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Effect modification of air pollution on the association between heat and mortality in five European countries

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ABSTRACT

Background: Evidence suggests that air pollution modifies the association between heat and mortality. However, most studies have been conducted in cities without rural data. This time-series study examined potential effect modification of particulate matter (PM) and ozone (O_3) on heat-related mortality using small-area data from five European countries, and explored the influence of area characteristics.

Methods: We obtained daily non-accidental death counts from both urban and rural areas in Norway, England and Wales, Germany, Italy, and the Attica region of Greece during the warm season (2000–2018). Daily mean temperatures and air pollutant concentrations were estimated by spatial-temporal models. Heat effect modification by air pollution was assessed in each small area by over-dispersed Poisson regression models with a tensor smoother between temperature and air pollution. We extracted temperature-mortality relationships at the 5th (low), 50th (medium), and 95th (high) percentiles of pollutant distributions. At each air pollution level, we estimated heat-related mortality for a temperature increase from the 75th to the 99th percentile. We applied random-effects meta-analysis to derive the country-specific and overall associations, and mixed-effects meta-regression to examine the influence of urban-rural and coastal typologies and greenness on the heat effect modification by air pollution.

Results: Heat-related mortality risks increased with higher PM levels, rising by 6.4% (95% CI: −2.0%–15.7%), 10.7% (2.6%–19.5%), and 14.1% (4.4%–24.6%) at low, medium, and high PM levels, respectively. This effect modification was consistent in urban and rural regions but more pronounced in non-coastal regions. In addition, heat-mortality associations were slightly stronger at high O_3 levels, particularly in regions with low greenness.

Conclusion: Our analyses of both urban and rural data indicate that air pollution may intensify heat-related mortality, particularly in non-coastal and less green regions. The synergistic effect of heat and air pollution implies a potential pathway of reducing heat-related health impacts by improving air quality.

1. Introduction

Numerous studies have reported associations between heat and increased mortality risks (Breitner et al., 2014; Gasparrini et al., 2015; Rai et al., 2023; Zhao et al., 2021). Over the last decades, population exposure to heat has intensified due to global warming, leading to an

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increased health burden of heat. The *Lancet* Countdown on health and climate change reported an average of 15.1 (95% CI: −1.5, 31.6) additional heat-related deaths per million inhabitants per decade associated with global warming between 2000 and 2020 in 990 European regions (van Daalen et al., 2022). This number is projected to continuously increase without accelerated mitigation and adaptation measures (van Daalen et al., 2022).

Climate change can influence ambient air pollution, which is another well-recognized environmental health risk factor (GBD 2019 Risk Factors Collaborators, 2020). Concentrations of air pollutants, such as fine particulate matter ($PM_{2.5}$) and ozone (O_3), can be influenced by climatic factors through mechanisms including alterations in natural and anthropogenic emissions, chemical reactions, atmospheric transport and mixing, and pollutant deposition (Isaksen et al., 2009). In addition, air pollution is one of the contributing factors to climate change. For example, black carbon, one component of $PM_{2.5}$ and an important product of incomplete combustion of fuels, can absorb solar radiation in the atmosphere and thus can induce a warming effect (Ramanathan and Carmichael, 2008). Moreover, certain synoptic weather patterns, such as blocking high-pressure systems, can lead to the stagnation of warm air masses, resulting in prolonged heat exposure accompanied by elevated levels of air pollutants (Miralles et al., 2014; Salvador et al., 2021; Stefanon et al., 2012).

Most previous research has analyzed heat and air pollution separately in the health risk assessment. However, the connections between these two environmental factors motivate studies on their interactive effects. Because of the interplay between thermoregulation and physiological response to environmental toxicants, the interaction between heat and air pollution is biologically plausible (Gordon et al., 2011). In recent years, there has been emerging epidemiological evidence showing greater health effects of air pollution on days with high air temperatures; whether air pollution modifies the relationship between heat and health effects is less understood (Anenberg et al., 2020). A meta-analysis of 11 studies published until June 2021 reported significant modification of the heat associations with all-cause and non-accidental mortality by particulate matter (PM) with an aerodynamic diameter of ≤10 μm (PM_{10}) and O_3 (Hu et al., 2022). The overall strength of the evidence was rated as "limited", considering the small number of included studies and their inconsistent findings. Consistent with this, a more recent study involving 482 cities found effect modification on the association between heat and cardiorespiratory mortality by elevated levels of air pollution during summer months (Rai et al., 2023).

Higher heat-related mortality risks have been observed in more urbanized areas (Gasparrini et al., 2022), which are characterized by greater heat exposure due to the urban heat island (UHI) effect and more traffic-related air pollution. Therefore, we hypothesized that the interactive health effect of heat and air pollution may differ between urban and rural areas. To the best of our knowledge, this hypothesis has not been extensively tested since existing studies have primarily focused on urban settings. In addition, we hypothesized that the interaction between heat and air pollution might be influenced by greenness and coastal proximity, both of which have been shown to modify the health impacts of heat and air pollution (Burkart et al., 2016; Kasdagli et al., 2021).

