Environment International 179 (2023) 108154

Contents lists available at ScienceDirect

Environment International

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

Full length article

Assessment of short-term heat effects on cardiovascular mortality and vulnerability factors using small area data in Europe

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ARTICLE INFO

Keywords:
Air temperature
Cardiovascular
Effect modification
Meta-regression
Urbanization
Air pollution

ABSTRACT

Background: Short-term associations between heat and cardiovascular disease (CVD) mortality have been examined mostly in large cities. However, different vulnerability and exposure levels may contribute to spatial heterogeneity. This study assessed heat effects on CVD mortality and potential vulnerability factors using data from three European countries, including urban and rural settings.

Methods: We collected daily counts of CVD deaths aggregated at the small-area level in Norway (small-area level: municipality), England and Wales (lower super output areas), and Germany (district) during the warm season (May-September) from 1996 to 2018. Daily mean air temperatures estimated by spatial–temporal models were assigned to each small area. Within each country, we applied area-specific Quasi-Poisson regression using distributed lag nonlinear models to examine the heat effects at lag 0–1 days. The area-specific estimates were pooled by random-effects meta-analysis to derive country-specific and overall heat effects. We examined individual- and area-level heat vulnerability factors by subgroup analyses and meta-regression, respectively.

Results: We included 2.84 million CVD deaths in analyses. For an increase in temperature from the 75th to the 99th percentile, the pooled relative risk (RR) for CVD mortality was 1.14 (95% CI: 1.03, 1.26), with the country-specific RRs ranging from 1.04 (1.00, 1.09) in Norway to 1.24 (1.23, 1.26) in Germany. Heat effects were stronger among women [RRs (95% CIs) for women and men: 1.18 (1.08, 1.28) vs. 1.12 (1.00, 1.24)]. Greater heat vulnerability was observed in areas with high population density, high degree of urbanization, low green coverage, and high levels of fine particulate matter.

Conclusion: This study provides evidence for the heat effects on CVD mortality in European countries using high-resolution data from both urban and rural areas. Besides, we identified individual- and area-level heat vulnerability factors. Our findings may facilitate the development of heat-health action plans to increase resilience to climate change.

1. Introduction

Cardiovascular diseases (CVD) are the leading cause of death and accounted for 18.6 million deaths worldwide in 2019 (GBD 2019 Diseases and Injuries Collaborators, 2020). CVD is likely to remain a major threat to public health in the future, considering an increasing disease burden due to population growth and aging. Therefore, it is essential to identify CVD risk factors to develop prevention measures.

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https://doi.org/10.1016/j.envint.2023.108154
Received 21 April 2023; Received in revised form 15 August 2023; Accepted 16 August 2023
Available online 16 August 2023

Numerous studies have established an association between high air temperature and CVD mortality. According to the Global Burden of Disease study estimation, more than 93,000 CVD deaths were attributable to high air temperature in 2019 (GBD, 2019). This number is projected to increase further due to a warming climate if no effective adaptation strategies are adopted (Vicedo-Cabrera et al., 2018).

Under the threat of global warming, there is an urgent need to determine heat vulnerability factors to increase resilience to heat. This will help develop targeted interventions and protect those most at risk. Previous studies have reported heterogeneity in heat-related health impacts across different populations. A meta-analysis including 61 studies found greater heat vulnerability among the elderly aged over 65 years and individuals of low socioeconomic status (Benmarhnia et al., 2015). In addition to individual characteristics, several contextual factors have been shown to modify the association between heat and mortality. For example, a multi-country analysis of daily mortality data from 340 cities estimated stronger heat effects in more developed cities as well as cities with high population density, inequalities, air pollution levels, and low levels of green spaces (Sera et al., 2019). Similarly, high population density and impervious coverage conferred greater heat vulnerability in the Greater Athens Area, Greece (Zafeiratou et al., 2019).

Current evidence for the heat-related mortality risk and heat effect modification was mostly from research using city-level data with a focus on urban areas. These findings might not be generalizable to suburban or rural areas due to different sociodemographic and land-use characteristics. Besides, many of the previous studies on contextual heat vulnerability factors only assessed all-cause or non-accidental mortality, and there is still a lack of studies on CVD mortality, especially in Europe. In this study, we first assessed the association between heat and CVD mortality using national small-area data from Norway, England and Wales, and Germany, including both urban and rural settings. Second, we examined potential heat vulnerability factors at the individual and contextual levels. We hypothesized that heat exposure would be associated with a higher risk for CVD mortality and that individual and contextual factors can modify the heat effect.

