Supplemental materials

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

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Text S1. Air pollution data

Norway

Daily mean concentrations of $PM_{2.5}$ and O_3, for 2000-2015 at a spatial resolution of 1 × 1 km, were provided by the DEHM-UBM model setup, which combines the chemical-transport model DEHM (Danish Eulerian Hemispheric Model) with the Gaussian dispersion model UBM (Urban Background Model). The geographic domain of DEHM covers the Northern hemisphere with higher resolution nests over Europe and Scandinavia. In contrast, UBM in the setup used here covers the continental Nordic countries with a high spatial resolution (1 × 1 km). Full non-linear chemistry is included in DEHM, while a simple chemical model for the NO-NO_2-O_3 equilibrium is included in UBM. This combination makes it possible to describe the long-range atmospheric transport of pollutants into and within Europe while still having a high spatial resolution in the output over, e.g., populated areas. In the current setup, a new high-resolution emission inventory for the Nordic region has been used as input to the DEHM and UBM models for the Nordic countries, while the emissions applied in DEHM on a European scale are based on the EMEP emission database.

England and Wales (UK)

Daily mean $PM_{2.5}$ concentrations on a 1 km grid across the UK from 2008-2018 were estimated by a 4-stage modelling approach. In the first stage, $PM_{2.5}$ monitored data were imputed in locations where only PM_{10} data were available to expand the set of monitoring points. Similarly, in the second stage, missing data on satellite-based Aerosol Optical Depth (AOD) were imputed using co-located estimates of AOD from CAMS. The third stage represented the core of the model because monitored data from stage 1 were calibrated using gap-filled AOD (stage 2) plus multiple spatial (NDVI, land cover, road networks, imperviousness surface areas, population density) and spatiotemporal predictors (meteorological parameters, outputs from CAMS dispersion models, etc.). Finally, in the fourth stage, the output of stage 3 was used to predict daily mean concentrations of $PM_{2.5}$ over all 1 km×1 km grid cells of the UK and days in the study period (2008-2018).

Daily mean concentrations of O_3 were not available in the UK.

Germany

Daily mean concentrations of $PM_{2.5}$ and O_3 across Germany from 2004-2016 were estimated at ~ 2 × 2 km using a spatiotemporal model based on optimal interpolation. Briefly, the approach combines air quality measurements (around 100 monitoring stations from the network of the German environmental Agency) with the simulated fields of the photochemical transport model REM-CALGRID. Bias correction was performed based on the rural and suburban monitoring stations, as these have a higher spatial relevance. Among the predictors, topography, land-use data, emissions, and meteorological data (wind, temperature, humidity, precipitation rates, and cloud cover) were the most relevant ones.

Area-specific air pollution concentrations

We derived the daily mean air pollution concentrations for each NUTS 3 area by calculating the area-weighted average of air pollution concentrations in grids that intersected with this NUTS 3 area. The weights were proportional to the overlap between the grid cells and the NUTS 3 area boundary: grids that totally intersected with the NUTS 3 areas weighted 1, and those partially intersected weighted a fraction of 1.

Text S2. Poisson regression model

We used the following Quasi-Poisson regression model to assess the association between temperature and CVD mortality in each NUTS-3 region:

$$log[E(Y_{ij})] = \alpha + crossbasis(Tmean_{ij}) + small\ area_j \times year_i \times month_i \times dow_i$$

Where: Y_{ij} is the number of deaths on day *i* in small area *j*; $Tmean_{ij}$ is the daily mean temperature on day *i* in small area *j*, fitted in a cross-basis with a B-spline for the exposure-response function and a lag window of 0-1 days; $small\ area_j \times year_i \times month_i \times dow_i$ is a four-way interaction between small area *j*, year, month and day of week of day *i*, defined as a categorical variable, to control for seasonality. It is equivalent to a case-crossover design with the “time-stratified” approach for the selection of control days.

Text S3. Meta-regression model

We used the following mixed-effects meta-regression model to assess the potential heat effect modification by contextual factors:

$$y_t = X_t\beta + Z_t b_t + \epsilon_t$$

Where: Subscript *t* denotes the t^{th} NUTS-3 region. y_t is the coefficient matrix of heat effect estimate for the t^{th} NUTS-3 region; the weight assigned to the effect estimate was inverse to its variance, ensuring more weight for more precise effect estimates. X_t is the contextual factor (meta predictor) level for the t^{th} NUTS-3 region; β is the fixed-effects coefficient. $Z_t b_t$ donates the random effects of NUTS-3 regions nested in countries; it captures the between-country and between-NUTS-3 region variabilities. ϵ_t is the error term that is assumed to be independent and identically normally distributed.

