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

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ABSTRACT

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

1. Introduction

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

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

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

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

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

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

2. Methods

2.1. Dataset

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

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

2.2. Statistical analysis

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

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

$$Tensor(Tmean, Poll) = \sum_{i=1}^{n_1} \sum_{l=1}^{n_2} a_{il}(Poll)\alpha_{il} b_i(\mathrm{Tmean})$$

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

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

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

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

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

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

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

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

3. Results

3.1. Descriptives

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

3.2. Heat effect

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

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

3.3. Effect modification by air pollution

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

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

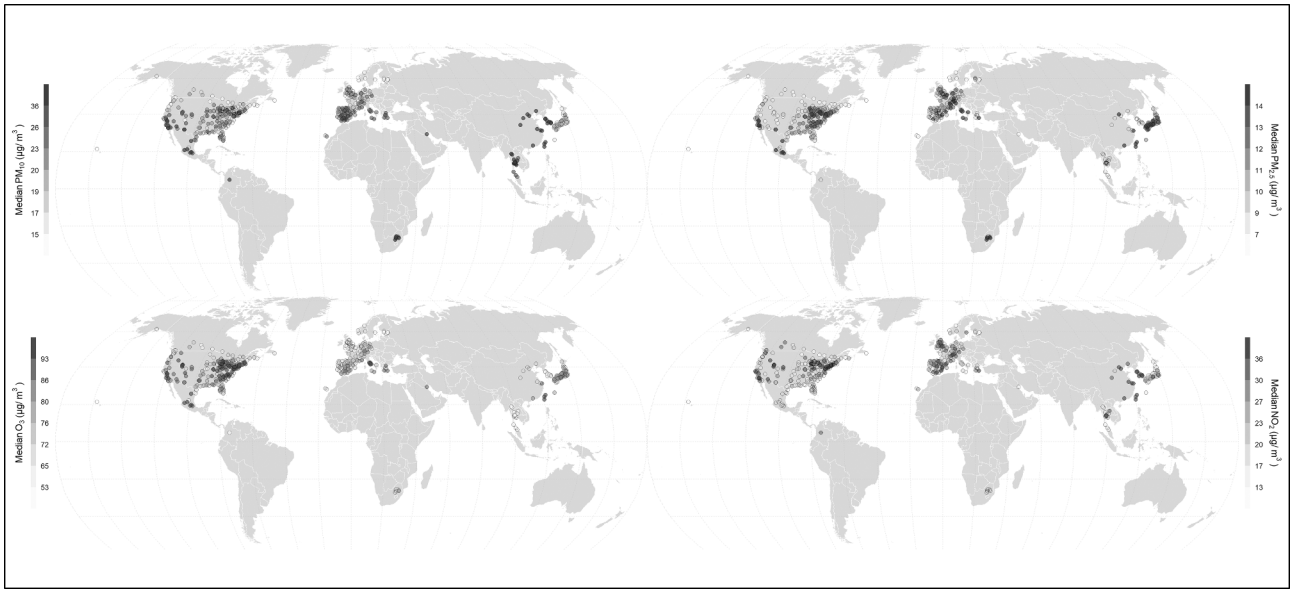

Fig. 1. Median air pollutant (particulate matter [PM] with diameter of 10 μm or less [PM_{10}], 2.5 μm or less [$PM_{2.5}$], ozone [O_3], and nitrogen dioxide [NO_2]) concentrations across study locations. [Country-specific estimates and different percentiles are inlcuded in Supplementary Material section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