2. Materials and methods

2.1. Study area

This study analyzed data from three countries in Northern and Central Europe: Norway, England and Wales [United Kingdom (UK)], and Germany, with a population of 5.21 million, 58.38 million, and 82.52 million, respectively, in 2016. The average annual mean temperature from 1996 to 2018 was 2.20 ℃ in Norway, 9.78 ℃ in England and Wales, and 9.57 ℃ in Germany (World Bank Group, Climate Change Knowledge Portal). In all three countries, the monthly temperature was higher between May and September.

2.2. Cardiovascular mortality

Daily counts of deaths from CVD causes [International Classification of Diseases (ICD) 9th revision: 390–459; ICD 10th revision: I00–I99] were obtained across Norway (for the years 1996–2018), England and Wales (2000–2018), and Germany (2000–2016). These time-series data of CVD mortality were aggregated at the level of small areas, defined as municipalities in Norway, lower super output areas (LSOA) in England and Wales, and districts in Germany. Mortality counts were collected overall, as well as by age groups (65+ and 75+) and sex (males and females).

2.3. Exposure assessment

Daily mean air temperatures in 1 × 1 km grid cells were available across the three study countries. We derived the daily mean temperatures for each small area (same spatial level as the mortality data) by calculating the area-weighted temperature average in grids that intersected with this small area. The weights were proportional to the overlap between the grid cells and the small area boundary: grids that totally intersected with the small areas weighted 1, and those partially intersected weighted a fraction of 1. The country-specific temperature modeling approach was detailed as follows.

In Norway, gridded daily temperature data were obtained from the seNorge2 dataset released by the Norwegian Meteorological Institute (Lussana et al., 2019). The seNorge2 data were based on daily surface air temperature observations from a weather station network operated by public institutions. These temperature observations were spatially interpolated on a high-resolution grid of 1 × 1 km using the Optimal Interpolation approach and successive correction schemes.

In England and Wales, daily temperatures were extracted from the HadUK-Grid database, which was developed by the UK Meteorological Office (Hollis et al., 2019). The gridded daily temperatures in the HadUK-Grid database were created by interpolating the observations from the UK conventional climate observing stations to a grid of 1 × 1 km using inverse-distance weighted averaging. This process took into account geographical effects such as latitude and longitude, altitude and terrain shape, coastal influence, and urban land use.

In Germany, daily temperature data were acquired from the environmental exposures database developed by Helmholtz Munich. The gridded daily temperature dataset was generated in 1 × 1 km resolution by using a 3-stage regression-based modeling approach (Nikolaou et al., 2022). Multiple data from various sources, including weather stations temperature observations and remote sensing information on spatio-temporal predictors such as land surface temperature and greenness, were incorporated in a modeling procedure, which consisted of two linear mixed models and a thin plate spline interpolation technique.

2.4. Area-level characteristics

We collected area characteristics at the Nomenclature of Territorial Units for Statistics level 3 (NUTS-3) from the Eurostat database (https://ec.europa.eu/eurostat/web/regions/data/database). NUTS-3 regions generally have a population of 150,000–800,000 inhabitants. In our study, the NUTS-3 level in Norway and UK is an aggregation of respective administrative unit of small areas, corresponding to the county level in Norway and groups of unitary authorities and districts level in the UK. In Germany, the NUTS-3 level is equivalent to the district level, the administrative unit of small areas. The analyzed number of NUTS-3 regions in Norway, England and Wales, and Germany was 11, 144, and 380, respectively. The investigated characteristics included demographic status (population density and the percentage of the population aged 65 years or above), socio-economic status (employment rate and gross domestic product (GDP) per capita in euros), and regional typology (urban–rural, mountain, and coastal typology). The definitions of these characteristics are given in Supplementary Table S1. Since the data on employment rate and GDP in England and Wales were unavailable in the Eurostat database, we obtained the data from the Office of National Statistics (https://www.ons.gov.uk). The GDP in Pounds was converted to Euros (1.00 British Pound = 1.1794641 Euros, accessed on July 18, 2022). We calculated the average values of the area characteristics across all available years during the study period for each country.

In addition, we obtained land use characteristics at the NUTS-3 level from the Corine Land Cover dataset (https://land.copernicus.eu/pan-european/corine-land-cover) for the year 2012, including the percentage of urbanized areas and green areas per 100,000 persons. Daily mean concentrations of fine particulate matter ($PM_{2.5}$) and ozone (O_3) were estimated at 1 × 1 km resolution using the DEHM-UBM model setup in Norway and a four-stage modeling approach based on ground and satellite monitoring data in the UK (only $PM_{2.5}$). In Germany, daily mean concentrations of $PM_{2.5}$ and O_3 were estimated at ~2 × 2 km using

a spatiotemporal model based on optimal interpolation. The country-specific data sources of air pollution were detailed in Supplementary Text S1. Air pollution exposure at the NUTS-3 level were derived by averaging the daily mean air pollutant concentrations over all available years during the study period.