Table S1. Definitions of the area-level characteristics.

Characteristic	Type	Definition
Population density	continuous	Ratio of the annual average population to the land area (inhabitants per km^2)
Percentage of the population aged 65 years or over	continuous	Ratio of the population aged 65 years or over to the total population (%)
Employment rate	continuous	Ratio of the employed population to the population aged 20-64 (16-64 for England and Wales)
GDP per capita	continuous	Gross domestic product per inhabitant at current market prices [Euro (€)]
Urban-rural typology	categorical	Predominantly urban regions: >80 % of the population lives in urban clusters; Intermediate regions: 50 % to 80 % of the population lives in urban clusters; Predominantly rural regions: >50 % of the population lives in rural grid cells
Mountain typology	categorical	1: >50% of the population lives in mountain areas; 2: >50% of the surface is covered by mountain areas; 3: >50% of the population lives in mountain areas and >50% of the surface is covered by mountain areas; 4: Non-mountain regions
Coastal typology	categorical	1: Regions with a sea border; 2: Regions that have more than half of the population within 50 km of the coastline, based on population data for 1 km^2 grid cells; 3: Non-coastal regions

Urban cluster: a cluster of contiguous grid cells of 1 km^2 (including diagonals) with a population density of at least 300 inhabitants per km^2 and a minimum population of 5,000 inhabitants. Rural grid cells: grid cells that are not identified as urban clusters.

GDP=Gross domestic product.

Table S2. Descriptive statistics of area-level characteristics by country.

Vulnerability factor	Country	5th perc	25th perc	Median	75th perc	95th perc
Population density (persons/km^2)	Norway	3	7	17	45	1328
	England and Wales	94	306	673	3128	8869
	Germany	74	120	203	661	2059
Population aged ≥ 65 years (%)	Norway	12.3	15.7	15.8	17.7	19.6
	England and Wales	11.3	14.8	18.3	20.7	25.0
	Germany	17.7	19.4	20.6	21.9	24.6
Employment rate (%)[a]	Norway	36.6	38.9	42.8	44.4	84.4
	England and Wales	66.4	73.1	76.9	80.6	83.7
	Germany	56.7	70.0	77.3	89.7	130.3
GDP per capita (€)	Norway	40088.9	45866.7	47244.5	56211.1	94088.9
	England and Wales	18321.7	21259.0	25691.3	30960.0	48813.2
	Germany	15550.0	19835.3	25120.0	29140.0	35380.0
Urbanized areas (%)	Norway	0	0	1	2	24
	England and Wales	2	7	16	55	79
	Germany	3	5	7	16	35
Green areas (km^2/100,000 persons)	Norway	50.2	1782.7	3373.5	6844.1	13408.4
	England and Wales	0.8	9.7	109.8	276.0	1025.7
	Germany	22.0	112.2	452.0	767.7	1265.6
$PM_{2.5}$ (µg/m^3)	Norway	2.3	3.0	4.2	4.8	6.8
	England and Wales	9.2	11.3	12.5	13.6	15.7
	Germany	10.0	11.4	12.0	13.1	15.5
O_3 (µg/m^3)	Norway	48.6	63.7	65.8	67.5	69.5
	England and Wales	--	--	--	--	--
	Germany	38.3	43.9	47.5	51.1	56.4

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

Table S3. Percentage of NUTS3 areas in different categories of typology by country.

Urban type	Predominantly urban regions	Intermediate regions	Predominantly rural regions	
Norway	11.11 %	44.44 %	44.44 %	
England and Wales	75.86 %	19.31 %	4.83 %	
Germany	24.13 %	47.99 %	27.88 %	
Mountain type	> 50% of population in mountain	> 50% of surface in mountain	> 50% of population and 50% of surface in mountain	Non-mountain region
Norway	0.00 %	50.00 %	37.50 %	12.50 %
England and Wales	0.00 %	3.45 %	0.69 %	95.86 %
Germany	0.53 %	4.22 %	7.65 %	87.60 %
Coastal type	Sea border	> 50% of population within 50 km of coastline	Non-coastal region	
Norway	90.91 %	0.00 %	9.09 %	
England and Wales	50.34 %	29.66 %	20.00 %	
Germany	5.29 %	2.38 %	92.33 %	

Table S4. Spearman correlation coefficients of the area-level characteristics in all NUTS-3 regions.

