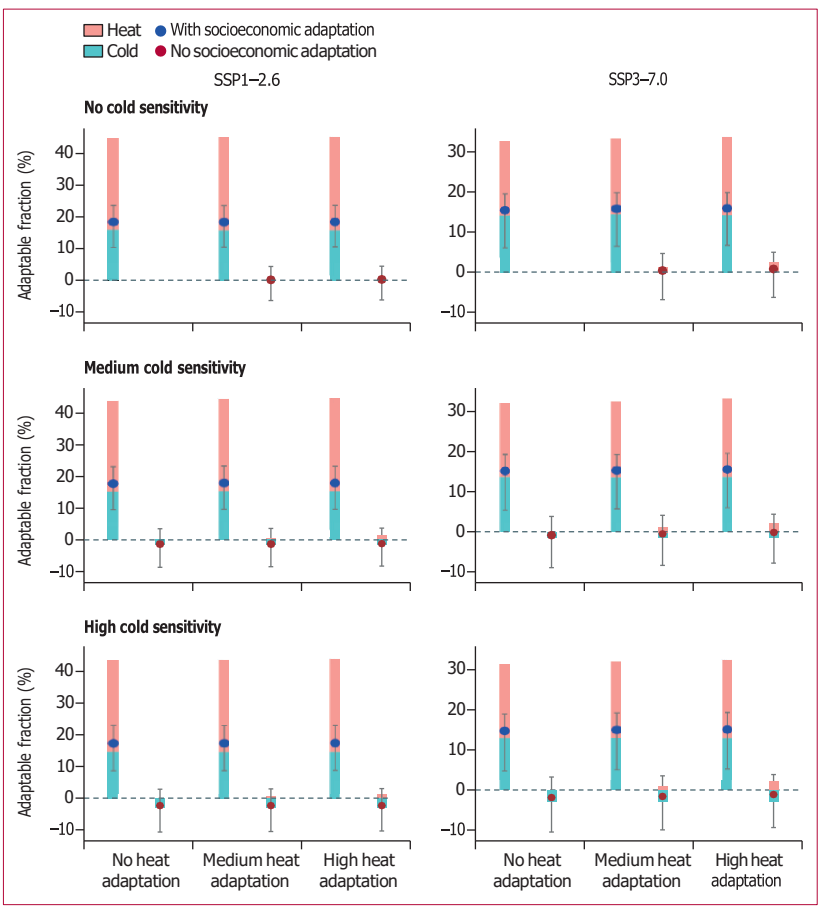

Figure 4: **Adaptable fraction for total mortality under combination of future physiological and socioeconomic adaptation scenarios**
No heat adaptation corresponds to a decrease in the excess relative risk (RR) by 0%, medium adaptation to a decrease in the excess RR by 5%, and high adaptation to a decrease in the excess RR by 10%. No cold sensitivity corresponds to an increase in the excess RR by 0%, medium sensitivity to an increase in the excess RR by 15%, and high sensitivity to an increase in the excess RR by 30%. SSP=shared socioeconomic pathway.

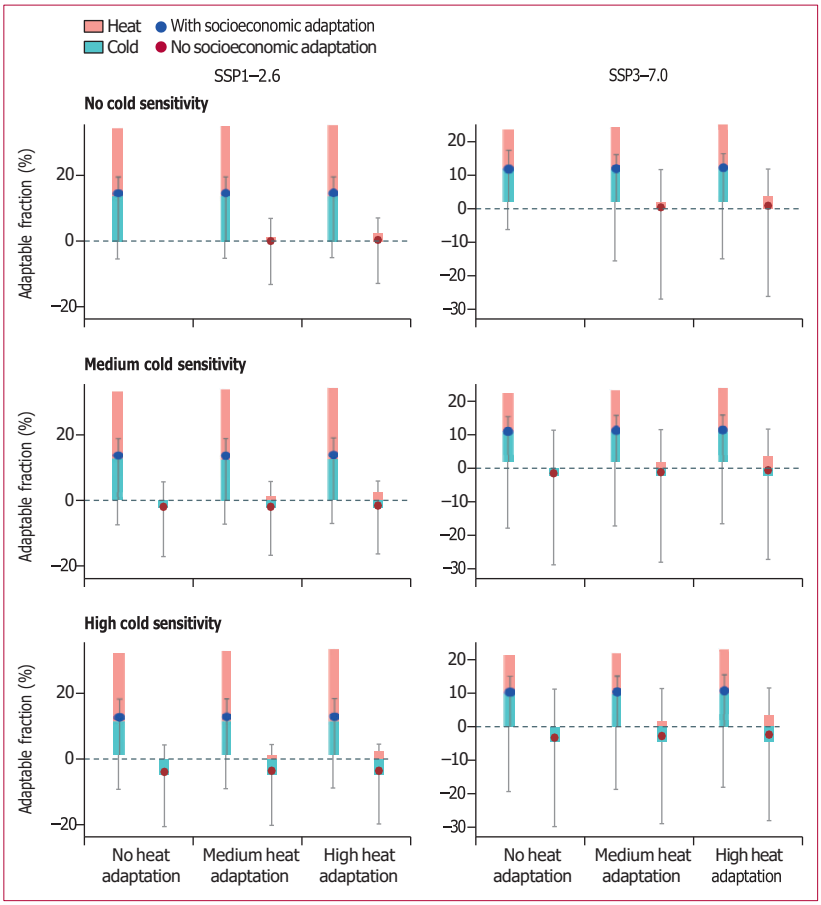

Figure 5: **Adaptable fraction for cardiovascular disease mortality under combination of future physiological and socioeconomic adaptation scenarios**
No heat adaptation corresponds to a decrease in the excess relative risk (RR) by 0%, medium adaptation to a decrease in the excess RR by 5%, and high adaptation to a decrease in the excess RR by 10%. No cold sensitivity corresponds to an increase in the excess RR by 0%, medium sensitivity to an increase in the excess RR by 15%, and high sensitivity to an increase in the excess RR by 30%. SSP=shared socioeconomic pathway.

for temperate regions such as the UK, whereas an increasing trend was noted for countries such as Australia.[31] These studies suggest that the future population in some locations might not adapt to heat as expected but could rather develop a sensitivity to heat. Therefore, for temperate regions such as Bavaria, where the population is not used to heat (especially heatwaves), the heat ERF might increase in the future or at least stay constant. An increase in both heat and cold sensitivity would mean much higher excess mortality in the future. In the scenario in which the cold ERF largely determines the mortality burden and is potentially expected to increase, socioeconomic adaptation would be the solution to increase climate change resilience. Such adaptation could be achieved with efficient adaptation strategies targeting vulnerable population subgroups, such as older people and those with underlying health conditions.

In any case, the future adaptable fraction in our case study in Bavaria is dominated largely by socioeconomic adaptation. Changes in future infrastructure related to increasing GDP could improve adaptive capacities. Increasing GDP could mean an increase in the heating and cooling (eg, increased prevalence and usage of air conditioning) capacity of the population, and the possibility of increased investments in urban green space projects, efficient urban planning measures with reduction of urban heat islands, and an overall increase in the stakeholder capacity to design adaptation measures such as heat warning systems.[32]

Our study provides a framework of future adaptation to temperature-related health outcomes incorporating measures of both physiological adaptation-sensitivity and socioeconomic adaptive capacities, to both hot and cold temperatures under climate change. The strength of our study comprises the projection of future adaptable fraction under the proposed scenarios incorporating all major aspects of future uncertainty, including climate, population, demographic, socioeconomic, and mortality changes. Furthermore, high-resolution, bias-corrected, and downscaled GCMs participating in the CMIPG were used to derive air temperatures under each of the climate scenarios as well as a downscaled, high-resolution data frame to derive the corresponding population projection under each SSP. We also captured and addressed the sources of uncertainties in our analysis, including the baseline temperature–mortality ERF, the temperature projection, and the population projection. The primary limitation of our case study is that the adaptation framework and modelling choices might not be directly applicable in a larger dataset across various climatic and geographical locations because they were based on observations of our case-study data. Furthermore, we did not incorporate future shifts in the minimum mortality temperature because we did not observe this for our case study dataset. In addition, we only used fixed weather stations for temperature exposure assessment during the baseline period, which might have introduced some bias in the exposure classification. However, this type of bias is rather towards null (ie, it does not lead to over or under estimation).[23] Furthermore, the incorporatation of GDP to define the adaptive capacity might not have encompassed all aspects of socioeconomic adaptation.

In our Bavaria case study we found that socioeconomic adaptation plays a major role in determining the proportion of temperature-related deaths that can be averted through adaptation (adaptable fraction). In addition, we found that the cold ERF, rather than the heat ERF, and climate-sensitive outcomes such as cardiovascular disease mortality dominate our future temperature-related excess mortality estimates.In the absence of socioeconomic adaptation, we project excess mortality in the susceptible population. Strategic adaptation plans to increase socioeconomic adaptative capacity, such as effective early warning systems, equitable green infrastructure, targeted investments in health systems, and sustainable heating and cooling

strategies, would be crucial to facilitate a climate resilience development pathway as the world warms.

Contributors

MR, KC, and AS designed the study. MR coordinated the work, and took the lead in drafting the manuscript and interpreting the results. MR, KC, and AS developed the statistical methods. MR did the statistical analysis and KC verified that analysis. KC and AS provided substantial scientific input in interpreting the results and drafting the manuscript. SB provided the data. MR, SB, and KW directly accessed and verified the underlying data. SB, KW, AP, AS, and KC reviewed and edited the manuscript. All authors had full access to all the data in the study and final responsibility to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The baseline mortality data was obtained from the Bavarian State Office for Statistics and Data Processing under a data agreement and cannot be made publicly available. Researchers can refer to the corresponding author for data access upon reasonable request.

Acknowledgments

We thank the ISIMIP3b climate modelling team and Leiwen Jiang at Population Council for producing and making the climate and population data available. We are grateful towards Samir KC and Samuel Sellers for providing the total and cardiovascular disease mortality projections, and to Kristie Ebi for her valuable feedback in designing the analysis plan. This study has received funding from the EU Horizon 2020 research and innovation programme, under grant agreement number 820G55 (EXHAUSTION).

References

1 Masson-Delmotte V, Zhai P, Pirani A, et al. Climate change 2021: the physical science basis. Contribution of Working Group I to the sixth assessment report of the Intergovernmental Panel on Climate Change. Cambridge, UK, and New York, NY, USA: Cambridge University Press, 2022.

2 Gasparrini A, Guo Y, Sera F, et al. Projections of temperature-related excess mortality under climate change scenarios. *Lancet Planet Health* 2017; **1:** e3G0–G7.

3 Lee JY, Kim E, Lee WS, Chae Y, Kim H. Projection of future mortality due to temperature and population changes under representative concentration pathways and shared socioeconomic pathways. *Int J Environ Res Public Health* 2018; **15:** E822.