2.5. Statistical analysis

We used a three-stage statistical approach to assess associations between heat and CVD mortality during the warm season (May–September). In the first stage, we conducted Quasi-Poisson regression analyses allowing for overdispersion in each NUTS-3 region (see details in Supplementary Text S2). The association between temperature and CVD mortality was specified using distributed lag non-linear models (DLNMs). Specifically, we used a B-spline for the exposure–response function with one internal knot placed at the 50th percentile of the region-specific temperature distribution. The lag in the main analysis was restricted to 0–1 days to focus on the acute effects of heat. The regression model was adjusted for a four-way interaction between the small area (i.e., municipality in Norway or LSOA in England and Wales) located in this NUTS-3 region, year, month, and day of the week (DOW), defined as a categorical variable, in order to control for the small area-specific time trend using a resembled case-crossover design. In Germany, we used a three-way interaction between year, month, and DOW since the mortality data were aggregated at the NUTS-3 level, and therefore only one small area was analyzed per time.

In the second stage, we reduced the bi-dimensional exposure-lag-response to the overall cumulative exposure–response and applied multivariate meta-analysis in each country to derive the country-specific pooled relationship between temperature and CVD mortality. Heat effects are presented as the relative risks (RR) with 95% confidence intervals (95% CIs) for an increase in the daily mean temperature from the 75th to the 99th percentile of the country-specific distribution in the warm season. In the third stage, we conducted a univariate meta-analysis to pool the cumulative heat effects of all three countries under study.

To examine the effect modification by age and sex, we repeated the analyses and reported the heat effects in different age (65+ and 75+) and sex (males and females) groups.

In addition to the individual-level effect modifiers (age and sex), we assessed whether area characteristics would modify the heat effects on CVD mortality using multivariate mixed-effects meta-regression. Specifically, we included the region-specific Quasi-Poisson regression coefficients from all countries as the dependent variable in the meta-regression. The NUTS-3-level contextual factors were included individually as the explanatory variables (single-predictor model). The meta-regression model contained two levels of random effects – NUTS-3 regions nested in countries. Maximum likelihood estimator was selected to estimate the between-region variance. Weights assigned to the effect estimates in meta-regression were inverse to their variances, ensuring more weight for more precise effect estimates, which tended to be observed in larger NUTS-3 regions due to the large sample sizes. The equation of the meta-regression was detailed in Supplementary Text S3. Considering the potential influence of population density on the other characteristics, we further adjusted for population density in models of characteristics that had an absolute value of Spearman correlation coefficient$<$0.7 with population density (two-predictor model). The statistical significance of the associations with meta-predictors was assessed by Wald tests (Gasparrini et al., 2012). We estimated the heat effects at the low and high levels of continuous contextual variables, defined as the 5th and 95th percentiles of the variable distribution. Heat effects are reported as RRs with 95% CIs for an increase in temperature from the 75th to the 99th percentile of the overall temperature distribution.

As sensitivity analyses on heat and CVD mortality, we first extended the lag window to three days (lag0-3) to examine the potential delayed heat effects. Second, we restricted the study months to June–August - the hottest three months in all three countries. Moreover, we used the minimum mortality temperature (MMT) as the reference point instead of the 75th percentile of temperature distribution when calculating the heat effect estimates. For meta-regression, we conducted the sensitivity analyses of using the MMT as the reference point to calculate the effect estimates as well as using the 25th and 75th percentiles of the variable distribution in place of the 5th and 95th percentiles to define low and high levels of contextual factors.

All analyses were performed using the R software (version 4.2.1) with the “gnm”, “dlnm”, and “mixmeta” packages.

3. Results

3.1. Descriptions

The total number of CVD deaths during the study period was highest in Germany (N = 2,050,764) and lowest in Norway (N = 132,827, Table 1). The mean value of the daily number of CVD deaths across all small areas varied among countries (Table 1), partly due to the different small area sizes and population densities. The average daily mean air temperature during the warm season was lowest in Norway (mean ± SD: 10.5 ℃ ± 4.5 ℃). Despite similar average temperatures in England and Wales and Germany, the daily mean temperature at the 99th percentile in Germany was higher than that in England and Wales (24.9 ℃ vs. 22.7 ℃, Table 1).