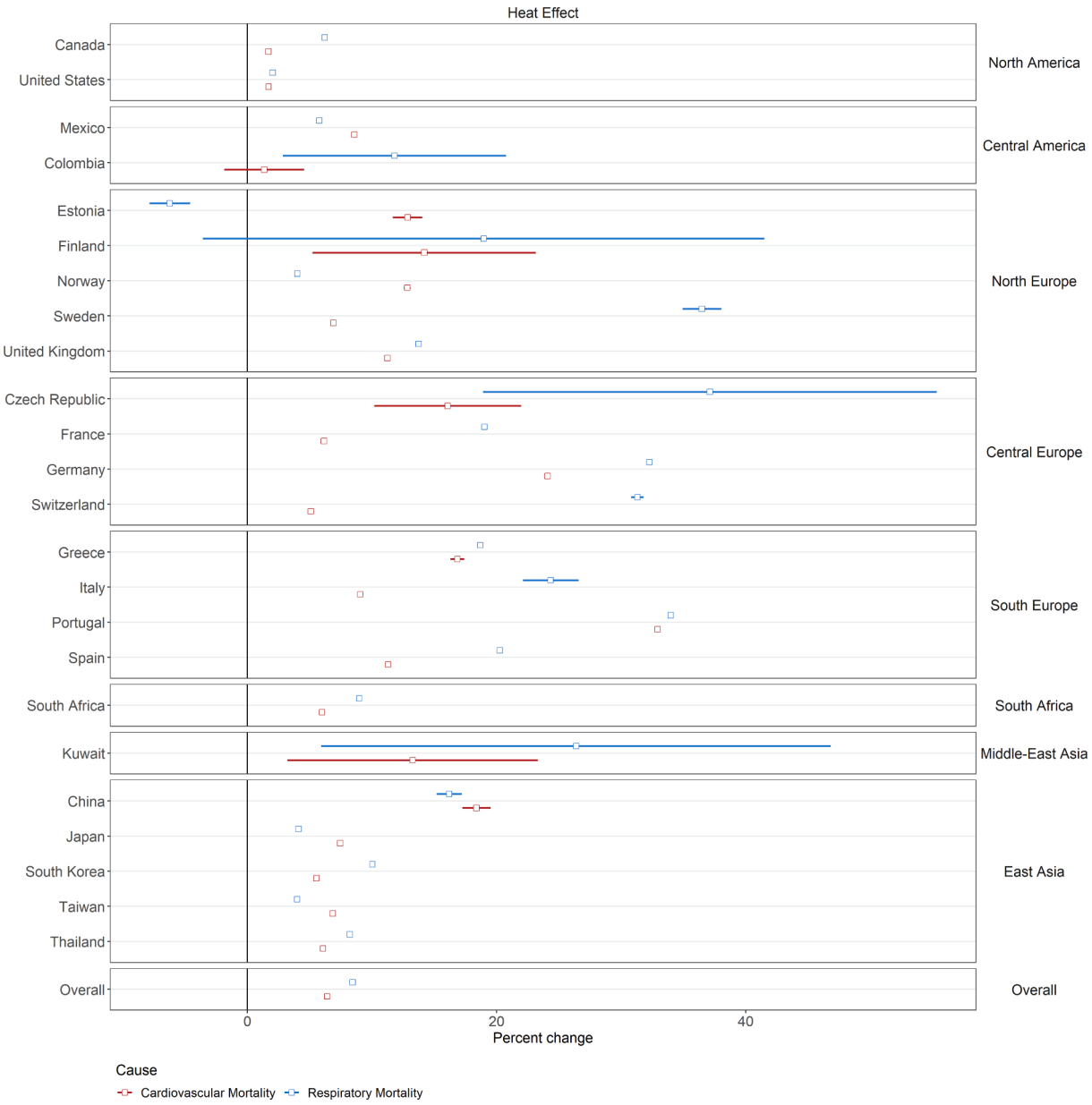

Fig. 2. Country-specific heat effects on cardiovascular and respiratory mortality. Estimates are represented as the percent change in cardiovascular and respiratory mortality (with 95% confidence intervals) per an increase in the 2-day mean temperature from the 75th to the 99th percentile of the location-specific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