4 Rai M, Breitner S, Wolf K, Peters A, Schneider A, Chen K. Impact of climate and population change on temperature-related mortality burden in Bavaria, Germany. *Environ Res Lett* 2019; **14:** 124080.

5 Chen K, Vicedo-Cabrera AM, Dubrow R. Projections of ambient temperature- and air pollution-related mortality burden under combined climate change and population aging scenarios: a review. *Curr Environ Health Rep* 2020; **7:** 243–55.

G Rodrigues M, Santana P, Rocha A. Modelling climate change impacts on attributable-related deaths and demographic changes in the largest metropolitan area in Portugal: a time-series analysis. *Environ Res* 2020; **190:** 109998.

7 Zhang B, Li G, Ma Y, Pan X. Projection of temperature-related mortality due to cardiovascular disease in Beijing under different climate change, population, and adaptation scenarios. *Environ Res* 2018; **162:** 152–59.

8 Petkova EP, Vink JK, Horton RM, et al. Towards more comprehensive projections of urban heat-related mortality: estimates for New York City under multiple population, adaptation, and climate scenarios. *Environ Health Perspect* 2017; **125:** 47–55.

9 Lee JY, Lee WS, Ebi KL, Kim H. Temperature-related summer mortality under multiple climate, population, and adaptation scenarios. *Int J Environ Res Public Health* 2019; **16:** e102G.

10 Knowlton K, Lynn B, Goldberg RA, et al. Projecting heat-related mortality impacts under a changing climate in the New York City region. *Am J Public Health* 2007; **97:** 2028–34.

11 Hayhoe K, Cayan D, Field CB, et al. Emissions pathways, climate change, and impacts on California. *Proc Natl Acad Sci USA* 2004; **101:** 12422–27.

12 Gosling SN, McGregor GR, Lowe JA. Climate change and heat-related mortality in six cities, part 2: climate model evaluation and projected impacts from changes in the mean and variability of temperature with climate change. *Int J Biometeorol* 2009; **53:** 31–51.

13 Dessai S. Heat stress and mortality in Lisbon, part II: an assessment of the potential impacts of climate change. *Int J Biometeorol* 2003; **48:** 37–44.

14 Anderson GB, Oleson KW, Jones B, Peng RD. Projected trends in high-mortality heatwaves under different scenarios of climate, population, and adaptation in 82 US communities. *Clim Change* 2018; **146:** 455–70.

15 Wang Y, Wang A, Zhai J, et al. Tens of thousands additional deaths annually in cities of China between 1.5 °C and 2.0 °C warming. *Nat Commun* 2019; **10:** 337G.

1G Vicedo-Cabrera AM, Sera F, Gasparrini A. Hands-on tutorial on a modeling framework for projections of climate change impacts on health. *Epidemiology* 2019; **30:** 321–29.

17 Ebi KL, Mills D. Winter mortality in a warming climate: a reassessment. *Wiley Interdiscip Rev Clim Change* 2013; **4:** 203–12.

18 Oudin Åström D, Ebi KL, Vicedo-Cabrera AM, Gasparrini A. Investigating changes in mortality attributable to heat and cold in Stockholm, Sweden. *Int J Biometeorol* 2018; **62:** 1777–80.

19 Chen K, Breitner S, Wolf K, et al. Temporal variations in the triggering of myocardial infarction by air temperature in Augsburg, Germany, 1987–2014. *Eur Heart J* 2019; **40:** 1G00–08.

20 Chung Y, Noh H, Honda Y, et al. Temporal changes in mortality related to extreme temperatures for 15 cities in northeast Asia: adaptation to heat and maladaptation to cold. *Am J Epidemiol* 2017; **185:** 907–13.

21 Petkova EP, Gasparrini A, Kinney PL. Heat and mortality in New York City since the beginning of the 20th century. *Epidemiology* 2014; **25:** 554–G0.

22 Gasparrini A, Guo Y, Hashizume M, et al. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *Lancet* 2015; **386:** 3G9–75.

23 Breitner S, Wolf K, Peters A, Schneider A. Short-term effects of air temperature on cause-specific cardiovascular mortality in Bavaria, Germany. *Heart* 2014; **100:** 1272–80.

24 Hempel S, Frieler K, Warszawski L, Schewe J, Piontek F. A trend-preserving bias correction—the ISI-MIP approach. *Earth Syst Dynam* 2013; **4:** 219–3G.

25 Gao J. Downscaling global spatial population projections from 1/8-degree to 1-km grid cells. ISSN Electronic Edition 2153-2400. Boulder, CO: National Center for Atmospheric Research, 2017.

2G Kc S, Lutz W. The human core of the shared socioeconomic pathways: popul ation scenarios by age, sex and level of education for all countries to 2100. *Glob Environ Change* 2017; **42:** 181–92.

27 Sellers S. Cause of death variation under the shared socioeconomic pathways. *Clim Change* 2020; **163:** 559–77.

28 Carleton TAJA, Jina A, Delgado MT, et al. Valuing the global mortality consequences of climate change accounting for adaptation costs and benefits. *Q J Econ* 2022; published online April 21. https://doi.org/10.1093/qje/qjac020.

29 Gasparrini A, Leone M. Attributable risk from distributed lag models. *BMC Med Res Methodol* 2014; **14:** 55.

30 Peters A, Schneider A. Cardiovascular risks of climate change. *Nat Rev Cardiol* 2021; **18:** 1–2.

31 Gasparrini A, Guo Y, Hashizume M, et al. Temporal variation in heat-mortality associations: a multicountry study. *Environ Health Perspect* 2015; **123:** 1200–07.

32 Romanello M, McGushin A, Di Napoli C, et al. The 2021 report of the *Lancet* Countdown on health and climate change: code red for a healthy future. *Lancet* 2021; **398:** 1G19–G2.

III. References

1. Lancet Commission on Health and Climate Change. Briefing for the global health community. 2015.
2. IPCC. Global Warming of 1.5°C. An IPCC Special Report on the impacts of global warming of 1.5°C above pre-industrial levels and related global greenhouse gas emission pathways, in the context of strengthening the global response to the threat of climate change, sustainable development, and efforts to eradicate poverty. In Press; 2018.
3. IPCC. Climate Change 2021: The Physical Science Basis.; 2021.
4. European Environmental Agency (EEA) Extreme Temperatures and Health. 2017.
5. Ebi KL, McGregor G. Climate change, tropospheric ozone and particulate matter, and health impacts. Environ Health Perspect. 2008;116(11):1449-55.
6. Baker KR, Woody MC, Tonnesen GS, Hutzell W, Pye HOT, Beaver MR, et al. Contribution of regional-scale fire events to ozone and PM2.5 air quality estimated by photochemical modeling approaches. Atmospheric Environment. 2016;140:539-54.
7. Schnell JL, Prather MJ. Co-occurrence of extremes in surface ozone, particulate matter, and temperature over eastern North America. Proc Natl Acad Sci U S A. 2017;114(11):2854-9.
8. Vicedo-Cabrera AM, Scovronick N, Sera F, Roye D, Schneider R, Tobias A, et al. The burden of heat-related mortality attributable to recent human-induced climate change. Nat Clim Chang. 2021;11(6):492-500.
9. European Environmental Agency (EEA) Air Quality in Europe. 2016.
10. WHO. Heatwaves 2023 [Available from: https://www.who.int/health-topics/heatwaves#tab=tab_1
11. Roye D, Sera F, Tobias A, Lowe R, Gasparrini A, Pascal M, et al. Effects of hot nights on mortality in Southern Europe. Epidemiology. 2021.
12. Williams S, Venugopal K, Nitschke M, Nairn J, Fawcett R, Beattie C, et al. Regional morbidity and mortality during heatwaves in South Australia. Int J Biometeorol. 2018;62(10):1911-26.
13. Gasparrini A, Armstrong B. The impact of heat waves on mortality. Epidemiology. 2011;22(1):68-73.
14. Basu R. High ambient temperature and mortality: a review of epidemiologic studies from 2001 to 2008. Environ Health. 2009;8:40.
15. Turner LR, Barnett AG, Connell D, Tong S. Ambient temperature and cardiorespiratory morbidity: a systematic review and meta-analysis. Epidemiology. 2012;23(4):594-606.

16. Bai L, Li Q, Wang J, Lavigne E, Gasparrini A, Copes R, et al. Hospitalizations from Hypertensive Diseases, Diabetes, and Arrhythmia in Relation to Low and High Temperatures: Population-Based Study. Sci Rep. 2016;6:30283.
17. WHO. Air Pollution 2021 [Available from: https://www.who.int/health-topics/air-pollution#tab=tab_1.
18. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. 2020;396(10258):1204-22.
19. Chen K, Wolf K, Breitner S, Gasparrini A, Stafoggia M, Samoli E, et al. Two-way effect modifications of air pollution and air temperature on total natural and cardiovascular mortality in eight European urban areas. Environ Int. 2018;116:186-96.
20. Analitis A MP, D'Ippoliti D, de'Donato F, Menne B, et. al. Effects of Heat Waves on Mortality. 2014.
21. Kioumourtzoglou MA, Schwartz J, James P, Dominici F, Zanobetti A. PM2.5 and Mortality in 207 US Cities: Modification by Temperature and City Characteristics. Epidemiology. 2016;27(2):221-7.
22. Ren C, Williams GM, Tong S. Does Particulate Matter Modify the Association between Temperature and Cardiorespiratory Diseases? Environmental Health Perspectives. 2006;114(11):1690-6.
23. Breitner S, Wolf K, Devlin RB, Diaz-Sanchez D, Peters A, Schneider A. 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. 2014;485-486:49-61.
24. Chen F, Fan Z, Qiao Z, Cui Y, Zhang M, Zhao X, et al. Does temperature modify the effect of PM10 on mortality? A systematic review and meta-analysis. Environmental Pollution. 2017;224:326-35.
25. Zhang B, Li G, Ma Y, Pan X. Projection of temperature-related mortality due to cardiovascular disease in beijing under different climate change, population, and adaptation scenarios. Environ Res. 2018;162:152-9.
26. Marinucci GD, Luber G, Uejio CK, Saha S, Hess JJ. Building Resilience Against Climate Effects-a novel framework to facilitate climate readiness in public health agencies. Int J Environ Res Public Health. 2014;11(6):6433-58.
27. Watts N, Amann M, Arnell N, Ayeb-Karlsson S, Beagley J, Belesova K, et al. The 2020 report of The Lancet Countdown on health and climate change: responding to converging crises. The Lancet. 2021;397(10269):129-70.
28. Potsdam Institutue for Climate Impact Research and Helmholtz Center Munich. The Lancet Countdown on Health and Climate Change: Policy Brief für Deutschland.; 2021.