In this study, we investigated the effect modification of (fine) PM and O_3 on the association between heat and mortality using small-area data from Norway, England and Wales, Germany, Italy, and the Attica region in Greece. Furthermore, we explored whether urban-rural and coastal typologies and greenness could affect the effect modification pattern. These countries/regions were selected due to their diverse climates and varying air pollution concentrations, allowing for a comprehensive assessment across different exposure levels. Our focus on small areas provided necessary spatial coverage and exposure attribution to accurately assess potentially complex interactions.

2. Materials and methods

2.1. Mortality data

This study analyzed mortality data from five European countries, including Norway, England and Wales in the United Kingdom (UK), Germany, Italy, and the Attica region in Greece. Our study population comprised the entire population of Norway, Germany, and Italy, 89% of the UK population, and 35% of the population of Greece. Specifically, daily counts of non-accidental deaths (International Classification of Diseases [ICD]-9: 001–799; ICD-10: A00-R99) were obtained from the Norwegian Cause of Death Registry for Norway (for the period 2000–2015), the German Research Data Center for Germany (2004–2016), and the Hellenic Statistical Authority for the Attica region (2001–2016). In the UK and Italy, we collected all-cause mortality data for 2008–2018 and 2013–2015, respectively. The analysis was conducted at the smallest area level available in each country, defined as municipalities in Norway, Italy, and the Attica region, Lower Layer Super Output Areas (LLSOA) in England and Wales, and districts in Germany (Supplementary Fig. S1).

2.2. Air temperature

Daily mean air temperatures in 1 × 1 km grid cells were estimated by country-specific spatial-temporal models (Supplementary Table S1). In Norway, temperature data were obtained from the seNorge2 dataset, which was created based on daily surface air temperature observations from a national weather station network (Lussana et al., 2019). The Optimal Interpolation approach and successive correction schemes were used to spatially interpolate the observed temperature data on high-resolution fields. Temperature data in the UK were extracted from the HadUK-Grid database (Hollis et al., 2019). The gridded temperature data were generated using inverse-distance weighted interpolation of temperatures from the UK conventional climate observing stations, accounting for spatial characteristics including latitude, longitude, altitude, urban land use, and coastal influence. In Germany and Italy, the gridded daily temperature data were estimated by 3-stage regression-based modeling approaches (de' Donato, 2019; Nikolaou et al., 2022). Data from ground monitoring networks and remote sensing information on spatiotemporal predictors, such as land surface temperature and land use characteristics, were incorporated into the modeling procedure, which consisted of two linear mixed models and a thin plate spline interpolation technique. The temperature data in Greece were generated by hybrid statistical-dynamical downscaling techniques. The downscaling procedure linearly interpolated the SURFEX-MESCAN reanalysis data (with a spatial resolution of ~5.5 × 5.5 km) for the grid centroids based on a high-resolution simulation of the Weather Research and Forecasting model for a typical year.

We estimated the daily mean air temperatures for small areas in all countries except for the Attica region, Greece, by calculating the area-weighted temperature average in grids intersecting with each small area. The weights were proportional to the overlap between the grid cells and the small area boundary: grids that completely intersected with the small areas weighted 1, and those partially intersected weighted a fraction of 1. In the Attica region, we calculated the average of temperatures at the grid centroids falling into each small area.

2.3. Air pollution

An overview of the country-specific spatiotemporal models of air pollutants is presented in Supplementary Table S2. In brief, daily mean concentrations of $PM_{2.5}$ and O_3 in Norway were estimated at a spatial resolution of 1 × 1 km by a chemical-transport model (Danish Eulerian Hemispheric Model) combined with a Gaussian dispersion model (Urban Background Model), both using a new high-resolution emission inventory for the Nordic region as input. In the UK and Italy, daily mean

$PM_{2.5}$ and O_3 (only in Italy) concentrations on a 1 × 1 km grid were predicted by spatiotemporal random forest models, which were developed by calibrating monitored air pollution data using satellite-based Aerosol Optical Depth data and multiple spatial and spatiotemporal predictors (land cover/use, road networks, population density, meteorological parameters, outputs from dispersion models, and others) (Schneider et al., 2020; Stafoggia et al., 2019). Daily gridded O_3 data were not available in the UK. Daily mean concentrations of $PM_{2.5}$ and O_3 across Germany were estimated at ~2 × 2 km using a spatiotemporal model based on optimal interpolation. This approach combined air quality measurements from the monitoring network of the German Environmental Agency with the simulated fields of the photochemical transport model REM-CALGRID (Nordmann et al., 2020). In Greece, spatiotemporal land-use regression models were fitted to estimate daily mean PM_{10} and daily 8-h maximum O_3 concentrations. These models used monitored air pollution concentrations and included spatial and temporal covariates and a bivariate smooth thin plate function of longitude and latitude to smooth the spatiotemporal surface across the Attica region. Daily gridded $PM_{2.5}$ data were not available in Greece.