The overall and country-specific distributions of the area characteristics across all NUTS-3 regions are presented in Table 2 and Supplementary Tables S2-S3. We observed a strong positive relationship between population density and the percentage of urbanized areas (Spearman correlation coefficient $r = 0.98$). These two variables were negatively related to the green areas per 100,000 persons ($r = -0.99$ and -0.98, respectively). The relationships between other characteristics were weak or moderate ($r < 0.7$, Supplementary Table S4). A similar pattern was found in country-specific correlations (Supplementary Tables S5-S7).

3.2. Heat effects on cardiovascular mortality

When pooling the heat effects across three countries, we observed a heat-related increase in the risk for CVD mortality during the warm season. For an increase in daily mean air temperature from the 75th to the 99th percentile of the temperature distribution, the pooled RR of CVD mortality was 1.14 (95% CI: 1.03–1.26). The exposure–response functions between air temperature and CVD mortality showed a J shape in all countries (Supplementary Fig. S1). The country-specific heat effect estimates ranged from 1.04 (95% CI: 1.00–1.09) in Norway to 1.24 (95% CI: 1.23–1.26) in Germany (Table 3).

We observed a slightly stronger heat effect on CVD mortality among women than men [pooled RR (95% CI): 1.18 (1.08, 1.28) vs. 1.12 (1.00, 1.24)] in the sex-specific analyses. The subgroup analyses by age showed similar heat effects between the general population and the elderly [pooled RR (95% CI): 1.15 (1.05, 1.27) for age $\geq$65 years and 1.16 (1.06, 1.28) for age $\geq$75 years].

In sensitivity analyses, the heat effects on CVD mortality remained stable when restricting the warm season to June–August or using an extended lag of 0–3 days (Table 3). When we used the MMT as the reference point, the effect estimates were slightly higher due to a wider temperature interval, except in Norway, where the effect estimate became non-significant.

3.3. Heat effect modification

When investigating effect modification by area sociodemographic characteristics using single-predictor meta-regressions, we observed stronger heat effects in areas with high population density, low

Table 1
Descriptive statistics of CVD deaths and daily mean air temperature in each country from May to September of the study period.

Country	Population (Mill.)	CVD deaths			Daily mean temperature (°C)			
		N. events	Daily mean	SD	Mean	SD	75th	99th
Norway	5.21	132,827	0.11	0.42	10.5	4.5	13.7	20.2
England and Wales	58.38	658,452	0.01	0.10	15.3	3.1	17.4	22.7
Germany	82.52	2,050,764	2.07	2.71	15.8	3.9	18.4	24.9

CVD = cardiovascular diseases, SD = standard deviation.

Table 2
Descriptive statistics of area characteristics across all NUTS-3 regions in three countries.

Characteristic	Median	5th–95th
Population density (persons/km^2)	271	65–3942
Population aged ≥65 years (%)	20.2	13.4–24.7
Employment rate (%)[a]	77.1	56.4–122.5
GDP per capita (€)	25889.5	17570.6–54541.2
Urbanized areas (%)	8.1	2.6–65.5
Green areas (km^2/ 100,000 persons)	323.9	4.4–1447.1
$PM_{2.5}$ (μg/m^3)	12.0	9.2–15.6
O_3 (μg/m^3)[b]	47.6	38.4–57.9
Characteristic	**Category**	**Percentage (%)**
Urban-rural typology	Predominantly urban regions	38.1
	Intermediate regions	40.0
	Predominantly rural regions	21.8
Mountain typology	>50% of population in mountain	0.4
	>50% of surface in mountain	4.7
	>50% of population and > 50% surface in mountain	6.2
	Non-mountain region	88.7
Coastal typology	Sea border	19.3
	>50% of population within 50 km of coastline	9.7
	Non-coastal region	71.0

GDP = Gross domestic product, O_3 = ozone, $PM_{2.5}$ = particulate matter with a diameter of 2.5 μm or less.
[a] Employment rate over 100% was due to employed people residing in another NUTS-3 region.
[b] O_3 data were available only in Norway and Germany.

percentage of people aged 65 or above, high employment rate, and high GDP per capita (Fig. 1). The Wald tests and between-level differences in effect estimates indicated the most significant effect modification by population density (Supplementary Table S8). In two-predictor meta-regressions with adjustment for population density, the heat effect modification by the remaining three sociodemographic factors became insignificant (Supplementary Table S9).