29. Intergovernmental Panel on Climate Change (IPCC). Climate Change 2013: The Physical Science Basis. Contribution of Working Group I to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge University Press, Cambridge, United Kingdom and New York, NY, USA; 2013.
30. Huang C, Barnett AG, Wang X, Vaneckova P, FitzGerald G, Tong S. Projecting future heat-related mortality under climate change scenarios: a systematic review. Environ Health Perspect. 2011;119(12):1681-90.
31. Gasparrini A, Guo Y, Hashizume M, Lavigne E, Zanobetti A, Schwartz J, et al. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. The Lancet. 2015;386(9991):369-75.
32. Gasparrini A, Guo Y, Hashizume M, Kinney PL, Petkova EP, Lavigne E, et al. Temporal Variation in Heat-Mortality Associations: A Multicountry Study. Environ Health Perspect. 2015;123(11):1200-7.
33. Chung Y, Noh H, Honda Y, Hashizume M, Bell ML, Guo YL, et al. Temporal Changes in Mortality Related to Extreme Temperatures for 15 Cities in Northeast Asia: Adaptation to Heat and Maladaptation to Cold. Am J Epidemiol. 2017;185(10):907-13.
34. Breitner S, Wolf K, Peters A, Schneider A. Short-term effects of air temperature on cause-specific cardiovascular mortality in Bavaria, Germany. Heart. 2014;100(16):1272-80.
35. Yang C, Meng X, Chen R, Cai J, Zhao Z, Wan Y, et al. Long-term variations in the association between ambient temperature and daily cardiovascular mortality in Shanghai, China. Sci Total Environ. 2015;538:524-30.
36. Alahmad B, Khraishah H, Royé D, Vicedo-Cabrera AM, Guo Y, Papatheodorou SI, et al. Associations Between Extreme Temperatures and Cardiovascular Cause-Specific Mortality: Results From 27 Countries. Circulation. 2023;147(1):35-46.
37. Liu L, Breitner S, Pan X, Franck U, Leitte AM, Wiedensohler A, et al. Associations between air temperature and cardio-respiratory mortality in the urban area of Beijing, China: a time-series analysis. Environ Health. 2011;10:51.
38. Yang J, Yin P, Zhou M, Ou CQ, Guo Y, Gasparrini A, et al. Cardiovascular mortality risk attributable to ambient temperature in China. Heart. 2015;101(24):1966-72.
39. Irmela Schlegel SM, Hans-Guido Mücke and Andreas Matzarakis. Comparison of Respiratory and Ischemic Heart Mortality and its Relationship to Thermal Environment. 2020.
40. Michelozzi P, Accetta G, De Sario M, D'Ippoliti D, Marino C, Baccini M, et al. High temperature and hospitalizations for cardiovascular and respiratory causes in 12 European cities. Am J Respir Crit Care Med. 2009;179(5):383-9.

41. Chen K, Breitner S, Wolf K, Hampel R, Meisinger C, Heier M, et al. Temporal variations in the triggering of myocardial infarction by air temperature in Augsburg, Germany, 1987-2014. Eur Heart J. 2019;40(20):1600-8.
42. Petkova EP, Gasparrini A, Kinney PL. Heat and mortality in New York City since the beginning of the 20th century. Epidemiology. 2014;25(4):554-60.
43. Stafoggia M, Schwartz J, Forastiere F, Perucci CA, Group S. Does temperature modify the association between air pollution and mortality? A multicity case-crossover analysis in Italy. Am J Epidemiol. 2008;167(12):1476-85.
44. Stafoggia M, Forastiere F, Faustini A, Biggeri A, Bisanti L, Cadum E, et al. Susceptibility factors to ozone-related mortality: a population-based case-crossover analysis. Am J Respir Crit Care Med. 2010;182(3):376-84.
45. Burkart K, Canario P, Breitner S, Schneider A, Scherber K, Andrade H, et al. Interactive short-term effects of equivalent temperature and air pollution on human mortality in Berlin and Lisbon. Environ Pollut. 2013;183:54-63.
46. Pascal M, Wagner V, Alari A, Corso M, Le Tertre A. Extreme heat and acute air pollution episodes: A need for joint public health warnings? Atmospheric Environment. 2021;249:118249.
47. Li J, Woodward A, Hou XY, Zhu T, Zhang J, Brown H, et al. Modification of the effects of air pollutants on mortality by temperature: A systematic review and meta-analysis. Sci Total Environ. 2017;575:1556-70.
48. Jhun I, Fann N, Zanobetti A, Hubbell B. Effect modification of ozone-related mortality risks by temperature in 97 US cities. Environ Int. 2014;73:128-34.
49. Scortichini M, De Sario M, de'Donato FK, Davoli M, Michelozzi P, Stafoggia M. Short-Term Effects of Heat on Mortality and Effect Modification by Air Pollution in 25 Italian Cities. Int J Environ Res Public Health. 2018;15(8).
50. Gasparrini A, Guo Y, Sera F, Vicedo-Cabrera AM, Huber V, Tong S, et al. Projections of temperature-related excess mortality under climate change scenarios. The Lancet Planetary health. 2017;1(9):e360-e7.
51. Lee JY, Kim E, Lee WS, Chae Y, Kim H. Projection of Future Mortality Due to Temperature and Population Changes under Representative Concentration Pathways and Shared Socioeconomic Pathways. Int J Environ Res Public Health. 2018;15(4).
52. Rai M, Breitner S, Wolf K, Peters A, Schneider A, Chen K. Impact of climate and population change on temperature-related mortality burden in Bavaria, Germany. Environmental Research Letters. 2019;14(12):124080.
53. Chen K, Vicedo-Cabrera AM, Dubrow R. Projections of Ambient Temperature- and Air Pollution-Related Mortality Burden Under Combined Climate Change and Population Aging Scenarios: a Review. Current Environmental Health Reports. 2020;7(3):243-55.

54. Gasparrini A, Guo Y, Sera F, Vicedo-Cabrera AM, Huber V, Tong S, et al. Projections of temperature-related excess mortality under climate change scenarios. The Lancet Planetary health. 2017;1(9):e360-e7.
55. Wang Y, Wang A, Zhai J, Tao H, Jiang T, Su B, et al. Tens of thousands additional deaths annually in cities of China between 1.5 °C and 2.0 °C warming. Nat Commun. 2019;10(1):3376.
56. Weinberger KR, Haykin L, Eliot MN, Schwartz JD, Gasparrini A, Wellenius GA. Projected temperature-related deaths in ten large U.S. metropolitan areas under different climate change scenarios. Environ Int. 2017;107:196-204.
57. Petkova EP, Horton RM, Bader DA, Kinney PL. Projected heat-related mortality in the U.S. urban northeast. Int J Environ Res Public Health. 2013;10(12):6734-47.
58. Anderson GB, Oleson KW, Jones B, Peng RD. Projected trends in high-mortality heatwaves under different scenarios of climate, population, and adaptation in 82 US communities. Clim Change. 2018;146(3-4):455-70.
59. Ebi KL, Mills D. Winter mortality in a warming climate: a reassessment. Wiley Interdisciplinary Reviews: Climate Change. 2013;4(3):203-12.
60. Wang Y, Wang A, Zhai J, Tao H, Jiang T, Su B, et al. Tens of thousands additional deaths annually in cities of China between 1.5 degrees C and 2.0 degrees C warming. Nat Commun. 2019;10(1):3376.
61. IPCC. Climate Change 2014: Synthesis Report. Contribution of Working Groups I, II and III to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change. Geneva, Switzerland; 2014.
62. Sellers S, Ebi KL. Climate Change and Health under the Shared Socioeconomic Pathway Framework. Int J Environ Res Public Health. 2017;15(1).
63. Gasparrini A. MCC Collaborative Research Network: London School of Hygiene and Tropical Medicine; 2022 [Available from: https://ghhin.org/resources/mcc-collaborative-research-network/.
64. ISIMIP. The Inter-Sectoral Impact Model Intercomparison Project 2020 [Available from: https://www.isimip.org/.
65. Gao J. Downscaling Global Spatial Population Projections from 1/8-degree to 1-km Grid Cells. National Center for Atmospheric Research; 2017.
66. Kc S, Lutz W. The human core of the shared socioeconomic pathways: Population scenarios by age, sex and level of education for all countries to 2100. Glob Environ Change. 2017;42:181-92.
67. Sellers S. Cause of death variation under the shared socioeconomic pathways. Clim Change. 2020:1-19.
68. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing Vienna, Austria2017 [Available from: http://www.R-project.org/.

69. Schneider A, Ruckerl R, Breitner S, Wolf K, Peters A. Thermal Control, Weather, and Aging. Curr Environ Health Rep. 2017;4(1):21-9.
70. Liu C, Yavar Z, Sun Q. Cardiovascular response to thermoregulatory challenges. Am J Physiol Heart Circ Physiol. 2015;309(11):H1793-812.
71. Konstantinoudis G, Minelli C, Vicedo-Cabrera AM, Ballester J, Gasparrini A, Blangiardo M. Ambient heat exposure and COPD hospitalisations in England: a nationwide case-crossover study during 2007-2018. Thorax. 2022;77(11):1098-104.
72. Zhao Q, Li S, Coelho M, Saldiva PHN, Xu R, Huxley RR, et al. Ambient heat and hospitalisation for COPD in Brazil: a nationwide case-crossover study. Thorax. 2019;74(11):1031-6.
73. Cox B, Vicedo-Cabrera AM, Gasparrini A, Roels HA, Martens E, Vangronsveld J, et al. Ambient temperature as a trigger of preterm delivery in a temperate climate. J Epidemiol Community Health. 2016;70(12):1191-9.
74. Bind MA, Zanobetti A, Gasparrini A, Peters A, Coull B, Baccarelli A, et al. Effects of temperature and relative humidity on DNA methylation. Epidemiology. 2014;25(4):561-9.
75. Abraham E, Rousseaux S, Agier L, Giorgis-Allemand L, Tost J, Galineau J, et al. Pregnancy exposure to atmospheric pollution and meteorological conditions and placental DNA methylation. Environ Int. 2018;118:334-47.
76. Martens DS, Cox B, Janssen BG, Clemente DBP, Gasparrini A, Vanpoucke C, et al. Prenatal Air Pollution and Newborns' Predisposition to Accelerated Biological Aging. JAMA Pediatr. 2017;171(12):1160-7.
77. Mudway IS, Kelly FJ, Holgate ST. Oxidative stress in air pollution research. Free Radic Biol Med. 2020;151:2-6.
78. Breton CV, Song AY, Xiao J, Kim SJ, Mehta HH, Wan J, et al. Effects of air pollution on mitochondrial function, mitochondrial DNA methylation, and mitochondrial peptide expression. Mitochondrion. 2019;46:22-9.
79. Yauk C, Polyzos A, Rowan-Carroll A, Somers CM, Godschalk RW, Van Schooten FJ, et al. Germ-line mutations, DNA damage, and global hypermethylation in mice exposed to particulate air pollution in an urban/industrial location. Proc Natl Acad Sci U S A. 2008;105(2):605-10.
80. Neven KY, Saenen ND, Tarantini L, Janssen BG, Lefebvre W, Vanpoucke C, et al. Placental promoter methylation of DNA repair genes and prenatal exposure to particulate air pollution: an ENVIRONAGE cohort study. The Lancet Planetary health. 2018;2(4):e174-e83.
81. Janssen BG, Saenen ND, Roels HA, Madhloum N, Gyselaers W, Lefebvre W, et al. Fetal Thyroid Function, Birth Weight, and in Utero Exposure to Fine Particle Air Pollution: A Birth Cohort Study. Environ Health Perspect. 2017;125(4):699-705.