	Population density	Population ⩾65 yrs	Employment rate	GDP	Urbanized areas	Green areas	$PM_{2.5}$
Population density	1						
Population⩾65 yrs	-0.35	1					
Employment rate	0.27	0.18	1				
GDP	0.42	-0.34	0.62	1			
Urbanized areas	0.98	-0.31	-0.23	0.37	1		
Green areas	-0.99	0.34	-0.27	-0.42	-0.98	1	
$PM_{2.5}$	0.61	-0.22	0.17	0.24	0.63	-0.61	1
O_3	-0.60	0.22	-0.19	-0.26	-0.55	0.59	-0.64

GDP=Gross domestic product, O_3=ozone, $PM_{2.5}$= particulate matter with a diameter of 2.5 µm or less.

Table S5. Spearman correlation coefficients of the area characteristics in Norway.

	Population density	Population ⩾65 yrs	Employment rate	GDP	Urbanized areas	Green areas	$PM_{2.5}$
Population density	1						
Population⩾65 yrs	-0.62	1					
Employment rate	-0.10	-0.20	1				
GDP	0.53	-0.85	0.45	1			
Urbanized areas	0.98	-0.57	-0.20	0.45	1		
Green areas	-0.95	0.65	-0.09	-0.68	-0.91	1	
$PM_{2.5}$	0.94	-0.64	-0.09	0.50	0.95	-0.85	1
O_3	-0.21	-0.02	0.08	0.24	-0.28	0.08	-0.10

GDP=Gross domestic product, O_3=ozone, $PM_{2.5}$= particulate matter with a diameter of 2.5 μm or less.

Table S6. Spearman correlation coefficients of the area characteristics in England and Wales.

	Population density	Population ⩾65 yrs	Employment rate	GDP	Urbanized areas	Green areas
Population density	1					
Population⩾65 yrs	-0.80	1				
Employment rate	-0.50	0.37	1			
GDP	0.27	-0.49	0.25	1		
Urbanized areas	0.99	-0.77	-0.50	0.26	1	
Green areas	-0.99	0.79	0.52	-0.26	-0.99	1
$PM_{2.5}$	0.67	-0.70	0.00	0.47	0.65	-0.65

GDP=Gross domestic product, O_3=ozone, $PM_{2.5}$= particulate matter with a diameter of 2.5 μm or less.

Table S7. Spearman correlation coefficients of the area characteristics in Germany.

	Population density	Population ⩾65 yrs	Employment rate	GDP	Urbanized areas	Green areas	$PM_{2.5}$
Population density	1						
Population⩾65 yrs	-0.12	1					
Employment rate	0.47	0.08	1				
GDP	0.61	-0.27	0.82	1			
Urbanized areas	0.96	-0.03	0.44	0.55	1		
Green areas	-0.99	0.10	-0.47	-0.61	-0.97	1	
$PM_{2.5}$	0.56	-0.08	0.16	0.23	0.60	-0.56	1
O_3	-0.57	0.31	-0.14	-0.35	-0.52	0.56	-0.61

GDP=Gross domestic product, O_3=ozone, $PM_{2.5}$= particulate matter with a diameter of 2.5 μm or less.

Table S8. Heat effects on cardiovascular mortality at low and high levels of effect modifiers (5th and 95th percentile of the modifier's distribution) from single-predictor models.