For land use characteristics and air pollution, the single-predictor meta-regressions showed stronger heat effects in areas characterized by a high degree of urbanization, low percentage of green areas, high levels of $PM_{2.5}$, and low levels of O_3 (Fig. 1, Supplementary Table S8). The effect modification by air pollution remained significant in two-predictor models with population density (Supplementary Table S9; two-predictor meta-regressions were not performed for the degree of urbanization and green areas due to their high correlations with population density). Heat effects were consistently stronger in predominantly urban regions than in intermediate or predominantly rural regions (Table 4). We did not observe significant effect modification by mountain and coastal typology (Table 4 and Supplementary Table S10).

The results of effect modification were robust to using the MMT as the reference point in the sensitivity analysis (Supplementary Tables S11 and S12). Using the 25th and 75th percentiles of the distribution to define low and high levels of contextual factors, respectively, reduced the between-level differences in the heat effect estimates, but the significance of the effect modification, as indicated by the Wald tests, remained stable (Supplementary Table S13).

Table 3
Country-specific and meta-analyzed relative risk (95% CI) of cardiovascular mortality for an increase in air temperature (lag 0–1 days) from the 75th to the 99th percentile in the main and sensitivity analyses.

Analysis	Norway	England and Wales	Germany	Meta-analysis
Main analysis	1.04 (1.00, 1.09)	1.15 (1.13, 1.17)	1.24 (1.23, 1.26)	1.14 (1.03, 1.26)
June-August	1.06 (1.00, 1.11)	1.16 (1.14, 1.17)	1.26 (1.24, 1.28)	1.16 (1.05, 1.28)
Lag 0–3	1.03 (0.98, 1.08)	1.14 (1.12, 1.16)	1.28 (1.26, 1.30)	1.15 (1.02, 1.30)
99th pct versus MMT[a]	1.05 (0.86, 1.29)	1.16 (1.14, 1.18)	1.30 (1.29, 1.32)	1.20 (1.07, 1.33)
65 + years	1.05 (1.00, 1.10)	1.16 (1.14, 1.18)	1.25 (1.23, 1.26)	1.15 (1.05, 1.27)
75 + years	1.06 (1.01, 1.11)	1.17 (1.15, 1.19)	1.26 (1.24, 1.28)	1.16 (1.06, 1.28)
Males	1.01 (0.96, 1.06)	1.12 (1.10, 1.15)	1.22 (1.20, 1.24)	1.12 (1.00, 1.24)
Females	1.08 (1.02, 1.14)	1.18 (1.15, 1.20)	1.26 (1.24, 1.27)	1.18 (1.08, 1.28)

CI = confidence interval, MMT = minimum mortality temperature.
[a] Heat effects were estimated for an increase in air temperature from MMT to the 99th percentile.

4. Discussion

Our study assessed the heat effects on CVD mortality during the warm season in three European countries using small-area data. We included both urban and rural settings and evaluated potential individual- and area-level heat vulnerability factors. We found a higher risk for CVD mortality associated with heat exposure, and the country-specific heat impacts increased from north to south. Women were more susceptible to the effect of heat. In addition, heat-related CVD mortality risks were higher in areas characterized by high population density, high degree of urbanization, low percentage of green areas, high levels of $PM_{2.5}$, and low levels of O_3.

To the best of our knowledge, this is the first multi-country study in Europe that examined the heat-related CVD mortality risk using nationwide high spatial resolution data. Our analysis provides evidence for an association between heat exposure and a higher CVD mortality risk, which was consistent with the results of previous large-scale studies in urban areas or major cities from Europe, the US, and China (Anderson and Bell, 2009; Chen et al., 2018; Chen et al., 2018). Most previous studies on the health impacts of heat have been conducted at broad spatial scales and used temperature data from fixed-site monitoring stations (Liu et al., 2022), which may not well characterize the spatial variations in temperature and its health effects. So far, only a few studies within single cities have investigated temperature and CVD mortality at