2.4. Area characteristics

We collected data on regional urban-rural and coastal typologies and greenness as potential effect modifiers of the interactive effect between heat and air pollution. The regional typology data were obtained from the Eurostat database (https://ec.europa.eu/eurostat/web/regions/database). This database classifies data according to the Nomenclature of Territorial Units for Statistics (NUTS) system. The NUTS classification system provides a three-level hierarchy of regions harmonized across European countries based on existing national administrative subdivisions as well as minimum and maximum population thresholds. Our study collected data at NUTS level 3 (NUTS-3), the smallest territorial division in the NUTS system. The NUTS-3 regions generally have a population of 150,000 to 800,000 inhabitants. In this study, the NUTS-3 regions correspond to counties in Norway, groups of unitary authorities and districts in the UK, provinces in Italy, and regional units in Greece, which were an aggregation of respective administrative unit of small areas (Supplementary Fig. S1). In Germany, the NUTS-3 level was equivalent to the analyzed small-area level (district level). The analyzed number of NUTS-3 regions was 11 in Norway, 145 in England and Wales, 380 in Germany, 110 in Italy, and seven in the Attica region, Greece. Greenness data, quantified as green areas per 100,000 persons, were retrieved from the Corine Land Cover dataset (https://land.copernicus.eu/pan-european/corine-land-cover) for the year 2012. The greenness data were estimated at a spatial resolution of 100 m and assigned to each NUTS-3 region.

2.5. Statistical analysis

In this time-series analysis, the heat effect modification by air pollution on mortality was assessed only for the warm season (May–September) by a three-stage procedure. First, we applied a generalized additive regression model with a Poisson distribution allowing for overdispersion for each small area. The regression model was adjusted for the day of the week by a categorical variable and long-term and sub-seasonal trends by a spline of day of the season with four degrees of freedom per season, which was estimated separately for each year of examination. The interaction between temperature and air pollution was analyzed by a non-parametric response-surface model, which was implemented by incorporating two-day moving averages of the same- and previous-day air temperature and air pollutant concentrations in the regression model as a tensor smoother. The two exposures were fitted in the smoother term as cubic splines with three degrees of freedom. The lag period was chosen as lag 0–1 days to capture better the short-term interactive effect of heat and air pollutants. The model equation is included in Supplementary Text S1. This methodology represented the combined relationship between two exposures and the outcome by a tridimensional surface. From this surface, we extracted three temperature-mortality relationship curves at the low, medium, and high levels of air pollutants for each small area, defined as the 5th, 50th, and 95th percentile of small-area specific air pollutant distribution. The associations between heat and mortality at three levels of air pollutants were estimated as the percent changes in mortality risk for an increase in temperature from the 75th to the 99th percentile of small-area specific temperature distribution in the warm season. The 95% confidence intervals were calculated using a bootstrap procedure.

In the second stage, we conducted random-effects meta-analyses to derive NUTS-3-specific heat-mortality associations in Norway, England and Wales, Italy, and the Attica region, Greece, by pooling the heat effect estimates of small areas located within the NUTS-3 region. The stage-2 analysis was not carried out in Germany, where small areas were equivalent to NUTS-3 regions.

In the third stage, we pooled the NUTS-3-specific estimates to obtain the country (or region for Attica)-specific and overall associations between heat and mortality at three air pollution levels using random-effects meta-analyses.

We applied mixed-effects meta-regression to test whether area characteristics influenced the heat effect modification by air pollution. We used the NUTS-3-specific coefficients from the second-stage analysis in all countries as the dependent variable in the meta-regression. The independent variables included the air pollution level (low, medium, or high), each area characteristic (urban-rural typology, coastal typology, or greenness), and an interaction term between air pollution level and the area characteristic. Two levels of random effects – NUTS-3 regions nested in countries – were considered. We performed the likelihood ratio (LR) test to compare this full meta-regression model with a reduced model that excluded the interaction term between air pollution level and the area characteristic. Rejection of the null hypothesis of the LR test indicated a significant effect of the area characteristic on the modification of heat-mortality association by air pollution. We estimated the heat-mortality associations at three levels of air pollutants in regions of different urban-rural and coastal typologies (categorical variables) and regions with low (5th percentile) vs. high (95th percentile) green areas per 100,000 persons (continuous variables). Furthermore, we conducted country-specific meta-regression in England and Wales, Germany, and Italy to examine if the impacts of area characteristics were consistent across countries. Country-specific meta-regression was not performed in Norway or the Attica region in Greece due to the limited numbers of NUTS-3 regions.

We performed the following sensitivity analyses to test the robustness of our results. First, we restricted the warm season to the three warmest months from June to August, instead of the five warmest months. Second, we changed the lag from 0–1 to 0–3 days for both air temperature and air pollutants. Third, we defined low and high levels of air pollutants as the 25th and 75th percentiles of the small-area-specific temperature distribution instead of the 5th and 95th percentiles. Fourth, we excluded the Attica region in Greece from the meta-analysis for PM due to the use of PM_{10} rather than $PM_{2.5}$.

All analyses were performed with R (version 4.1.0) using packages "*mgcv*", "*metafor*", and "*mixmeta*".

3. Results

3.1. Description

We included 6,799,879 non-accidental deaths (all-cause deaths in the UK and Italy) from altogether 43,635 small areas in the five countries (Table 1). The country-specific average of daily mean air temperature over the warm season of the study period ranged from 10.6 °C [standard deviation (SD) = 4.5 °C] in Norway to 25.0 °C (SD = 3.9 °C) in the Attica region, Greece (Table 2). We observed moderate positive correlations between air temperature and $PM_{2.5}$ in Norway (Spearman

Table 1
Descriptive statistics of non-accidental deaths in each country from May to September of the study period.