82. Bollati V, Angelici L, Rizzo G, Pergoli L, Rota F, Hoxha M, et al. Microvesicle-associated microRNA expression is altered upon particulate matter exposure in healthy workers and in A549 cells. J Appl Toxicol. 2015;35(1):59-67.
83. Mutlu EA, Comba IY, Cho T, Engen PA, Yazıcı C, Soberanes S, et al. Inhalational exposure to particulate matter air pollution alters the composition of the gut microbiome. Environ Pollut. 2018;240:817-30.
84. Peters A, Veronesi B, Calderón-Garcidueñas L, Gehr P, Chen LC, Geiser M, et al. Translocation and potential neurological effects of fine and ultrafine particles a critical update. Part Fibre Toxicol. 2006;3:13.
85. Peters A, Nawrot TS, Baccarelli AA. Hallmarks of environmental insults. Cell. 2021;184(6):1455-68.
86. World Health O. WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. Geneva: World Health Organization; 2021 2021.
87. Peters A, Schneider A. Cardiovascular risks of climate change. Nat Rev Cardiol. 2020.
88. Rai M, Breitner S, Zhang S, Rappold AG, Schneider A. Achievements and gaps in projection studies on the temperature-attributable health burden: Where should we be headed? Frontiers in Epidemiology. 2022;2.

Publication: Achievements and gaps in projection studies on the temperature-attributable health burden: Where should we be headed?

Title:	Achievements and gaps in projection studies on the temperature-attributable health burden: Where should we be headed?
Authors:	**Masna Raj**, Susanne Breitner, Siqi Zhang, Ana G. Rappold, and Alexandra Schneider
Journal:	*Frontiers in Epidemiology*
Year:	2022
Volume:	2:1063871
DOI:	10.3389/fepid.2022.1063871
Rights declaration:	This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY)

frontiers | Frontiers in Epidemiology

TYPE Review
PUBLISHED 16 December 2022
DOI 10.3389/fepid.2022.1063871

OPEN ACCESS

EDITED BY
Pin Wang,
Yale University, United States

REVIEWED BY
Lina Madaniyazi,
Nagasaki University, Japan
Barrak Alahmad,
Harvard University, United States
Vijendra Ingole,
Instituto Salud Global Barcelona (ISGlobal), Spain

*CORRESPONDENCE
Masna Rai
masna.rai@helmholtz-muenchen.de

SPECIALTY SECTION
This article was submitted to Occupational and Environmental Epidemiology, a section of the journal Frontiers in Epidemiology

RECEIVED 07 October 2022
ACCEPTED 21 November 2022
PUBLISHED 16 December 2022

CITATION
Rai M, Breitner S, Zhang S, Rappold AG and Schneider A (2022) Achievements and gaps in projection studies on the temperature-attributable health burden: Where should we be headed?
Front. Epidemiol. 2:1063871.
doi: 10.3389/fepid.2022.1063871

Achievements and gaps in projection studies on the temperature-attributable health burden: Where should we be headed?

Masna Rai[1,2]*, Susanne Breitner[1,2], Siqi Zhang[1], Ana G. Rappold[3] and Alexandra Schneider[1]

[1]Institute of Epidemiology, Helmholtz Center Munich, Neuherberg, Germany, [2]Institute for Medical Information Processing, Biometry, and Epidemiology, LMU Munich, Munich, Germany, [3]Center for Public Health and Environmental Assessment, Office of Research and Development, United States Environmental Protection Agency, Research Triangle Park, Durham, NC, United States

Future projection of the temperature-related health burden, including mortality and hospital admissions, is a growing field of research. These studies aim to provide crucial information for decision-makers considering existing health policies as well as integrating targeted adaptation strategies to evade the health burden. However, this field of research is still overshadowed by large uncertainties. These uncertainties exist to an extent in the future climate and population models used by such studies but largely in the disparities in underlying assumptions. Existing studies differ in the factors incorporated for projection and strategies for considering the future adaptation of the population to temperature. These differences exist to a great degree because of a lack of robust evidence as well as gaps in the field of climate epidemiology that still require extensive input from the research community. This narrative review summarizes the current status of projection studies of temperature-attributable health burden, the guiding assumptions behind them, the common grounds, as well as the differences. Overall, the review aims to highlight existing evidence and knowledge gaps as a basis for designing future studies on temperature-attributable health burden estimation. Finding a robust methodology for projecting the future health burden could be a milestone for climate epidemiologists as this would largely benefit the world when applying this technique to project the climate-attributable cause-specific health burden and adapt our existing health policies accordingly.

KEYWORDS

climate change, projection studies, health burden, review, gaps

Introduction

Projection studies estimate the future health burden directly or indirectly caused by the changing climate. These studies, giving us a future picture of the climate-attributable health burden, are crucial in that they urge stakeholders, policymakers, civil society, scientists, and the public to practice and enforce mitigation measures for climate

protection. *Mitigation*, as defined by the fourth assessment report of the Intergovernmental Panel on Climate Change (IPCC), is an "anthropogenic intervention to reduce the sources or enhance the sinks of greenhouse gases" (1). Management of the climate crisis through climate change mitigation seemed hopeful until recently, when the recent IPCC report was released. The report states that unless there are immediate large-scale mitigation measures to reduce greenhouse gas emissions, it is beyond reach to limit global warming to 1.5°C or even 2°C (2). Therefore, mitigation is not enough to combat the harms of the rapidly changing climate. Amidst this crisis, adaptation strategies can help to build climate resilience. The IPCC report defines *adaptation* as "adjustment in natural or human systems in response to actual or expected climatic stimuli or their effects, which moderates harm or exploits beneficial opportunities" (1).

The goal of today is to build a climate-resilient society that can be possible only in the presence of efficient adaptation strategies in addition to mitigation measures. For this, evidence-based planning of health policies and adaptation measures need to be designed by public health professionals, implemented by health authorities, and incorporated by society. In this regard, studies projecting the climate-attributable future health burden can support laying a foundation of evidence and aid in planning effective adaptation strategies. Projection studies help in the planning of adaptation strategies in the following ways:

i. They estimate the future climate-related health burden, allowing for the planning of healthcare resources.
ii. They estimate the climate-related health burden for different causes, which enables us to focus on adaptation plans for specific diseases or health outcomes.
iii. They estimate the climate-related health burden for different population subgroups, which enables us to identify those who are especially at risk of climate change, allowing us to target and adapt our adaptation policies for the vulnerable and susceptible population groups.

Projection studies emerged during the late 1900s (3, 4). Early studies projected temperature-related deaths for 2020 and 2050 for selected cities. During the 2000s, research in the field started growing (5–10); however, studies focused on North America (5–8) and Europe (8–10). After 2010, climate epidemiology started being prioritized, and projection studies were expanding (11–21), with research still focused on the US and Europe. In the mid-2010s, projection studies started in China (22–29) and Latin America (30), while projection studies in the US, Europe, and Australia continued to expand (31–44). The era of 2010 was a remarkable period for climate epidemiology, not only because of the expanding field with large epidemiological studies incorporating methodological advancements but also because projection on other critical aspects related to climate change, apart from the previously explored temperature-related total mortality, was initiated. Researchers started exploring the burden of cardiovascular and respiratory diseases (27), vector-borne diseases like Malaria (45), and sensitive issues like children's health were highlighted (46).

The field of climate-attributable health impact research is expanding rapidly, however, still overshadowed by large uncertainties and differing largely in their guiding principles. These differences exist to a great degree because of a lack of robust evidence as well as gaps in the field of climate epidemiology that still require extensive input from the research community. In this context, the research community would largely benefit from a review that summarizes current status, assumptions, and evidences, which would facilitate the planning of future studies. Existing reviews of the field either focused only on heat-related mortality (47) or climate change mitigation outcomes (48). This narrative review, therefore, aims to summarize the current status of projection studies of temperature-attributable health burden, the guiding assumptions behind them, the common grounds, as well as the differences. Overall, the review aims to highlight existing evidence and knowledge gaps as a basis for designing future studies on temperature-attributable health burden estimation.

Temperature attributable health burden and earlier misconceptions

The results from early projection studies partly raised misconceptions in that climate change looked beneficial. For example, the study by Martens et al., which included various cities from around the world, found for most cities that climate change is likely to cause a reduction in mortality rates due to decreasing winter mortality. The study claimed this effect was more pronounced for cardiovascular mortality in older people in cities with temperate or cold climates at present (4). In addition, the result of the study was not generalizable to other regions of the world with different climatic conditions. Conversely, another study by Kalkstein et al., projecting mortality in US cities for 2020 and 2050, found summer mortality to increase dramatically while winter mortality to decrease slightly, as a result of climate change (3), illustrating that the net impact of climate change would be more harmful than beneficial. Nevertheless, this study was done in a single country and needed validation by a larger study across regions of varying climatic and socio-economic conditions.

From these studies, it was evident that there exists a temperature-related health burden in association with future temperatures, with losses from heat-related deaths on the one hand and benefits from cold-related deaths on the other. Therefore, for valid future projections, studies were needed that estimated the net future temperature-related burden

incorporating both heat and cold impacts. A 2011 study by Ballester et al. (14) systematically estimated the heat- and cold-related deaths in 200 European regions. The results showed that the rise in deaths from heat would start to compensate completely the reduction of cold-related mortality during the second half of the 21st century. This study provided evidence that climate change would not be beneficial in the long run, at least for the European regions included in the study. To validate the results, the climate epidemiology community needed a large study investigating such associations across regions with varying climatic and socio-economic conditions. In 2017, a multi-country and multi-city study by Gasparrini et al. (49) projected the net temperature-related health burden in 451 locations from 23 countries. This study is one of the most comprehensive studies in terms of including cities from around the world in a single study. The results were seen to vary across regions. In temperate areas such as northern Europe, East Asia, and Australia, the less intense warming and the large decrease in cold-related deaths would induce a null or marginally negative net effect. In contrast, warmer regions, including central and southern America, Europe, and Southeast Asia, would expect steep increases in heat-related mortality resulting in a large net burden. The study concluded that the negative health impacts of climate change would disproportionately affect warmer regions of the world, and regions lagging in infrastructures and technology. From this observation, it is clear that people worldwide are vulnerable to climate change—but not equally. Nevertheless, it is essential to note that this study did not account for influential factors like differing health effects of heat or cold across different population age groups and changing demographic structures over time (i.e., population aging). Therefore, the observed decrease in the net burden in temperate first-world nations might have been rather biased.