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

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

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

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

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

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

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

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

4. Discussion

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

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

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

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

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

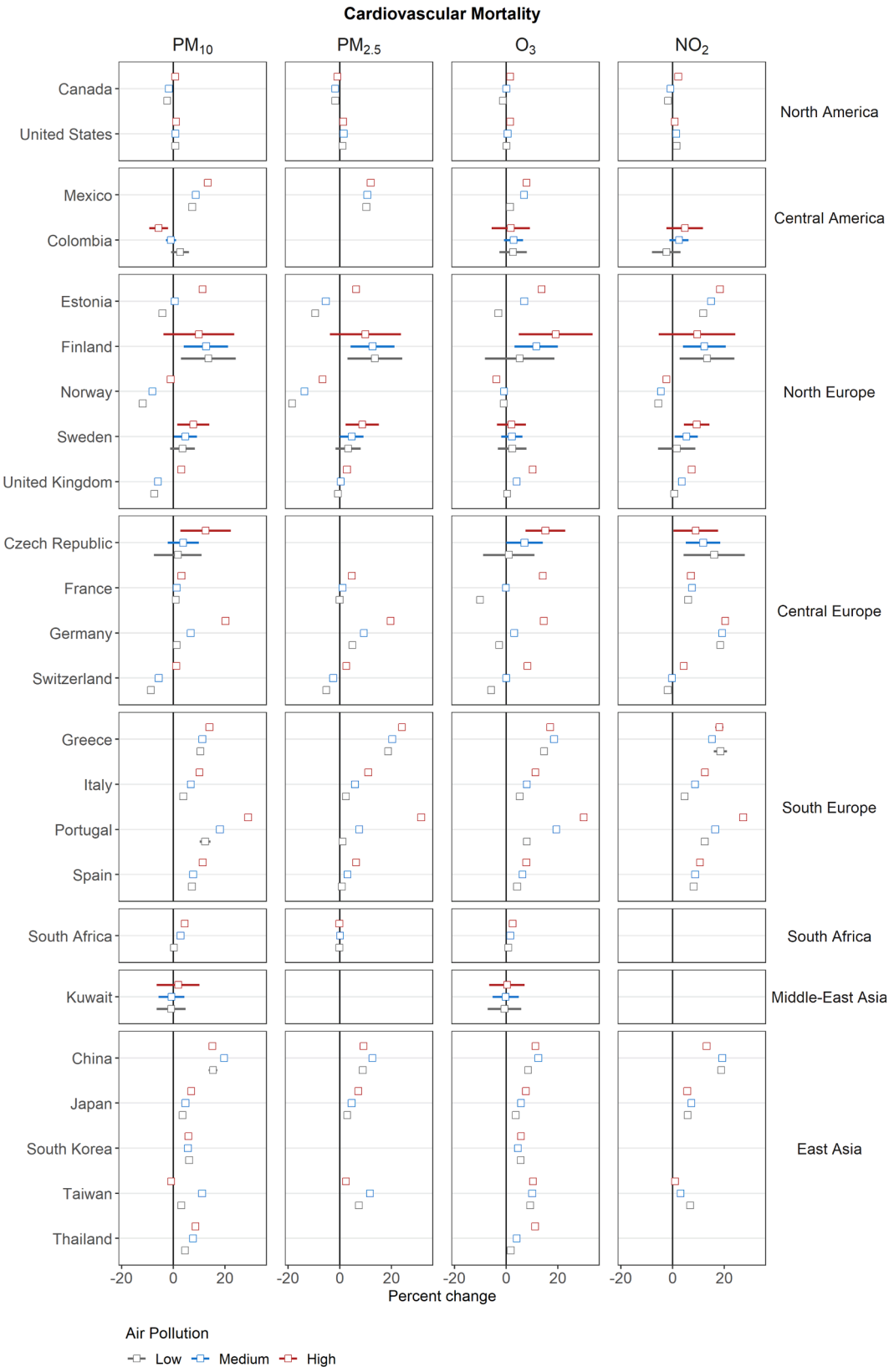

Fig. 3. Country-specific heat effects on cardiovascular mortality stratified by air pollutant levels.Estimates are presented as the percent change CVD mortality with the corresponding 95% confidence intervals per an increase in the 2-day mean temperature from the 75th to the 99th percentile of the location-specific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