Characteristic	5th percentile		95th percentile		*p*-Wald
	Value	RR (95% CI)	Value	RR (95% CI)	
Population density (persons/km^2)	65	1.12 (1.07, 1.17)	3942	1.25 (1.19, 1.31)	<0.001
Population aged≥65 years (%)	13.4	1.19 (1.11, 1.28)	24.7	1.08 (1.00, 1.16)	<0.001
Employment rate (%)	56.4	1.15 (1.12, 1.17)	122.5	1.20 (1.16, 1.23)	0.03
GDP per capita (€)	17570.6	1.12 (1.04, 1.19)	54541.2	1.16 (1.08, 1.24)	<0.001
Urbanized areas (%)	3	1.11 (1.07, 1.16)	66	1.28 (1.22, 1.34)	<0.001
Green areas (km^2/100,000 persons)	4.4	1.18 (1.16, 1.21)	1447.1	1.13 (1.11, 1.16)	<0.001
$PM_{2.5}$ (μg/m^3)	9.2	1.10 (1.08, 1.12)	15.6	1.25 (1.23, 1.27)	<0.001
O_3 (μg/m^3)	38.4	1.24 (1.22, 1.27)	57.9	1.10 (1.08, 1.13)	<0.001

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

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 S9. Heat effects on cardiovascular mortality at low and high levels of effect modifiers (5th and 95th percentile of the modifier's distribution) from two-predictor models with adjustment for population density.

Characteristic	5th percentile		95th percentile		*p*-Wald
	value	RR (95% CI)	value	RR (95% CI)	
Population aged ≥ 65 years (%)	13.4	1.14 (1.08, 1.19)	24.7	1.12 (1.07, 1.17)	0.76
Employment rate (%)	56.4	1.12 (1.08, 1.17)	122.5	1.13 (1.08, 1.19)	0.68
GDP per capita (€)	17570.6	1.12 (1.08, 1.17)	54541.2	1.12 (1.07, 1.17)	0.30
$PM_{2.5}$ (μg/m^3)	9.2	1.10 (1.07, 1.13)	15.6	1.21 (1.18, 1.25)	<0.001
O_3 (μg/m^3)	38.4	1.22 (1.18, 1.26)	57.9	1.10 (1.07, 1.14)	<0.001

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

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 S10. Heat effects on cardiovascular mortality at different categories of typology from two-predictor models with adjustment for population density.

Characteristic	Category	RR (95% CI)	*p*-Wald
Mountain typology	> 50% of population in mountain	1.17 (1.03, 1.35)	0.65
	> 50% of surface in mountain	1.11 (1.05, 1.17)	
	> 50% of population and 50% of surface in mountain	1.11 (1.05, 1.17)	
	Non-mountain region	1.13 (1.08, 1.18)	
Coastal typology	Sea border	1.11 (1.06, 1.15)	0.02
	> 50% of population within 50 km of coastline	1.15 (1.10, 1.20)	
	Non-coastal region	1.13 (1.09, 1.18)	

p-Wald: *p*-value of the Wald test. *p*-Wald < 0.05 indicate statistically significant associations with area characteristics in meta-regression models.
CI=confidence interval, RR=relative risk.

Table S11. Relative risk (95% CI) of cardiovascular mortality for an increase in air temperature from the Minimum Mortality Temperature (MMT) to the 99th percentile at low and high levels of effect modifiers from single-predictor models.

Characteristic	5th percentile		95th percentile		*p*-Wald
	value	RR (95% CI)	value	RR (95% CI)	
Population density (persons/km^2)	65	1.13 (1.07, 1.19)	3942	1.27 (1.20, 1.34)	<0.001
Population aged ≥ 65 years (%)	13.4	1.21 (1.11, 1.31)	24.7	1.08 (1.00, 1.17)	<0.001
Employment rate (%)	56.4	1.16 (1.12, 1.19)	122.5	1.21 (1.16, 1.26)	0.03
GDP per capita (€)	17570.6	1.13 (1.04, 1.22)	54541.2	1.17 (1.08, 1.26)	<0.001
Urbanized areas (%)	3	1.12 (1.06, 1.18)	66	1.30 (1.22, 1.37)	<0.001
Green areas (km^2/100,000 persons)	4.4	1.20 (1.16, 1.23)	1447.1	1.15 (1.11, 1.18)	<0.001
$PM_{2.5}$ (µg/m^3)	9.2	1.11 (1.08, 1.13)	15.6	1.27 (1.24, 1.30)	<0.001
O_3 (µg/m^3)	38.4	1.26 (1.20, 1.32)	57.9	1.12 (1.07, 1.17)	<0.001

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

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 S12. Relative risk (95% CI) of cardiovascular mortality for an increase in air temperature from the Minimum Mortality Temperature (MMT) to the 99th percentile at different categories of typology from single-predictor models.