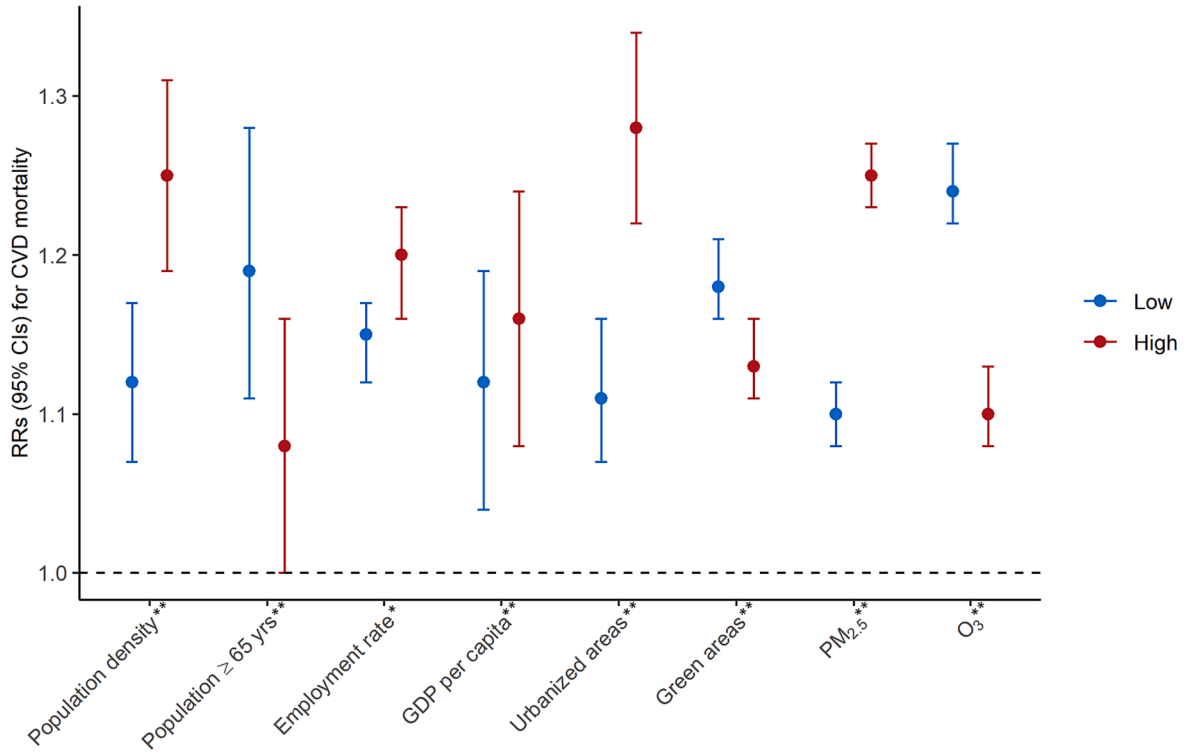

Fig. 1. Heat effects on cardiovascular mortality (lag 0–1 days) at low and high levels of effect modifiers (5th and 95th percentile of the modifier's distribution) from single-predictor models. *p-value of Wald test <0.05; **p-value of Wald test <0.01. CI = confidence interval, GDP = Gross domestic product, O_3 = ozone, $PM_{2.5}$ = particulate matter with a diameter of 2.5 μm or less, RR = relative risk.

Table 4
Heat effects on cardiovascular mortality (lag 0–1 days) at different categories of typology from single-predictor models.

Characteristic	Category	RR (95% CI)	p-Wald[a]
Urban-rural typology	Predominantly urban regions	1.19 (1.14, 1.24)	<0.001
	Intermediate regions	1.13 (1.08, 1.17)	
	Predominantly rural regions	1.11 (1.06, 1.16)	
Mountain typology[b]	>50% of population in mountain	1.20 (1.05, 1.39)	0.19
	>50% of surface in mountain	1.12 (1.07, 1.18)	
	>50% of population and 50% of surface in mountain	1.12 (1.07, 1.17)	
	Non-mountain region	1.16 (1.13, 1.19)	
Coastal typology	Sea border	1.14 (1.11, 1.18)	0.06
	>50% of the population within 50 km of coastline	1.19 (1.15, 1.23)	
	Non-coastal region	1.16 (1.13, 1.19)	

CI = confidence interval, RR = relative risk.

[a] p-Wald: p-value of the Wald test. p-Wald < 0.05 indicate statistically significant associations with area characteristics in meta-regression models.

[b] After excluding two NUTS-3 regions in the category "greater than 50% of population in mountain", the RRs (95% CIs) for the remaining three categories were 1.11 (1.06, 1.16), 1.13 (1.10, 1.17), and 1.16 (1.13, 1.19), respectively, and the p-value of the Wald test was 0.07.

the small-area level. Using data from 42 municipalities within the Greater Athens Area, Greece, Zafeiratou et al. (2019) (Zafeiratou et al., 2019) reported a 5.3% (95% CI: 4.7%, 5.9%) increase in CVD mortality per 1 °C increase in daily maximum temperature above the threshold (31.5 °C). Another study in Montreal, Canada estimated an odds ratio of 1.09 (95% CI: 1.04, 1.14) for CVD mortality per increase in daily mean temperature from 26 °C to 28 °C (Smargiassi et al., 2009).