Fundamental concepts: Exposure response functions

Future projections of the health burden are primarily based on present-day observations. Studies usually start with time-series data of health outcome during a reference baseline period to explore the association between temperature and the health outcome of interest (49, 50). This association is often termed *Exposure Response Function* (ERF). From the ERFs, the risk of the health outcome at each temperature point is obtained, which is then extrapolated to the future temperature observations (50). Researchers obtain future temperature data from climate modelers, estimate the future risk under these temperature projections and quantify the differences in the health burden in the future compared to the baseline. Figure 1 summarizes the standard practiced methodology of temperature-attributable health outcome projection.

Until recent years, most studies have applied an overall baseline ERF for future projections, assuming all population subgroups to act similarly to a given temperature (49). However, this approach underestimates the future health burden as the most vulnerable and susceptible population subgroups, like the elderly, are assumed to have the same baseline rate of risk as the younger population. A study by Rai et al. elaborates on this drawback of using an overall ERF by projecting future temperature-related total mortality burden by applying two frameworks; an overall ERF and age-specific ERFs (42). The results show a considerable underestimation of the health burden when not considering the age-specific ERFs. Therefore, projection studies incorporating age-specific ERFs might provide a more valid estimation of the future health burden (19, 51–53).

Nonetheless, all the above principles of projection studies assume that the ERFs of the future population remain constant as the present-day ERF, i.e., no adaptation of the human body to the changing climate occurs. This might introduce large biases. So far, few studies have considered population adaptation when estimating the future temperature-related health burden (5, 6, 8, 9, 54–57). These studies differ in their approaches. Some of the earlier approaches used ERFs of analogous summers or cities for future projections (5, 6); for example, a test city was assumed to be similar to a larger reference city in the future. For present-day large cities, some harsh summers with a temperature distribution similar to the modelled future temperature were selected as the reference summer. The population of the test city was then assumed to react to temperature increases in the same way as the population from the reference city or the reference summer in the future. However, these approaches were largely based on untestable assumptions, resulting in large uncertainties. More recent studies assume population acclimatization over a few degrees (8, 9) or a shift in the ERF between temperature and health outcomes (50). However, there is no established general methodological procedure to account for physiological adaptation to changing climate.

Scenarios

Projecting health burden is estimating health outcomes under uncertainty in a number of systems including the environmental, human, and socio-economic systems, and the complex interaction between them. For this reason, climate change research has been working with future scenarios, which include a set of climatic and socio-economic assumed conditions that we might experience in the future.

Earlier projection studies estimated the health burden under different climate scenarios, i.e., the Representative Concentration Pathways (RCPs) (19, 38, 49, 51, 52, 58). While these studies

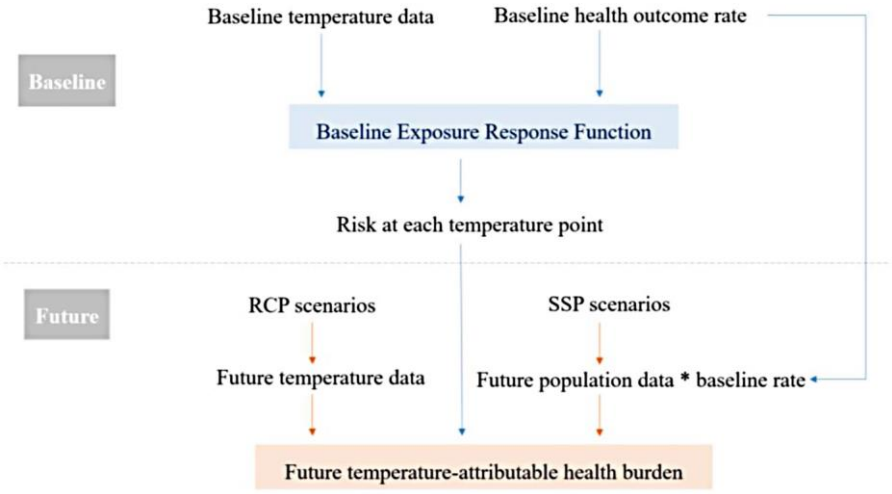

FIGURE 1
A flowchart of the standard methodology of temperature-attributable health outcome projections.

addressed climate uncertainty and some aspects of population and economic changes incorporated within the RCPs, they did not account for other possible changes in societal factors such as demographics, human development (for example, health and education), economic growth, inequality, governance, technological change, and policy orientations. All these factors are considered by the different scenarios under the Shared Socio-Economic Pathways (SSPs) (59). Comparatively few studies have considered the SSP scenarios when estimating the future temperature-related health burden (42, 53). Although practiced, using a combination of all four RCPs (60) and five SSPs (61) was not the most efficient and convincing methodology because many RCP-SSP combinations seem implausible. A publication by O'Neill et al., explains the plausibility of various RCP-SSP scenario combinations (62). For example, the combination of RCP 8.5 (the worst climate change scenario) and SSP1 (the scenario with lowest challenge to adaptation and mitigation) seems implausible. In 2021, IPCC revised the RCPs and released an update of the climate scenarios integrating the plausible SSP scenarios into the RCPs, termed SSP- RCP scenarios (2).

Apart from the RCP-SSP scenarios, a crucial aspect to be considered for a justifiable future projection is population aging. The SSP scenarios consider the change in population; however, like with the age-specific ERFs, a key aspect to be integrated is the age-specific population growth (demographic change), which had been ignored until recently (28, 29, 42). Not considering the increasing proportion of older people, especially in first-world nations, would lead to underestimating the climate-related health burden as this population subgroup is one of the most susceptible.

Uncertainties and assumptions

The field of climate epidemiology dominated largely by uncertainties and assumptions. Some of the determining sources of uncertainties are the modelled future climate and societal scenarios, i.e., the RCPs and the SSPs. These scenarios, providing us with a range of plausible future scenarios, are largely based on assumptions. However, the efforts to continuously reevaluate and update these scenarios have helped in overcoming uncertainties (59). Table 1 lists the major sources of uncertainties and underlying assumptions.

TABLE 1 Summary of uncertainties and assumptions in climate-attributable health burden projection.

Sources of uncertainties	Underlying assumptions
Climate models	Assumptions made while defining various atmospheric parameters under future climate scenarios to obtain the future temperature data.
Population projections	Assumptions made while defining future demographics, human development (for example, health and education), economic growth, inequality, governance, technological change, and policy orientations under future socioeconomic scenarios to obtain the future population data.
Physiological adaptation of human body to the changing climate	Use of analogous cities or summers or changing the slope of the baseline ERFs.
Socioeconomic changes, technological advancements and changes in healthcare system and settings	Using GDP as a factor determining the adaptive capacity and using it as a factor potentially changing the temperature-related health risk.

Gaps

Although the field of climate epidemiology is progressing rapidly, there still exist significant research gaps. The gaps have been listed and elaborated in the following sections.

Focus on heat and not the entire temperature range

One of the largest needs for climate epidemiology research is to shift the focus from heat-related mortality projections to total temperature-related mortality projections, which include both heat- and cold-related mortality. Most earlier projection studies focused on heat-related mortality (5, 8, 16, 18, 22, 27, 40, 63), leaving behind the cold-related future attributable burden. However, it is important to consider that cold-related mortality is only minimally attributable to extreme cold but mostly to moderate cold or air temperature changes (temperature variability) that would persist in the future, even with a warming climate. Therefore, projection studies would not be complete without considering the cold-related mortality and estimating the net temperature-related mortality burden (64).

Use of overall ERF rather than sub-group specific ERF

Another overshadowed aspect is the failure to incorporate the age-specific ERFs and the age-specific population growth rates when estimating the future temperature-related health burden. Although some recent studies considered this aspect (28, 29), these studies focused only on heat-related impacts and ignored the cold-related impacts. Only a handful of studies have considered age-specific ERFs and population growth rates to estimate the future net temperature-related health burden (42). Moreover, other climate vulnerability and susceptibility factors apart from age have been left entirely unaddressed.

Considering a constant ERF

Majority of the projection studies consider constant response of the population to a given temperature. However, response of the human body to a given temperature might change in the future, leading to either adaptation or sensitivity. Only a small number of studies have considered physiological adaptation of the human body (9, 55, 57) to heat and no studies have considered the physiological changes in response to cold. As discussed above, cold-related mortality would continue to dominate a large fraction of temperature-related mortality. Therefore, projection studies would not be complete without considering the future changes in the cold-mortality relationships, i.e., taking into account also the adaptation or increasing sensitivity to cold in the future (64). Existing evidence on non-decreasing (65, 66) or even increasing cold effects (67) over time suggests that together with adaptation to heat, on the one hand, the future population might be increasingly susceptible to cold on the other (64). Furthermore, it is essential to note that physiological adaptation pathways cannot be generalized but need to be considered specifically for a population of interest. A large multi-country study investigating the temporal variation in the heat-mortality association has demonstrated that the adaptation pattern or heat sensitivity varies across locations (68).

Lack of simultaneous consideration of socioeconomic adaptation

A crucial aspect not yet fully accounted for is the future population adaptation particularly in the context of social and economic inequalities. The future population is foreseen to undergo not just single but multiple simultaneous adaptation pathways (69). In addition to physiological adaptation, future infrastructure changes, technological advancements, and socio-economic challenges might play an important role in influencing how the human body reacts to temperature. Some recent studies (29) have explored this aspect of adaptation by defining future adaptive capacity as a factor of the future Gross Domestic Product (GDP). However, physiological and socioeconomic adaptation have not been yet considered simultaneously but rather independently. A recently proposed methodological framework for health burden projections aims to overcome this gap by systematically incorporating future physiological adaptation-sensitivity and socio-economic adaptive capacities as factors potentially changing the ERF in the future (69).

Future shifts in infrastructure, healthcare, as well as technological advancements might change the mortality rate. These might be changes in the overall mortality rate (70) or cause-specific mortality rates (71). Failure to incorporate these changes in studies estimating the future overall or cause-specific mortality might lead to overestimating the future temperature-related burden. Only a limited number of projection studies have so far incorporated expected changes in mortality rates while estimating the future temperature-related mortality burden (69).

Focus only on specific health outcomes

Another major gap is the focus of projection studies on total mortality. Although recent studies also project cause-specific

mortality under different ranges of future climate and population change scenarios (42, 44, 49, 53, 43), these studies are limited to specific regions. Furthermore, no studies have looked into other critical aspects like cause-specific hospitalizations.

No studies in rural areas

In addition, all projection studies, including the largest multi-country study, have focused on cities (49) leaving behind the rural areas. It is yet unknown if rural areas might show different temperature effects in the future compared to cities or rather similar effects as, depending on location, exposure intensity, population structure, and susceptibility might be quite different. The results from the EU HORIZON2020 project EXHAUSTION show that temperature effects vary among European regions. Within this project, it was observed that the heat effects on mortality in Northern Europe were stronger in urban areas than that in rural areas, whereas, both heat and cold effects in the rural areas were found to be similar to that observed in cities in other parts of Europe (72). Extensive studies in other regions with different climatic and socio-economic conditions are required to verify this finding.