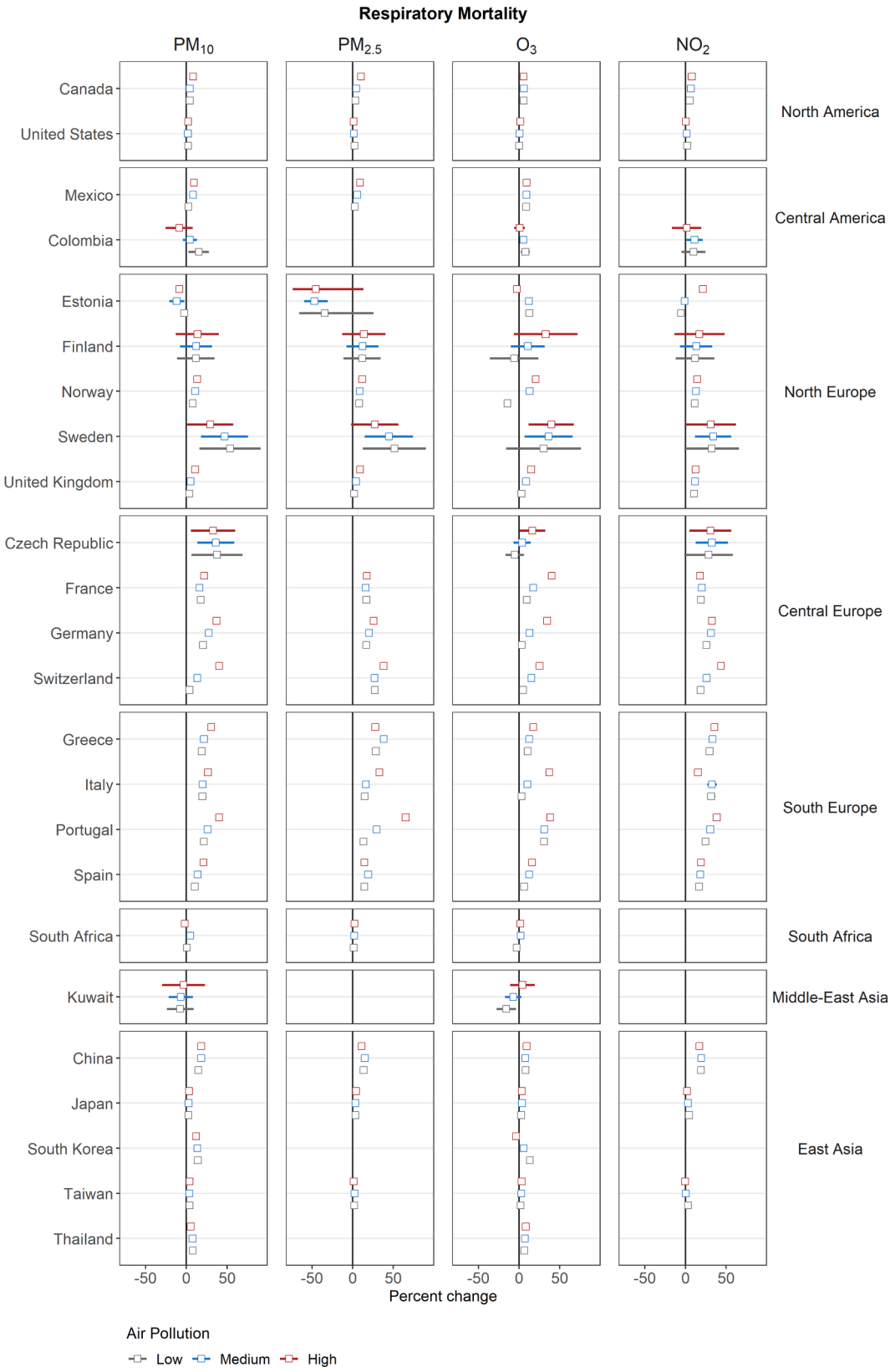

Fig. 4. Country-specific heat effects on respiratory mortality stratified by air pollutant levels. Estimates are presented as the percent change respiratory mortality with the corresponding 95% confidence intervals per an increase in the 2-day mean temperature from the 75th to the 99th percentile of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

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

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

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

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

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

CRediT authorship contribution statement

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

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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Role of the funding source

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

Author Contribution

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

Appendix A. Supplementary material

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

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