Several biological mechanisms have been proposed that might underlie the association between heat and cardiovascular deaths (Stewart et al., 2017; Peters and Schneider, 2021). One immediate physiological response to heat stress is the redirection of blood flow to the skin to lower core body temperature. Such blood flow distribution is facilitated by increased cardiac output through compensatory increases in cardiac workloads, such as elevated heart rate and stroke volume (Cheng and MacDonald, 2019). Besides, heat stress is associated with decreased plasma volume via excessive sweating and increased circulating levels of platelets, red blood cells, and blood viscosity. These alterations can lead to a prothrombotic condition due to hemoconcentration, increasing the risk of thromboembolic events. Heat-related vasodilatation and dehydration may also cause decreases in blood pressure. Furthermore, the release of pro- and anti-inflammatory cytokines, such as tumor necrosis factor α, interleukin-1, and interleukin-6, has been observed during heat exposure, particularly in the presence of heat stroke, which results from thermoregulatory failure (Bouchama and Knochel, 2002). The inflammatory responses may induce endothelial cell injury and microvascular thrombosis.

Including both urban and rural areas in this study enabled a more comprehensive assessment of heat effect modification by urbanization compared with previous studies restricted in major cities. Our findings of higher heat effects on CVD mortality in highly urbanized areas might be due to the urban heat island (UHI) effect. UHI is characterized by higher ambient temperature and smaller diurnal temperature variation in urban than surrounding suburban and rural environments. The main causes include the lack of vegetation, urban building materials that

retain heat, and high anthropogenic heat release in urban areas (Heaviside et al., 2017). UHI may intensify the heat stress, leading to an increased cardiac workload in the urban population on hot days. Notably, the UHI intensity is greatest at night (Peng et al., 2012), thereby exacerbating the urban heat exposure during night-time. Hot nights have been recently associated with increased mortality risks in Southern Europe and Asia (He et al., 2022; Royé et al., 2021). Therefore, it is likely to contribute to greater health impacts of heat in urban areas. UHI may also explain the more substantial heat effect in densely populated areas because population density is a commonly used indicator for urbanization, and these two characteristics were highly correlated in our study.

Another heat vulnerability factor identified in this study is a low percentage of green areas. This finding is consistent with the results from most previous studies evaluating heat effect modification by land use characteristics in urban areas. For example, stronger heat effects on mortality in less green areas have been reported in six out of seven studies included in a systematic review by Son et al. (2019) (Son et al., 2019), as well as in a multi-country study including 340 cities across the world (Sera et al., 2019). Green spaces are capable of cooling the microclimate through shading and evapotranspiration. Using remote sensing data, Du et al. (Du et al., 2017) observed an average temperature drop of 3.02 °C inside green spaces in Shanghai, China. Another modeling study in Lisbon, Portugal found that even green spaces small in size can produce a cooling island effect, lowering the temperature by 1–3 °C. Besides, green spaces with a high density of trees have a stronger cooling capacity than grassland (Grilo et al., 2020). In addition to the direct impact on temperature, green spaces may modify the heat effects indirectly by influencing air pollution and noise levels (Gascon et al., 2016). Our finding of this heat vulnerability factor suggests that increasing green spaces in land use planning can be an important measure to enhance urban heat resilience.

We found a stronger heat effect on CVD mortality in areas with high levels of $PM_{2.5}$. This result remained significant in the two-predictor model with adjustment for population density, indicating the effect modification by $PM_{2.5}$ was independent of that by urbanization. Long-term exposure to $PM_{2.5}$ has been shown to increase thrombogenic activity, induce oxidative stress and systemic inflammation, and affect the cardiac autonomic balance (Viehmann et al., 2015; Wolf et al., 2016; Mordukhovich et al., 2015). These pathophysiological responses are also involved in thermoregulation or mediate the health impact of heat, which may explain the synergistic effects of heat and air pollution on the cardiovascular system. The annual $PM_{2.5}$ concentrations in most of the areas in this study were well above the World Health Organization (WHO) air quality guideline limit of 5 μg/m (Vicedo-Cabrera et al., 2018; World Health Organization, 2021). Our result implies that air pollution regulation according to WHO air quality guidelines would facilitate the prevention of heat-related CVD deaths. The larger heat effect estimate in areas with low levels of O_3 in this study should be interpreted with caution. O_3 concentrations are generally lower in urban areas compared to rural areas due to high emissions of nitrogen oxides from traffic in cities, which can deplete O_3 locally (Klumpp et al., 2006). Therefore, the observed association between O_3 and heat-related CVD mortality might result from the negative correlation between O_3 and the degree of urbanization (Spearman correlation coefficient $= -0.55$), rather than a protective effect of high O_3 concentrations. The heat effect modification by long-term O_3 exposure needs to be examined in further studies.