Lack of representation

One of the largest gaps of projection studies is that they are limited to certain regions of the world, mostly North America, Europe, and East Asia. Other regions of the world, which might be facing the largest consequences of climate change (73), like Africa, South Asia, and the Middle East have been largely underrepresented. This issue also arises due to lack of data availability from those regions.

Needs and recommendations

The following section lists and describes the needs and recommendations:

a) Inclusion and representativeness

i. The climate epidemiology community needs more inclusive projection studies from across regions of diverse geographic, climatic, and socio-economic conditions.

ii. Studies from rural areas and less urbanized areas are needed for a comprehensive understanding of climate-health association. In addition, studies projecting health burden at a finer geographical resolution with calibrated temperature models would be helpful for stakeholders in understanding and addressing the future risks at a community level.

b) Methodology

i. Projection studies need to be designed to look at not just the heat- or cold-related burden separately, but a combined net temperature-related burden.

ii. Future studies should incorporate sub-group specific ERFs (e.g., age-specific ERFs), rather than the overall ERFs, as they provide a reasonable and less biased estimation of the future health burden (19, 51–53).

iii. Extensive baseline studies to explore susceptible and vulnerable population subgroups other than the elderly are recommended for a substantially valid projection of the future health burden. To achieve this, establishment of cohorts with all-encompassing individual characteristics and large enough to cover regions of varying climatic and socio-economic conditions is recommended.

iv. The establishment of a standard procedure for accounting for future population adaptation is recommended.

c) For driving policy

i. Extensive investigation on potential further adaptation factors which could be influenced by policy makers and stakeholders and health care provides or public health institutions is needed.

Summary

Projection studies estimating the future climate-attributable health burden are crucial as they would aid in designing, adapting, and implementing targeted adaptation measures, as well as stressing the urgency of mitigation actions. This would help public health professionals in building a climate change resilient community.

Climate epidemiologists should focus on advancing projection studies but also on gathering extensive and unbiased baseline associations between temperature and cause-specific health outcomes, identifying the most vulnerable and susceptible population subgroups in regions with varying climatic and socio-economic conditions. As these baseline associations are the backbone of projection studies, researchers should focus on gathering valid and extensive baseline evidence.

Further validation studies are required to establish a common framework and guidelines for future projection. Future studies in the field should focus on other health outcomes in addition to total mortality. The studies should attempt to estimate the net temperature-related health burden considering the subgroup-specific ERFs, future subgroup-specific population change, future mortality or hospital admission rates, and above all, the possible physiological and socio-economic adaptation. To summarize, future studies should account for all the complex dynamics, which play a role in determining temperature-related mortality (Figure 2).

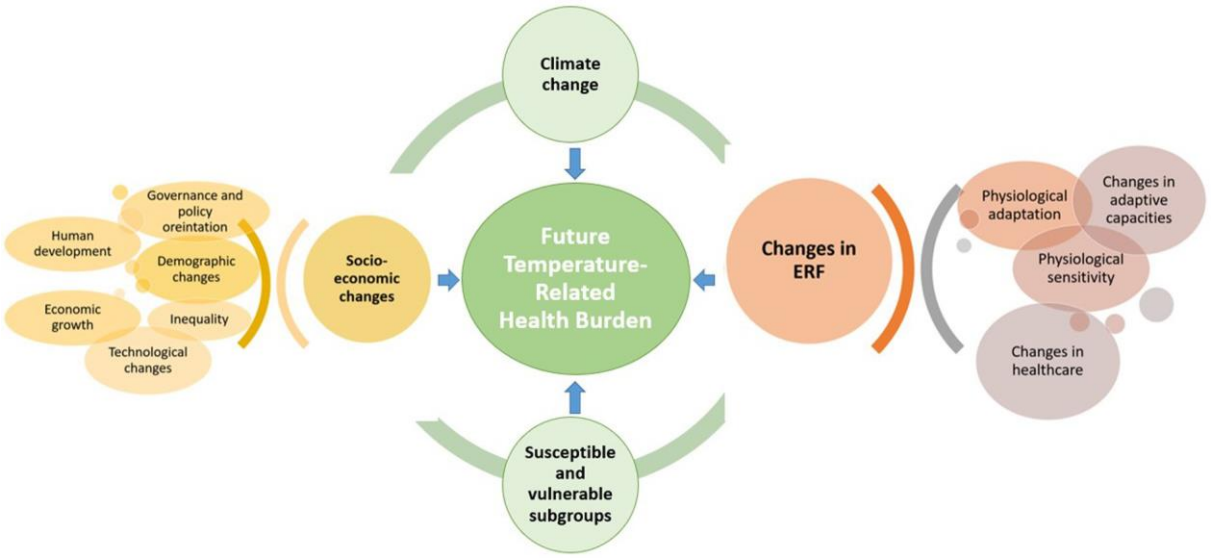

FIGURE 2
Dynamics influencing the future temperature-related health burden.

Author contributions

MR and AS conceptualized the review. MR coordinated the work, and took the lead in drafting the review. MR and AS performed literature search. SB, SZ, and AR provided substantial scientific input in drafting the review. All authors reviewed the final draft and accept responsibility to submit for publication. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by a fellowship of the German Academic Exchange Service (DAAD) and the European Union's Horizon 2020 Project Exhaustion (grant ID: 820655). The funder of the study had no role in study conceptualization, design, data collection, data interpretation, or writing of the report.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Author disclaimer

The research described in this article has been reviewed by the Center for Public Health and Environmental Assessment, EPA, and approved for publication. The contents of this article should not be construed to represent agency policy. The views expressed in this manuscript are those of the individual authors and do not necessarily reflect the views and policies of the U.S. Environmental Protection Agency. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

References

1. Klein RJT, Huq S, Denton F, Downing TE, Richels RG, Robinson JB, et al. Inter-relationships between adaptation and mitigation. In: ML Parry OFC, JP Palutikof, PJ van der Linden, CE Hanson, editors. *Climate change 2007: impacts, adaptation and vulnerability. Contribution of working group II to the*

fourth assessment report of the intergovernmental panel on climate change. Cambridge, UK: Cambridge University Press (2007). p. 750.

2. IPCC. Climate change 2021: the physical science basis (2021).

3. Kalkstein LS, Greene JS. An evaluation of climate/mortality relationships in large U.S. cities and the possible impacts of a climate change. *Environ Health Perspect*. (1997) 105:84–93. doi: 10.1289/ehp.9710584

4. Martens WJ. Climate change, thermal stress and mortality changes. *Soc Sci Med*. (1998) 46(3):331–44. doi: 10.1016/S0277-9536(97)00162-7

5. Knowlton K, Lynn B, Goldberg RA, Rosenzweig C, Hogrefe C, Rosenthal JK, et al. Projecting heat-related mortality impacts under a changing climate in the New York city region. *Am J Public Health*. (2007) 97(11):2028–34. doi: 10.2105/AJPH.2006.102947

6. Hayhoe K, Cayan D, Field CB, Frumhoff PC, Maurer EP, Miller NL, et al. Emissions pathways, climate change, and impacts on California. *Proc Natl Acad Sci U S A*. (2004) 101(34):12422–7. doi: 10.1073/pnas.0404500101

7. Cheng CS, Campbell M, Li Q, Li G, Auld H, Day N, et al. Differential and combined impacts of extreme temperatures and air pollution on human mortality in south–central Canada. Part II: future estimates. *Air Qual Atmos Health*. (2009) 1(4):223–35. doi: 10.1007/s11869-009-0026-2

8. Gosling SN, McGregor GR, Lowe JA. Climate change and heat-related mortality in six cities part 2: climate model evaluation and projected impacts from changes in the mean and variability of temperature with climate change. *Int J Biometeorol*. (2009) 53(1):31–51. doi: 10.1007/s00484-008-0189-9

9. Dessai S. Heat stress and mortality in Lisbon part II. An assessment of the potential impacts of climate change. *Int J Biometeorol*. (2003) 48(1):37–44. doi: 10.1007/s00484-003-0180-4

10. Casimiro E, Calheiros J, Santos FD, Kovats S. National assessment of human health effects of climate change in Portugal: approach and key findings. *Environ Health Perspect*. (2006) 114(12):1950–6. doi: 10.1289/ehp.8431

11. Cueto RO, Martínez AT, Ostos EJ. Heat waves and heat days in an arid city in the northwest of México: current trends and in climate change scenarios. *Int J Biometeorol*. (2010) 54(4):335–45. doi: 10.1007/s00484-009-0283-7

12. Muthers S, Matzarakis A, Koch E. Climate change and mortality in Vienna–a human biometeorological analysis based on regional climate modeling. *Int J Environ Res Public Health*. (2010) 7(7):2965–77. doi: 10.3390/ijerph7072965

13. Baccini M, Kosatsky T, Analitis A, Anderson HR, D'Ovidio M, Menne B, et al. Impact of heat on mortality in 15 European cities: attributable deaths under different weather scenarios. *J Epidemiol Community Health*. (2011) 65 (1):64–70. doi: 10.1136/jech.2008.085639

14. Ballester J, Robine JM, Herrmann FR, Rodó X. Long-term projections and acclimatization scenarios of temperature-related mortality in Europe. *Nat Commun*. (2011) 2:358. doi: 10.1038/ncomms1360

15. Ostro B, Rauch S, Green S. Quantifying the health impacts of future changes in temperature in California. *Environ Res*. (2011) 111(8):1258–64. doi: 10.1016/j.envres.2011.08.013

16. Peng RD, Bobb JF, Tebaldi C, McDaniel L, Bell ML, Dominici F. Toward a quantitative estimate of future heat wave mortality under global climate change. *Environ Health Perspect*. (2011) 119(5):701–6. doi: 10.1289/ehp.1002430

17. Petkova EP, Gasparrini A, Kinney PL. Heat and mortality in New York city since the beginning of the 20th century. *Epidemiology*. (2014) 25(4):554–60. doi: 10.1097/EDE.0000000000000123

18. Petkova EP, Horton RM, Bader DA, Kinney PL. Projected heat-related mortality in the U.S. Urban northeast. *Int J Environ Res Public Health*. (2013) 10(12):6734–47. doi: 10.3390/ijerph10126734

19. Hajat S, Vardoulakis S, Heaviside C, Eggen B. Climate change effects on human health: projections of temperature-related mortality for the UK during the 2020s, 2050s and 2080s. *J Epidemiol Community Health*. (2014) 68 (7):641–8. doi: 10.1136/jech-2013-202449

20. Honda Y, Kondo M, McGregor G, Kim H, Guo YL, Hijioka Y, et al. Heat-related mortality risk model for climate change impact projection. *Environ Health Prev Med*. (2014) 19(1):56–63. doi: 10.1007/s12199-013-0354-6

21. Wu J, Zhou Y, Gao Y, Fu JS, Johnson BA, Huang C, et al. Estimation and uncertainty analysis of impacts of future heat waves on mortality in the eastern United States. *Environ Health Perspect*. (2014) 122(1):10–6. doi: 10.1289/ehp.1306670