Country	Study period	Population (Mill.)[a]	Small areas	Non-accidental deaths[b]		
				N. events	Daily mean	SD
Norway	2000–2015	5.21	354	243,727	0.3	0.9
England and Wales	2008–2018	58.38	34,753	2,114,213	0.04	0.2
Germany	2004–2016	82.52	380	3,514,510	4.6	6.0
Italy	2013–2015	60.59	8,091	716,608	0.2	1.3
Attica (Greece)	2001–2016	3.81	57	210,821	1.5	2.9

[a] Population for each country/region in 2016. Data were collected from the respective national statistical offices.
[b] All-cause deaths for England and Wales and for Italy.

Table 2
Distribution of daily mean air temperatures and air pollutant concentrations in each country from May to September of the study period.

Country	Exposure	Mean ± SD	Min.	P5	P25	Median	P75	P95	P99	Max.	P75-P99[a]
Norway	Temperature (°C)	10.6 ± 4.5	−8.2	2.8	7.6	10.8	13.7	17.6	20.2	24.8	6.5
	$PM_{2.5}$ (μg/m^3)	3.7 ± 3.0	0.1	1.0	1.7	2.7	4.5	9.7	15.0	61.8	–
	O_3 (μg/m^3)	65.7 ± 12.9	1.9	46.0	57.2	64.7	73.8	88.0	98.3	149.5	–
England and Wales	Temperature (°C)	15.3 ± 3.1	0.1	10.1	13.2	15.3	17.3	20.2	22.4	28.7	5.1
	$PM_{2.5}$ (μg/m^3)	11.0 ± 4.5	1.7	6.1	8.1	9.9	12.6	20.0	27.5	68.1	–
Germany	Temperature (°C)	15.8 ± 3.9	0.5	9.3	13.1	15.7	18.4	22.3	24.9	31.0	6.5
	$PM_{2.5}$ (μg/m^3)	9.3 ± 4.4	0.5	3.9	6.2	8.4	11.5	17.7	23.7	59.6	–
	O_3 (μg/m^3)	59.2 ± 17.4	1.7	32.3	47.5	58.2	69.6	89.5	106.0	155.1	–
Italy	Temperature (°C)	20.3 ± 4.4	−5.5	13.0	17.4	20.4	23.5	27.3	29.2	34.8	5.7
	$PM_{2.5}$ (μg/m^3)	10.8 ± 4.1	2.3	5.9	7.9	10.0	12.8	18.5	24.0	65.8	–
	O_3 (μg/m^3)	79.6 ± 16.5	10.7	53.8	68.6	78.6	90.4	106.9	122.6	164.6	–
Attica (Greece)	Temperature (°C)	25.0 ± 3.9	10.3	18.2	22.1	25.6	28.0	30.7	32.1	38.3	4.1
	PM_{10} (μg/m^3)	30.6 ± 13.8	2.7	9.3	21.0	29.7	39.2	54.6	68.5	128.4	–
	O_3 (μg/m^3)	102.9 ± 27.7	0.1	56.6	88.1	103.5	117	151.6	177.5	204.8	–

Max. = maximum, Min. = minimum, O_3 = ozone, P5 = the 5th percentile, $PM_{2.5}$ = particulate matter with an aerodynamic diameter of ≤2.5 μm, PM_{10} = particulate matter with an aerodynamic diameter of ≤10 μm.
[a] The difference between the 75th and the 99th percentile is presented for daily mean temperature to show the average change in temperature for heat effect estimation in each country.

correlation coefficient $r = 0.43$) and Italy ($r = 0.60$), and between air temperature and O_3 in Germany ($r = 0.53$, Supplementary Table S3).

The distributions of the area characteristics across all NUTS-3 regions and within the NUTS-3 regions of each country are presented in Supplementary Table S4. Most regions were categorized as urban (36.8%) or intermediate (42.1%) regions, and 64.5% were non-coastal. The median of green areas per 100,000 persons was 366 km^2 (interquartile range = 648 km^2). Greenness was positively correlated with O_3 ($r = 0.43$) and negatively correlated with $PM_{2.5}$ ($r = -0.61$, Supplementary Table S5). In addition, greenness was higher in more rural areas ($r = 0.62$). Coastal typology, with regions categorized ordinally as coastal, intermediate, and non-coastal, showed a negative correlation with temperature ($r = -0.46$).

3.2. Effect modification of air pollution on heat-related mortality risk

When pooling the effect estimates across five countries, we observed stronger overall associations between heat and non-accidental mortality at higher levels of PM (Fig. 1). For an increment in air temperature from the 75th to the 99th percentiles of small-area-specific temperature distribution, the mortality risk increased by 6.4% (95% CI: −2.0%, 15.7%), 10.7% (2.6%, 19.5%), and 14.1% (4.4%, 24.6%), respectively, at the low, medium, and high levels of PM (Supplementary Table S6). There was a tendency for a greater heat-mortality association at high O_3 levels, but the effect modification was not evident due to the wide confidence intervals (Fig. 1).