Our subgroup analyses by individual characteristics indicated that women were more affected by heat. Current epidemiological evidence for the heat effect modification by sex is not conclusive but points to a higher risk in women, which is in line with our finding. In a meta-analysis of articles published between 1990 and 2022, the pooled heat-related RRs for CVD mortality in males and females were 1.016 (95% CI: 1.009, 1.022) and 1.021 (95% CI: 1.012, 1.030), respectively (Liu et al., 2022). The sex differences in heat vulnerability can be partly explained by their physiological differences in coping with excessive heat. For instance, women tend to have decreased heat dissipation capacity due to a higher body fat percentage and lower sweat rate (van Steen et al., 2019). In addition, menstrual cycle hormones can influence thermoregulatory function, resulting in increased body temperature and potentially different responses to heat stress compared with men. The changes in reproductive hormones during menopause, such as decreased estrogen levels, can also affect the thermoregulatory control of skin blood flow and have adverse impacts on cardiovascular health in older women (Nappi et al., 2022; Charkoudian, 2003).

4.1. Strengths and limitations

One strength of our study is the comprehensive collection of multi-country data from both urban and rural areas, which largely enhanced the generalization of our findings and allowed implications beyond the urban setting. Using standardized analytical protocols and harmonized area-level characteristic data in all countries improved the robustness of our results. Moreover, the long study period ensured sufficient statistical power to perform analysis at the small-area level, especially in areas with very few cases of CVD deaths per day. Compared to fixed-site monitoring in previous studies, our exposure assessment using high-resolution temperature data reduced the exposure measurement error and the related bias in the effect estimates.

We also acknowledge a few limitations of our study. First, our analysis only included countries in Northern and Central Europe. Therefore, our findings might not apply to other European regions due to different climatic and sociodemographic conditions. Second, we took the average values of the area characteristics over the study period in the meta-regression, which did not consider potential temporal variations in heat vulnerability factors. Third, our high-resolution temperature and air pollution data were estimated by different approaches in each country, using different predictors and sources for exposure observations. This might reduce the comparability of results across countries. Fourth, we did not examine the heat effect in people under 65 years due to the limited numbers of CVD deaths in this age group. Hence, our findings regarding the effect modification by age structure might be inconclusive. Fifth, similar to other ecological studies using aggregated data, our results should be interpreted at the population level, and no individual-level inferences can be made. Furthermore, the current analysis did not examine heat effects on cause-specific CVD mortality, which warrant further research.

5. Conclusions

This study supports the association between heat exposure and an increased risk for CVD mortality at the small-area level using nationwide data from three European countries. The heat effect was modified by sex and several contextual characteristics related to urbanization, greenness, and air pollution levels. Our findings can be used in evidence-informed policy formation and implementation, with the aim to enhance heat resilience and mitigate the heat-related health burden.

CRediT authorship contribution statement

Siqi Zhang: Conceptualization, Software, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Susanne Breitner:** Conceptualization, Methodology, Investigation, Resources, Writing – review & editing, Supervision, Project administration. **Masna Rai:** Software, Writing – review & editing. **Nikolaos Nikolaou:** Resources, Data curation, Writing – review & editing. **Massimo Stafoggia:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Writing – review & editing. **Francesca de' Donato:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Writing – review & editing. **Evangelia Samoli:** Resources, Writing – review & editing,

Supervision. **Sofia Zafeiratou:** Software, Formal analysis, Writing – review & editing. **Klea Katsouyanni:** Resources, Writing – review & editing, Supervision. **Shilpa Rao:** Resources, Writing – review & editing, Supervision. **Alfonso Diz-Lois Palomares:** Software, Formal analysis, Writing – review & editing. **Antonio Gasparrini:** Resources, Writing – review & editing, Supervision. **Pierre Masselot:** Writing – review & editing, Supervision. **Kristin Aunan:** Writing – review & editing, Project administration. **Annette Peters:** . **Alexandra Schneider:** Conceptualization, Methodology, Investigation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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

Data will be made available on request.

Acknowledgement

Source of mortality data in Germany: Research Data Centre of the Federal Statistical Office and Statistical Offices of the Federal States, DOI: 10.21242/23211.2000.00.00.1.1.0 to 10.21242/23211.2016.00.00.1.1.0, own calculations.

Funding

This work was supported by the European Union's Horizon 2020 Project Exhaustion (Grant ID: 820655). The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit the article for publication.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108154.

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