22. Li T, Horton RM, Bader DA, Zhou M, Liang X, Ban J, et al. Aging will amplify the heat-related mortality risk under a changing climate: projection for the elderly in Beijing, China. *Sci Rep*. (2016) 6:28161. doi: 10.1038/srep28161

23. Chen K, Horton RM, Bader DA, Lesk C, Jiang L, Jones B, et al. Impact of climate change on heat-related mortality in Jiangsu province, China. *Environ Pollut*. (2017) 224:317–25. doi: 10.1016/j.envpol.2017.02.011

24. Li G, Guo Q, Liu Y, Li Y, Pan X. Projected temperature-related years of life lost from stroke due to global warming in a temperate climate city, Asia: disease burden caused by future climate change. *Stroke*. (2018) 49(4):828–34. doi: 10.1161/STROKEAHA.117.020042

25. Li G, Jiang L, Zhang Y, Cai Y, Pan X, Zhou M. The impact of ambient particle pollution during extreme-temperature days in Guangzhou city, China. *Asia Pac J Public Health*. (2014) 26(6):614–21. doi: 10.1177/1010539514529811

26. Li G, Li Y, Tian L, Guo Q, Pan X. Future temperature-related years of life lost projections for cardiovascular disease in Tianjin, China. *Sci Total Environ*. (2018) 630:943–50. doi: 10.1016/j.scitotenv.2018.02.261

27. Li T, Ban J, Horton RM, Bader DA, Huang G, Sun Q, et al. Heat-related mortality projections for cardiovascular and respiratory disease under the changing climate in Beijing, China. *Sci Rep*. (2015) 5:11441. doi: 10.1038/srep11441

28. Li Y, Ren T, Kinney PL, Joyner A, Zhang W. Projecting future climate change impacts on heat-related mortality in large urban areas in China. *Environ Res*. (2018) 163:171–85. doi: 10.1016/j.envres.2018.01.047

29. Wang Y, Wang A, Zhai J, Tao H, Jiang T, Su B, et al. Tens of thousands additional deaths annually in cities of China between 1.5 degrees C and 2.0 degrees C warming. *Nat Commun*. (2019) 10(1):3376. doi: 10.1038/s41467-019-11283-w

30. Silveira IH, Cortes TR, de Oliveira BFA, Junger WL. Projections of excess cardiovascular mortality related to temperature under different climate change scenarios and regionalized climate model simulations in Brazilian cities. *Environ Res*. (2021) 197:110995. doi: 10.1016/j.envres.2021.110995

31. Schwartz JD, Lee M, Kinney PL, Yang S, Mills D, Sarofim MC, et al. Projections of temperature-attributable premature deaths in 209 U. S. cities using a cluster-based poisson approach. *Environ Health*. (2015) 14:85. doi: 10.1186/s12940-015-0071-2

32. Martinez GS, Baccini M, De Ridder K, Hooyberghs H, Lefebvre W, Kendrovski V, et al. Projected heat-related mortality under climate change in the metropolitan area of Skopje. *BMC Public Health*. (2016) 16:407. doi: 10.1186/s12889-016-3077-y

33. Martinez GS, Diaz J, Hooyberghs H, Lauwaet D, De Ridder K, Linares C, et al. Cold-related mortality vs heat-related mortality in a changing climate: a case study in Vilnius (Lithuania). *Environ Res*. (2018) 166:384–93. doi: 10.1016/j.envres.2018.06.001

34. Martinez GS, Diaz J, Hooyberghs H, Lauwaet D, De Ridder K, Linares C, et al. Heat and health in antwerp under climate change: projected impacts and implications for prevention. *Environ Int*. (2018) 111:135–43. doi: 10.1016/j.envint.2017.11.012

35. Åström C, Åström DO, Andersson C, Ebi KL, Forsberg B. Vulnerability reduction needed to maintain current burdens of heat-related mortality in a changing climate-magnitude and determinants. *Int J Environ Res Public Health*. (2017) 14(7):741. doi: 10.3390/ijerph14070741

36. Kendrovski V, Baccini M, Martinez GS, Wolf T, Paunovic E, Menne B. Quantifying projected heat mortality impacts under 21st-century warming conditions for selected European countries. *Int J Environ Res Public Health*. (2017) 14(7):729. doi: 10.3390/ijerph14070729

37. Guo Y, Li S, Liu L, Chen D, Williams G, Tong S. Projecting future temperature-related mortality in three largest Australian cities. *Environ Pollut*. (2016) 208:66–73. doi: 10.1016/j.envpol.2015.09.041

38. Weinberger KR, Haykin L, Eliot MN, Schwartz JD, Gasparrini A, Wellenius GA. Projected temperature-related deaths in ten large U. S. metropolitan areas under different climate change scenarios. *Environ Int*. (2017) 107:196–204. doi: 10.1016/j.envint.2017.07.006

39. Weinberger KR, Kirwa K, Eliot MN, Gold J, Suh HH, Wellenius GA. Projected changes in temperature-related morbidity and mortality in southern new England. *Epidemiology*. (2018) 29(4):473–81. doi: 10.1097/EDE.0000000000000825

40. Díaz J, Sáez M, Carmona R, Mirón IJ, Barceló MA, Luna MY, et al. Mortality attributable to high temperatures over the 2021-2050 and 2051-2100 time horizons in Spain: adaptation and economic estimate. *Environ Res*. (2019) 172:475–85. doi: 10.1016/j.envres.2019.02.041

41. Huber V, Krummenauer L, Pena-Ortiz C, Lange S, Gasparrini A, Vicedo-Cabrera AM, et al. Temperature-related excess mortality in German cities at 2 degrees C and higher degrees of global warming. *Environ Res*. (2020) 186:109447. doi: 10.1016/j.envres.2020.109447

42. Rai M, Breitner S, Wolf K, Peters A, Schneider A, Chen K. Impact of climate and population change on temperature-related mortality burden in bavaria, Germany. *Environ Res Lett*. (2019) 14(12):124080. doi: 10.1088/1748-9326/ab5ca6

43. Chen K, Vicedo-Cabrera AM, Dubrow R. Projections of ambient temperature- and air pollution-related mortality burden under combined

climate change and population aging scenarios: a review. *Curr Environ Health Rep*. (2020) 7(3):243–55. doi: 10.1007/s40572-020-00281-6

44. Rodrigues M, Santana P, Rocha A. Modelling climate change impacts on attributable-related deaths and demographic changes in the largest metropolitan area in Portugal: a time-series analysis. *Environ Res*. (2020) 190:109998. doi: 10.1016/j.envres.2020.109998

45. Tonnang HE, Kangalawe RY, Yanda PZ. Predicting and mapping malaria under climate change scenarios: the potential redistribution of malaria vectors in Africa. *Malar J*. (2010) 9:111. doi: 10.1186/1475-2875-9-111

46. Sheffield PE, Landrigan PJ. Global climate change and children's health: threats and strategies for prevention. *Environ Health Perspect*. (2011) 119 (3):291–8. doi: 10.1289/ehp.1002233

47. Huang C, Barnett AG, Wang X, Vaneckova P, FitzGerald G, Tong S. Projecting future heat-related mortality under climate change scenarios: a systematic review. *Environ Health Perspect*. (2011) 119(12):1681–90. doi: 10.1289/ehp.1103456

48. Hess JJ, Ranadive N, Boyer C, Aleksandrowicz L, Anenberg SC, Aunan K, et al. Guidelines for modeling and reporting health effects of climate change mitigation actions. *Environ Health Perspect*. (2020) 128(11):115001. doi: 10.1289/EHP6745

49. Gasparrini A, Guo Y, Sera F, Vicedo-Cabrera AM, Huber V, Tong S, et al. Projections of temperature-related excess mortality under climate change scenarios. *Lancet Planet Health*. (2017) 1(9):e360–e7. doi: 10.1016/S2542-5196(17)30156-0

50. Vicedo-Cabrera AM, Sera F, Gasparrini A. Hands-on tutorial on a modeling framework for projections of climate change impacts on health. *Epidemiology*. (2019) 30(3):321–9. doi: 10.1097/EDE.0000000000000982

51. Vardoulakis S, Dear K, Hajat S, Heaviside C, Eggen B, McMichael AJ. Comparative assessment of the effects of climate change on heat- and cold-related mortality in the United Kingdom and Australia. *Environ Health Perspect*. (2014) 122(12):1285–92. doi: 10.1289/ehp.1307524

52. Lee JY, Kim H. Projection of future temperature-related mortality due to climate and demographic changes. *Environ Int*. (2016) 94:489–94. doi: 10.1016/j.envint.2016.06.007

53. Lee JY, Kim E, Lee WS, Chae Y, Kim H. Projection of future mortality due to temperature and population changes under representative concentration pathways and shared socioeconomic pathways. *Int J Environ Res Public Health*. (2018) 15 (4):822. doi: 10.3390/ijerph15040822.

54. Zhang B, Li G, Ma Y, Pan X. Projection of temperature-related mortality due to cardiovascular disease in Beijing under different climate change, population, and adaptation scenarios. *Environ Res*. (2018) 162:152–9. doi: 10.1016/j.envres.2017.12.027

55. Petkova EP, Vink JK, Horton RM, Gasparrini A, Bader DA, Francis JD, et al. Towards more comprehensive projections of urban heat-related mortality: estimates for New York city under multiple population, adaptation, and climate scenarios. *Environ Health Perspect*. (2017) 125(1):47–55. doi: 10.1289/EHP166

56. Lee JY, Lee WS, Ebi KL, Kim H. Temperature-related summer mortality under multiple climate, population, and adaptation scenarios. *Int J Environ Res Public Health*. (2019) 16(6):1026. doi: 10.3390/ijerph16061026.

57. Anderson GB, Oleson KW, Jones B, Peng RD. Projected trends in high-mortality heatwaves under different scenarios of climate, population, and adaptation in 82 US communities. *Clim Change*. (2018) 146(3–4):455–70. doi: 10.1007/s10584-016-1779-x

58. Huynen MM, Martens P. Climate change effects on heat- and cold-related mortality in The Netherlands: a scenario-based integrated environmental health impact assessment. *Int J Environ Res Public Health*. (2015) 12(10):13295–320. doi: 10.3390/ijerph121013295

59. O'Neill BC, Carter TR, Ebi K, Harrison PA, Kemp-Benedict E, Kok K, et al. Achievements and needs for the climate change scenario framework. *Nat Clim Chang*. (2020) 10:1074–84. doi: 10.1038/s41558-020-00981-9

60. IPCC. Climate change 2014: synthesis report. Contribution of working groups I, II and III to the fifth assessment report of the intergovernmental panel on climate change. Geneva, Switzerland (2014).