The association of heat with mortality and effect modification by air pollution were heterogeneous across countries. The heat-related increase in mortality risk was stronger in Germany, Italy, and the Attica region in Greece. In Norway, heat was associated with decreased mortality risks at all three levels of $PM_{2.5}$ and at the high level of O_3 (Fig. 1). The most significant heat effect modification by $PM_{2.5}$ was observed in Germany, with heat-related increases of 11.4% (9.8%, 12.9%), 15.7% (14.9%, 16.5%), and 22.9% (21.7%, 24.0%) at low, medium, and high $PM_{2.5}$ levels, respectively (Supplementary Table S6). For O_3, the associations between heat and mortality were significantly stronger at high pollution levels in Germany and Italy (Fig. 1, Supplementary Table S7).

3.3. Meta-regression

The heat effect modification by air pollution was more pronounced in non-coastal regions for PM (p-value for LR test <0.001) and in regions with low greenness for O_3 (p-value for LR test = 0.05), showing greater differences in heat-related mortality risks across strata of air pollution (Fig. 2, Supplementary Table S8). In country-specific meta-regression, we observed more pronounced heat effect modification by PM in urban and less green regions in Germany (Supplementary Table S8, Supplementary Figs. S2–S4).

3.4. Sensitivity analysis

Our main findings were generally robust to restricting the warm season to the three warmest months from June to August and using lag 0–3 days for both air temperature and air pollution (Supplementary Tables S6 and S7). Using the 25th and 75th percentiles instead of the 5th and 95th percentiles to identify low and high air pollution days reduced the differences in heat effect estimates across strata of air pollution. After excluding the Attica region, Greece, the overall heat effect estimates decreased slightly to 4.9% (−5.0%, 16.0%), 8.7% (−0.3%, 18.4%), and 12.4% (0.9%, 25.3%), respectively, at the low, medium, and high levels of $PM_{2.5}$, but the increasing trend with higher levels of PM remained stable.

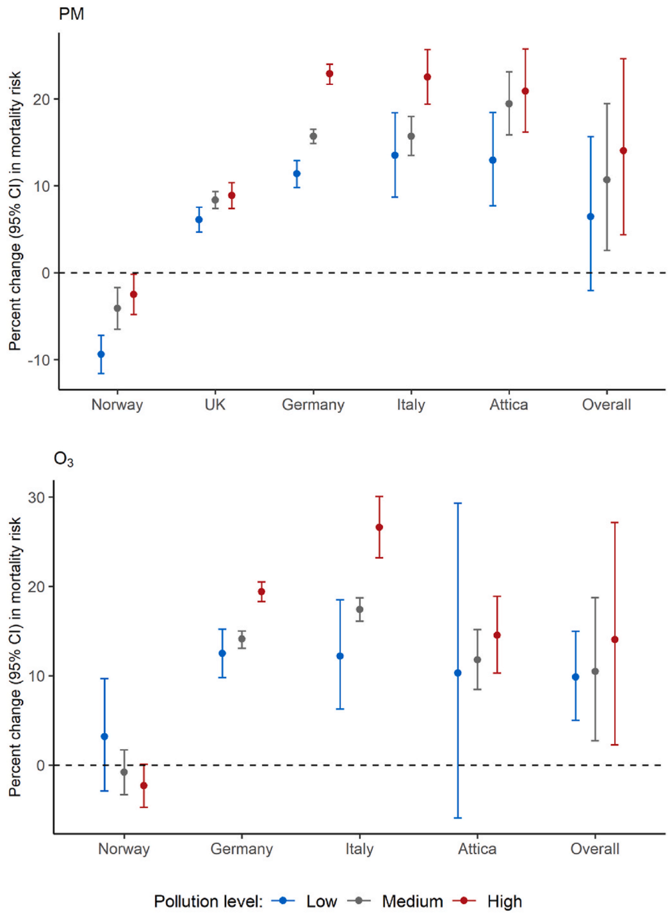

Fig. 1. Country-specific and overall percent changes (95% confidence interval) in the mortality risk associated with heat at low, medium, and high levels of air pollutants. CI = confidence interval, O_3 = ozone, PM = particulate matter.

4. Discussion

This study is among the first to examine the modification of the association between heat and mortality by air pollution using multi-country small-area data of both urban and rural settings. We further assessed whether urban-rural and coastal typologies and greenness impacted the modification effect. Our results show that the heat-related risk for non-accidental mortality was greater at higher levels of PM. Such effect modification was similar in urban and rural regions but more evident in non-coastal regions. Moreover, we observed greater heat-mortality associations at high O_3 levels in regions with low greenness.