Characteristic	Category	RR (95% CI)	*p*-Wald
Urban-rural typology	Predominantly urban regions	1.20 (1.15, 1.27)	<0.001
	Intermediate regions	1.13 (1.08, 1.19)	
	Predominantly rural regions	1.12 (1.06, 1.18)	
Mountain typology	> 50% of population in mountain	1.20 (1.03, 1.39)	0.19
	> 50% of surface in mountain	1.14 (1.07, 1.20)	
	> 50% of population and 50% of surface in mountain	1.13 (1.07, 1.19)	
	Non-mountain region	1.17 (1.13, 1.22)	
Coastal typology	Sea border	1.15 (1.11, 1.20)	0.06
	> 50% of the population within 50 km of coastline	1.21 (1.16, 1.26)	
	Non-coastal region	1.17 (1.13, 1.21)	

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

CI=confidence interval, RR=relative risk.

Table S13. Heat effects on cardiovascular mortality at low and high levels of effect modifiers (25th and 75th percentile of the modifier's distribution) from single-predictor models.

Characteristic	25th percentile		75th percentile		*p*-Wald
	Value	RR (95% CI)	Value	RR (95% CI)	
Population density (persons/km^2)	128	1.12 (1.08, 1.17)	947	1.15 (1.10, 1.19)	<0.001
Population aged≥65 years (%)	18.5	1.14 (1.06, 1.22)	21.7	1.11 (1.03, 1.19)	<0.001
Employment rate (%)	70.6	1.16 (1.13, 1.18)	84.0	1.17 (1.14, 1.19)	0.03
GDP per capita (€)	21617.6	1.12 (1.05, 1.20)	32476.5	1.13 (1.06, 1.21)	<0.001
Urbanized areas (%)	5.0	1.12 (1.07, 1.16)	20.0	1.15 (1.11, 1.20)	<0.001
Green areas (km^2/100,000 persons)	71.1	1.18 (1.16, 1.20)	714.0	1.16 (1.13, 1.18)	<0.001
$PM_{2.5}$ (μg/m^3)	11.3	1.17 (1.12, 1.21)	13.3	1.22 (1.17, 1.27)	<0.001
O_3 (μg/m^3)	44.1	1.21 (1.19, 1.22)	51.5	1.15 (1.13, 1.17)	<0.001

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

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.

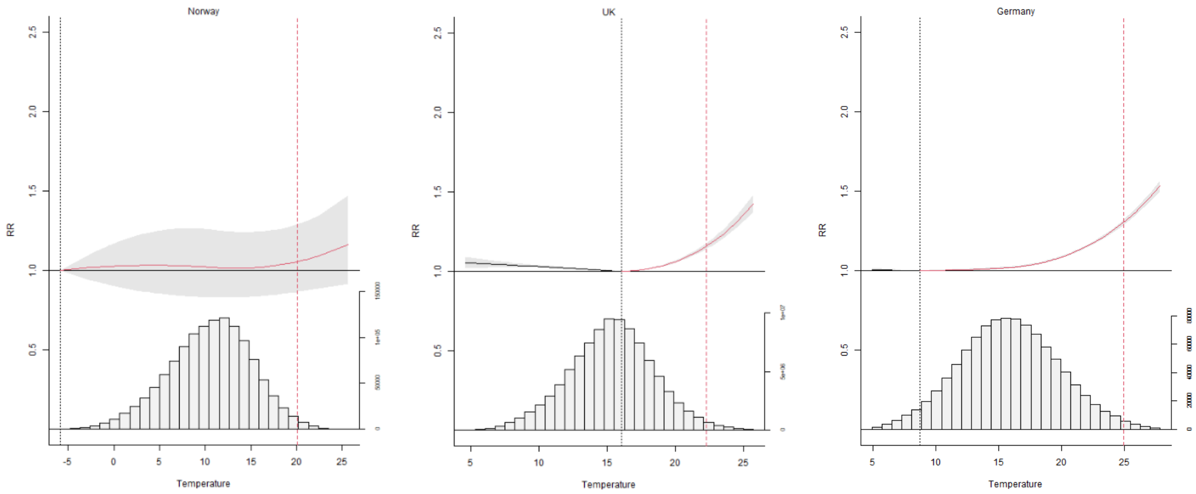

Figure S1. Country-specific exposure-response function between air temperature and CVD mortality in the warm season (May–September).