61. IIASA. SSP databse (shared socioeconomic pathways)-version 2.0 2018. Available at: https://tntcat.iiasa.ac.at/SspDb

62. O'Neill BC, Tebaldi C, van Vuuren DP, Eyring V, Friedlingstein P, Hurtt G, et al. The scenario model intercomparison project (ScenarioMIP) for CMIP6. *Geosci Model Dev*. (2016) 9(9):3461–82. doi: 10.5194/gmd-9-3461-2016

63. Petkova EP, Bader DA, Anderson GB, Horton RM, Knowlton K, Kinney PL. Heat-related mortality in a warming climate: projections for 12 U. S. cities. *Int J Environ Res Public Health*. (2014) 11(11):11371–83. doi: 10.3390/ijerph111111371

64. Ebi KL, Mills D. Winter mortality in a warming climate: a reassessment. *Wiley Interdiscip Rev Clim Change*. (2013) 4(3):203–12. doi: 10.1002/wcc.211

65. Oudin Astrom D, Ebi KL, Vicedo-Cabrera AM, Gasparrini A. Investigating changes in mortality attributable to heat and cold in Stockholm, Sweden. *Int J Biometeorol*. (2018) 62(9):1777–80. doi: 10.1007/s00484-018-1556-9

66. Chen K, Breitner S, Wolf K, Hampel R, Meisinger C, Heier M, et al. Temporal variations in the triggering of myocardial infarction by air temperature in augsburg, Germany, 1987-2014. *Eur Heart J*. (2019) 40 (20):1600–8. doi: 10.1093/eurheartj/ehz116

67. Chung Y, Noh H, Honda Y, Hashizume M, Bell ML, Guo YL, et al. Temporal changes in mortality related to extreme temperatures for 15 cities in northeast Asia: adaptation to heat and maladaptation to cold. *Am J Epidemiol*. (2017) 185(10):907–13. doi: 10.1093/aje/kww199

68. Gasparrini A, Guo Y, Hashizume M, Kinney PL, Petkova EP, Lavigne E, et al. Temporal variation in heat-mortality associations: a multicountry study. *Environ Health Perspect*. (2015) 123(11):1200–7. doi: 10.1289/ehp.1409070

69. Rai M, Breitner 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(10): e784–e92. doi: 10.1016/S2542-5196(22)00195-4

70. Kc S, Lutz W. The human core of the shared socioeconomic pathways: population scenarios by age, sex and level of education for all countries to 2100. *Glob Environ Change*. (2017) 42:181–92. doi: 10.1016/j.gloenvcha.2014.06.004

71. Sellers S. Cause of death variation under the shared socioeconomic pathways. *Clim Change*. (2020) 163:559–77. doi: 10.1007/s10584-020-02824-0.

72. Stafoggia M, Schneider A, Rai M, Zhang S, Breitner S, Gasparrin A, et al. Effects of air temperature on cardiopulmonary mortality and morbidity in Europe (2021).

73. IBERDROLA. Countries most affected by climate change 2022. Available at: https://www.iberdrola.com/sustainability/top-countries-most-affected-by-climate-change

PhD journey: Experience and involvements

I conducted this doctoral research within the framework of the EU H2020 funded project- Exposure to heat and air pollution in Europe – cardiopulmonary impacts and benefits of mitigation and adaptation: EXHAUSTION (https://www.exhaustion.eu/). 14 collaborating institutions from 10 EU countries were a part of this project. Helmholtz Center Munich was the collaborating institution from Germany and lead the epidemiological work package of the project.

This project, for me, was a gateway to abundant exposure and experience. Working with the lead of the epidemiological work package of the project, I was involved with coordinating the data collection, developing R software scripts for data analysis, coordinating the analysis among different partner institutions, and pooling the EU wide results. I participated and provided inputs in discussions for developing statistical analysis plans. I was directly involved in drafting and finalizing EU deliverables with results from the project. In addition to the epidemiological tasks, I worked closely with the dissemination work package, the team from Center for International Climate Research (CICERO), Norway. I was involved with designing communication materials including non-scientific audience-oriented reports, policy briefs, and social media posts based on the results from the project. Parts of these reports have been published in OpenAIRE. I presented the EU-wide results in stakeholder meetings with invited policy makers and members of parliament, including the *Bundestag*.

This project was an opportunity for me to polish my administrative as well as project management skills. I coordinated communications among the participating partners institutions, organized and facilitated meetings, and assisted in tracking the project progress as well as timely completion of EU deliverables. I was involved in organizing stakeholder meetings and inviting policy makers. In general, this project was a comprehensive intercultural and inter expertise experience; 3.5 years of working with multi-national experts with diverse academic backgrounds including epidemiologists, climatologists, physicians, economists, and journalists, to name a few.

Besides the project EXHAUSTION, I was involved in other scientific projects like Health Environment Research Agenda for Europe: HERA (https://www.heraresearcheu.eu/), as well as other project from the Environmental Risk group at the Institute of Epidemiology of the Helmholtz Center Munich. I also conducted Environment Epidemiology lectures for the MSc. Epidemiology students at the LMU. In addition, I was involved also with organizing the courses.

Presenting my research and networking with distinguished and highly influential scientists of field remains one of the most treasured parts of my PhD journey. I presented parts of my research at the 32nd, 33rd, and the 34th annual conference of the International Society for Environmental Epidemiology (ISEE). I presented the projection study in one of the largest scientific conferences in the world - the fall meeting of the American Geophysical Union (AGU) in December 2022 in Chicago. Besides, I presented the EU relevant results during various stakeholder meetings organized by the project EXHAUSTION, as well as at the general assembly of the project EXHAUSTION in May 2022 in London.

I spent the last months of my PhD journey, from September to December 2022, at the Human Study Facility of the Environment Protection Agency (EPA), Chapel Hill, North Carolina, USA as a visiting researcher. At the EPA, I lead a project “Disparities in climate related health effects”. This project builds upon this doctoral research and investigates the relationship between exposures to heat and the resulting health outcomes in various locations in the USA. The project estimates the future heat-related health burden for locations in the USA at a fine spatial resolution. The extensive analysis identifies health burdens specific to population subgroups including those most susceptible and vulnerable to the adverse effects of heat. The manuscript of the study is under the process of development and is planned to be submitted to an international peer reviewed journal.

Acknowledgements

In order to pursue my Masters in Epidemiology at the LMU, I had moved not just to a new city or a country but a new continent. Amongst all uncertainties, I was sure of one thing – of my plan to pursue a PhD. I got connected to Helmholtz Munich during my internship during Masters and continued with my Master Thesis. The amazing support I received from my then supervisor Dr. Kai Chen, now an associate professor at the Yale School of Public Health, was one of the driving forces that made me stay in the field of research and continue as a doctoral researcher. Thank you, Dr. Chen, for inspiring me and being an amazing mentor. I cannot thank enough, Dr. Alexandra Schneider, deputy of the Institute of Epidemiology at Helmholtz Munich who trusted my capabilities and offered me a position at her research unit.

As I stand ready to submit my doctoral thesis, I want to thank each and every one who made this journey not just possible but also a fulfilling experience. First of all, I deeply acknowledge the support and guidance of my reporting supervisor Dr. Alexandra Schneider. I am immensely grateful for providing me every opportunity of growth and learning, for supporting me in every possible way, and for not just being my supervisor but also my guardian. I am grateful to my supervisor Prof. Annette Peters for her valuable insights, feedback, and guidance which substantially improved my research work. I thank you both for involving me in fascinating projects and collaborations.

I take this opportunity to extend my gratitude to Prof. Dennis Nowak, a member of my Thesis Advisory Committee and Dr. Francesca de' Donato, my thesis advisor, for their expert counselling and their valuable time. I thank Dr. Susanne Breitner for sharing her statistical expertise and guiding me through statistical challenges during my research. I am grateful to the team of EU H2020 project EXHAUSTION for the immense knowledge and experience I obtained. It was a great pleasure working with each and every one of you. One of the highlights of my PhD journey is the time we spent together during the EXHAUSTION General Assembly in London. My special thanks to Dr. Massimo Stafoggia, Dr. Siqi Zhang, and Mr. Matteo Scortichini. I thank Dr. Ana Rappold and Prof. Ilona Jaspers for hosting me at the United States Environment Protection Agency (US EPA) and the University of North Carolina as a visiting researcher. My time in North Carolina was an enlightening experience.

My deepest acknowledgement goes to the EU H2020 project EXHAUSTION for funding my doctoral research. I acknowledge the fellowship award of the German Academic Exchange Service (DAAD) for funding my research stay in Chapel Hill, North Carolina. A special thanks to Helmholtz Graduate School Environmental Health (HELENA) travel grant for the opportunity to

present my works in Chicago amongst 25000 participants at the American Geophysical Union (AGU) conference, one of the largest science conferences in the world.

I thank all the members of the MCC collaborative research group and the Research Data Centres of the Federal States of Germany for proving me with datasets. I am grateful to all my co-authors for their constructive feedback. I thank the editors and reviewers who reviewed my manuscripts and provided insights and suggestions to add new dimensions to my research.

I would like to thank all my colleagues at the Helmholtz Center Munich for making my journey enjoyable, both professionally and personally. I thank Dr. Kathrin Wolf for her support, Dr. Regina Pickford for involving me in her projects, and all members of the working group – Environmental Risks for the pleasant work environment in the past years. Special thanks to my officemates Ms. Mahnaz Badpa and Ms. Yueli Yao for sharing the joys and sorrows of Ph.D. life. Thank you to Ms. Wenli Ni, Mr. Maximilian Schwarz, Mr. Nikolaos Nikolaou, and Dr. Megi Vogli for making the Ph.D. journey fun filled. I cherished the lunch break talks, birthday celebrations, and all times we spent together.

The events organized by my graduate schools, LMU Munich and HELENA Graduate School, were certainly the highlights of my journey as a PhD student. The orientation days, courses, and annual retreat was a great opportunity for me to learn, network, and enjoy my Ph.D. days. I appreciate Dr. Annette Hartmann and Ms. Monika Darchinger at the LMU Ph.D. office for their guidance and assistance. I will treasure the time we spent in Lenggries during the annual retreat.

This dissertation represents the culmination of my childhood dream, the dream of a first-generation graduate, and moreover, dream of my parents. I cannot thank enough my mother and father for every hard work they have put to make me what I am today, for the support they provided, and for encouragement they gave. Finally, I thank my partner Diwas, for always being there for me. You have made this journey significantly smoother.

I dedicate this thesis to my parents who gave up many of their dreams for me and to all first-generation graduates for whom academic journey is always extra challenging.

Affidavit

I hereby declare, that the submitted thesis entitled:

Exposure to Air Temperature and Air Pollution and Cardio-Respiratory Health

is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

I further declare that the dissertation presented here has not been submitted in the same or similar form to any other institution for the purpose of obtaining an academic degree.

Place, date: Munich, 25.05.2023

Signature: Masna Rai

Confirmation of congruency

I hereby declare that the electronic version of the submitted thesis entitled:

Exposure to Air Temperature and Air Pollution and Cardio-Respiratory Health

is congruent with the printed version both in content and format.

Place, date: Munich, 25.05.2023

Signature: Masna Rai