Our analyses provide evidence for the association between heat and mortality modified by PM during the warm season in both urban and rural regions. This finding is consistent with the results of several studies conducted in major cities. For example, Chen et al. (2018) investigated the association between temperature and mortality stratified by air pollutant concentrations in eight European urban areas and observed stronger heat-mortality association at high levels of $PM_{2.5}$ and PM_{10}. Similar increases in heat-related mortality at higher levels of PM_{10} were found in Northeast Asia, Australia, and France (Lee et al., 2019; Li et al., 2015; Pascal et al., 2021; Ren et al., 2006). In a recent multi-country multi-city study, Rai et al. (2023) examined the heat effects on cardio-respiratory mortality and the modification by air pollution in 482 cities across 24 countries, using a statistical approach identical to that in our analyses. Consistently, they reported heat effect modification by elevated levels of $PM_{2.5}$ and PM_{10}. In contrast, no evidence of heat effect modification by PM was found in Ahvaz, Iran (Iranpour et al., 2020), or nine United States cities (Zanobetti and Schwartz, 2008). The heterogeneous findings among studies could be attributed to differences in analytical methods and definitions of the heat effect. In addition, contextual factors, such as meteorological conditions, chemical components of PM, housing conditions (heat insulation, the prevalence of air conditioning, among others), the existence of heat-health action plans, area-level sociodemographic status, land use patterns, and regional typologies, might contribute to the inconsistency across regions, particularly to that observed within the same study (Rai et al., 2023; Scortichini et al., 2018).

We did not find heat effect modification by O_3 across all countries, contrary to most previous findings (Analitis et al., 2018; Breitner et al., 2014; Rai et al., 2023; Scortichini et al., 2018). One potential explanation of our null result could be the negative correlation between PM and O_3 in some countries. The interactive effects between air temperature and O_3 on days with higher O_3 levels might have been influenced by the interaction between temperature and concurrent lower levels of PM. Therefore, further studies are warranted to disentangle the modification effect of O_3 from that of other pollutants. The country-specific results indicated the most influential estimates from Norway, where heat was associated with a decrease in non-accidental mortality at high levels of O_3. The negative association could be attributed to the low temperature in the warm season (average daily mean: 10.6 °C), with a minimum mortality temperature higher than the 99th percentile of the temperature distribution.

Several biological mechanisms have been proposed that may explain the synergistic health effects between heat and air pollution. First, short-term air pollution exposure has been associated with increased risks for cardiopulmonary events (Newman et al., 2020) and triggering of symptoms, such as increased heart rate and blood pressure, as well as decreased heart rate variability (Dvonch et al., 2009; Schneider et al., 2010). These clinical and subclinical conditions enhance the susceptibility to heat (Martinez et al., 2021). Second, animal studies have associated air pollution with thermoregulation, mainly characterized by alterations in core body temperature (Gordon et al., 2012; Watkinson et al., 2000). Such changes can influence the physiological response to heat stress and interfere with heat dissipation. On the other hand, rising body temperature during heat exposure can modulate the physiological response to chemicals and exacerbate the toxic effects of air pollutants (Gordon et al., 2011). Third, heat and air pollution share common pathways that may underlie their health impacts. For instance, both heat and air pollution have been associated with autonomic dysfunction, inflammation, and a prothrombotic state (Bouchama and Knochel, 2002; Keatinge et al., 1986; Ren et al., 2011; Rich et al., 2012; Rückerl et al., 2006; Schneider et al., 2010). Following these pathways, concurrent exposure to high air pollution could exaggerate the heat effect on mortality. From the perspective of air pollution exposure, the thermoregulatory responses to heat, including increased ventilation rate and lung volumes, can increase the intake of air pollutants via respiratory surface (De Sario et al., 2013). In addition, the increased skin permeability during heat exposure facilitates the absorption of pollutants (Leon, 2008). Moreover, some behavioral changes on days with high air temperatures, such as keeping windows open for a longer time and spending more time outdoors, may lead to greater exposure to ambient air pollution (Chen et al., 2018).

Our analysis across the five countries suggests that non-coastal areas may be more susceptible to the interactive effect of heat and air pollution on mortality. This pattern could be attributable to higher summer temperatures in non-coastal regions due to the lack of the cooling effect of the oceans. In addition, these regions may experience more air stagnation, which leads to the accumulation of air pollutants, thereby intensifying the health impact of heat (Garrido-Perez et al., 2018). However, it is of note that the difference in effect modification between coastal and non-coastal regions was not statistically significant in country-specific analysis. This discrepancy indicates that while there may be an overall trend across countries, local factors such as geography, climate patterns, and sources and components of air pollutants are

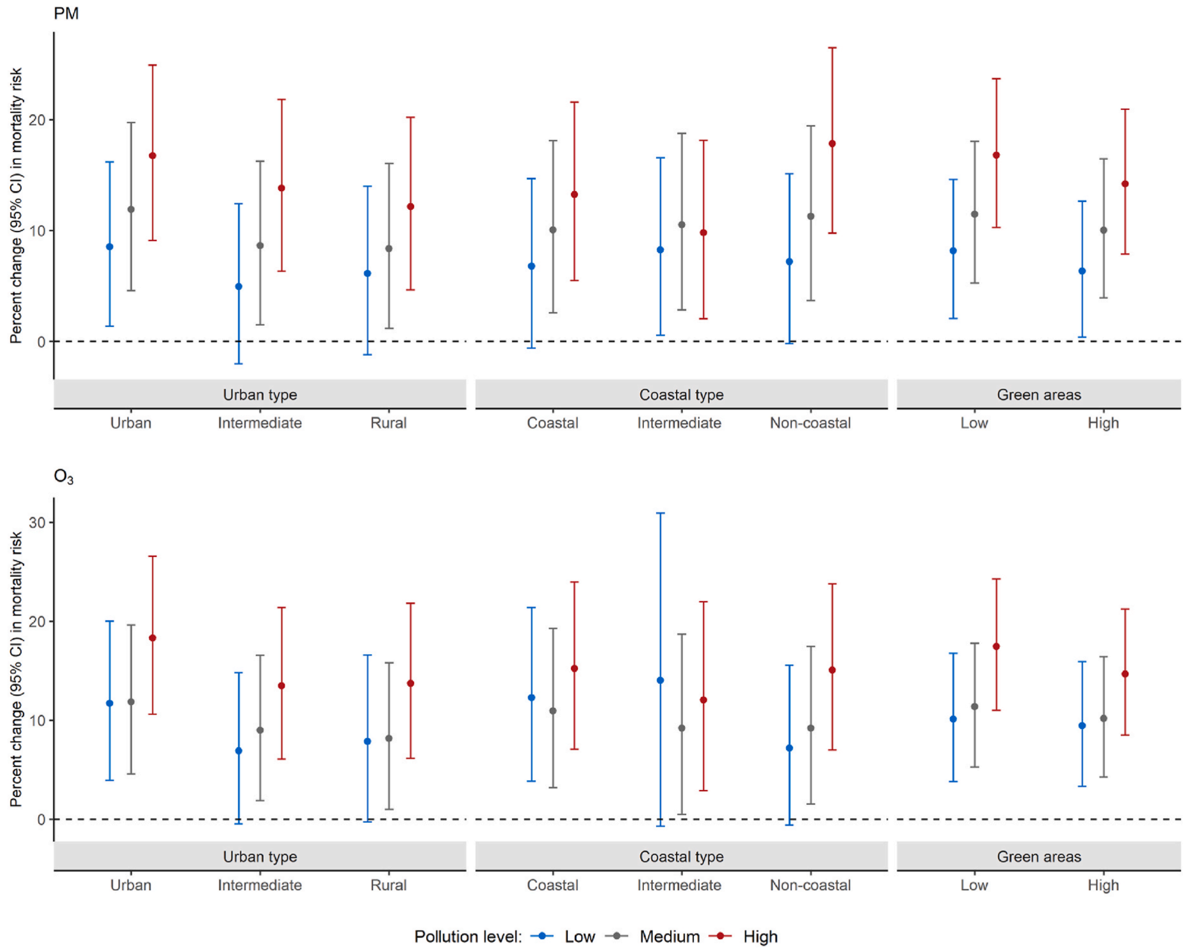

Fig. 2. Overall percent changes (95% confidence interval) in the mortality risk associated with heat at low, medium, and high levels of air pollutants in regions with different characteristics. CI = confidence interval, O_3 = ozone, PM = particulate matter.

important in determining the strength of this impact. Therefore, caution should be exercised in interpreting results at the individual country level.

Although we found no significant difference in heat effect modification by air pollution between urban and rural areas across all countries, our country-specific analysis showed more pronounced heat effect modification by $PM_{2.5}$ in urban regions in Germany. This could partly result from the coexistence of urban heat islands (UHI) and urban pollution islands (Ulpiani, 2021). UHI is characterized by substantially higher air temperatures in urban areas than corresponding temperatures in surrounding rural areas, which is most pronounced for night-time temperatures (Santamouris, 2015). This phenomenon principally arises from urban construction materials that absorb and store more heat during the daytime and re-emit it at night (Vargo et al., 2016). In addition, the urban street canyon geometry can block wind flow and retain solar radiation. The high population density in cities also causes more anthropogenic heat release (Ward et al., 2016). Due to the UHI effect, urban populations tend to suffer stronger heat stress and the resulting health impacts on hot days. Meanwhile, greater combustion of fossil fuels from industrial activities and road traffic contributes to higher PM concentrations in urban areas (Milojevic et al., 2017), and the urban-rural differences in $PM_{2.5}$ concentrations have been shown to be larger in summer (Han et al., 2020). Worse air quality in urban areas compared to rural ones can lead to more severe physiological responses such as inflammation and enhance the adverse health effect of heat. Furthermore, the vulnerability of urban populations to environmental risk factors could result from concentrated poverty and inequality (Vargo et al., 2016).

Increasing greenness has been proposed as an effective strategy to mitigate heat and air pollution. Green spaces can regulate microclimate and reduce temperature through direct shading and evapotranspiration (Kong et al., 2014), and trees have shown stronger cooling capacity than grassland (Grilo et al., 2020). A systematic review of 47 studies concluded that trees yielded a cooling effect of 0.3 °C per 0.1 canopy cover increase (Krayenhoff et al., 2021). Another study involving 93 European cities estimated that increasing city tree coverage to 30% (a mean increase of 17.7% in tree coverage) was associated with a mean decrease of 0.4 °C in summer temperature (June 1-Aug 31, 2015) and could prevent 2644 (95% CI: 2444–2824) premature deaths in adults (Iungman et al., 2023). Additionally, green spaces are demonstrated to reduce air pollution, especially PM, by facilitating the deposition and removal of particles (Diener and Mudu, 2021). As an indirect pathway, the cooling effect of green spaces reduce building energy demand, and thereby decrease air pollution emissions from energy production (Hartig et al., 2014). These mitigation effects of green spaces might underlie the observed weaker heat effect modification by air pollution in regions with more green areas per person in our study.

4.1. *Strengths and limitations*

A major strength of our study is the use of multi-country data in both urban and rural settings. Compared to previous studies conducted only in cities, our findings are based on a more comprehensive geographic data coverage and are, therefore, more generalizable. The extensive data also provided stronger statistical power and the possibility to assess potential sources of heterogeneity in the heat effect modification by air pollution across regions. To our knowledge, this is the first study that identified contextual factors that affected the synergistic effect between heat and air pollution on non-accidental mortality, including the coastal typology and greenness. In addition, the analysis at the basic administrative divisions is relevant for policy making and implementation. Furthermore, our study applied high-resolution temperature and air pollution data estimated by spatial-temporal models. This approach provided an accurate exposure assessment for small areas and enabled the detection of exposure variations at a localized level such as urban heat islands. Moreover, using a tensor smoother between temperature and air pollution in the regression model allowed for more flexibility than linear terms, and the standardized analytical protocol improved the robustness of our results.

We also acknowledge the following limitations of our study. First, since data on non-accidental mortality in the UK and Italy and gridded data on daily mean $PM_{2.5}$ in Attica, Greece were not available, we respectively used all-cause mortality and PM_{10} instead. This might have resulted in greater heterogeneity across country-specific results. However, the impacts of using alternative data were unlikely to be substantial given the fact that most deaths were due to non-accidental causes in the UK and Italy [over 96% in 2015 (World Health Organization)] as well as the strong correlation between daily mean PM_{10} and $PM_{2.5}$ concentrations at the monitoring sites in the Attica region (Pearson correlation coefficient = 0.744 for the warm period of 2007–2016). The high correlation suggests that the temporal variation in $PM_{2.5}$ can be well approximated by PM_{10}. Since our study used percentiles rather than specific concentrations to define low, medium, and high levels of air pollution, we anticipated that the association between heat and mortality at relative levels of PM_{10} would be similar to those at corresponding levels of $PM_{2.5}$. In addition, our sensitivity analysis of excluding the Attica region from the meta-analysis for heat effect modification by PM supported the robustness of our findings. Second, the spatial-temporal models of air temperature and air pollution in this study were developed using different approaches in each country, and the data sources and main predictors were not consistent. Considering the robust validation of exposure estimation approaches in all countries, the differences in modelling approaches are not expected to introduce substantial bias in the results. Third, the variation in the data collection periods across countries, primarily determined by the availability of air pollution data, might have increased heterogeneity in our results. Fourth, this assessment was conducted in the general population, and thus our findings might not be applicable to vulnerable subgroups, such as the elderly and individuals with comorbidities. Fifth, we did not examine the potential confounding effect of relative humidity (RH) since data on daily RH at a fine spatial resolution were not available in all study countries. Nevertheless, previous studies have reported that humidity had a limited confounding effect on the association of air temperature and air pollution with mortality (Armstrong et al., 2019; Ma et al., 2024), and temperature metrics with no or little humidity modification best fitted the models on temperature and mortality in the warm season in most of our examined countries (Lo et al., 2023). Finally, we only investigated the heat effect modification on non-accidental mortality by $PM_{2.5}$ and O_3 due to data availability. Future studies are needed to perform similar assessments on cause-specific mortality and other pollutants, such as nitrogen dioxide, to advance the understanding of the interactive health impacts between heat and air pollution.

5. Conclusions

Our multi-country study showed interactive effects of heat and particulate matter on mortality in five countries spanning Europe. Furthermore, the heat effect modification by air pollution was similar in urban and rural regions, and tended to be stronger in non-coastal regions and regions with lower green areas per person. Our findings suggest the importance of ambient air pollution emission control to mitigate the health impacts of heat in both urban and rural settings. In addition, increasing vegetation in land use planning and design would have potential health benefits to enhance resilience to climate change.

CRediT authorship contribution statement

Siqi Zhang: Writing – review & editing, Writing – original draft, Visualization, Software, Investigation, Formal analysis, Conceptualization. **Susanne Breitner:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Massimo Stafoggia:** Writing – review & editing, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Francesca de' Donato:** Writing – review & editing, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Evangelia Samoli:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Sofia Zafeiratou:** Writing – review & editing, Software, Formal analysis. **Klea Katsouyanni:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Shilpa Rao:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Alfonso Diz-Lois Palomares:** Writing – review & editing, Software, Formal analysis. **Antonio Gasparrini:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Pierre Masselot:** Writing – review & editing, Software, Formal analysis. **Nikolaos Nikolaou:** Writing – review & editing, Resources, Data curation. **Kristin Aunan:** Writing – review & editing, Project administration, Funding acquisition. **Annette Peters:** Writing – review & editing, Supervision. **Alexandra Schneider:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.120023.

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