Temporal Variation in the Association between Temperature and Cause-Specific Mortality in 15 German cities

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Abstract

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

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

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

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

1. Introduction

Cardiovascular [CVD] and respiratory [RD] diseases were listed as the top causes of Disability Adjusted Life-Years in the latest Global Burden of Diseases study[1]. In particular, ischemic heart disease, stroke, and Chronic Obstructive Pulmonary Disease [COPD] were among the top six causes[1]. Several studies have found CVD outcomes to be influenced by ambient temperature [2-13]. Although limited, evidence on the association between temperature and RD outcomes also shows increased risks attributable to non-optimal temperature, especially heat[4, 6, 7, 12-14]. To sum up, CVD and RD outcomes are among the most temperature-sensitive outcomes, projected to increase even further due to climate change [15, 16].

Studies projecting future health burden under climate change are mainly based on the present-day exposure-response relationship between temperature and different health outcomes[17]. Therefore, a systematic in-depth understanding of the present-day association between temperature and health outcomes, as well as changes in these associations over time is crucial for effective and valid projection of future health burden[18, 19] and efficient planning of adaptation strategies. To date, several single-city[9, 20-26] as well as multi-city[27-32] and multi-country[18, 19] studies have explored temporal trends of the temperature-mortality association. These studies present differing evidence of either physiological adaptation or sensitivity of the population over time, varying largely across geographical locations and climatic conditions[18, 19] or even mortality causes[25]. In Europe, a previous global study on temporal variation, has shown population adaptation to heat in locations from Spain. In contrast, there was no change in the temperature-mortality association in locations across the UK [18]. A similar study carried out in Augsburg, Germany showed increasing population sensitivity to both heat and cold over time for myocardial infarction [MI] as a specific CVD outcome [25]. The varying evidence infers that the trends of the temperature-mortality relationship are rather complex. Therefore, a systematic investigation of location- and cause-specific temperature-mortality associations over time is essential.

The majority of the studies on temporal variations have focused on total or non-accidental mortality[18, 21-23, 26-32], and most of these studies only considered heat-related mortality [23, 27-30]. Thus, limited evidence exists on the temporal variation of both heat- and cold-related temperature-mortality associations[9, 18, 21, 26, 31, 32]. In addition, the changes in the association between temperature and the two most climate-sensitive mortality outcomes - CVD and RD mortality - over time have not been investigated widely[9, 19, 20, 25, 31]. Furthermore, the variation in these cause-specific temperature-mortality associations across different age and sex groups has not been extensively studied.

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

2. Methods

2.1 Data Sources

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

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

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

2.2 Statistical Analysis

We applied a time-stratified time-series analysis to study the association between temperature and cause-specific mortality in each location. We stratified the overall study period into two sub-periods: 1993-2004 and 2005-16. For the twoperiods, quasi-Poisson regressions with distributed lag nonlinear models extending the lag period to 14 days were used to establish the location-specific exposure-response functions [ERFs]. The lag period was chosen to efficiently capture both heat and cold effects. The regressions also included an indicator for the day of the week and a penalized spline of the day of the study with four degrees of freedom [df] per calendar year to control the seasonal and long-term trends. For the ERFs, we used natural cubic splines with three internal knots placed at the 10th, 75th, and 90th percentiles of the location-specific mean temperature. The lag-response curves for temperature were modelled with a natural cubic spline with three knots placed at equally spaced values on the log scale. The location-specific associations were then reduced to overall temperature-mortality associations by cumulating the risk over the lag period. The location-specific overall cumulative ERFs were then pooled using a multivariate meta-analytical model to derive the overall temperature-mortality association in the 15 cities. This approach has been previously described [33, 34] and applied by a large international study [35]. We report the cold effect as the relative risk [RR] at the 1st temperature percentile relative to the 25th and the heat effect as the RR at the 75th temperature percentile relative to the 99th percentile of the temperature distribution of the overall period: 1990-2016, for obtaining comparable estimates.

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

Sensitivity analyses

In order to check the robustness of the main findings, we performed sensitivity analyses by changing the df (three and seven per year) for the trend spline to control for seasonal and long-term effects. Furthermore, to check the robustness of our effect estimates, we report the cold effect as the RR at the 2.5th temperature percentile relative to the Minimum Mortality Temperature [MMT] and the heat effect as the RR at the 97.5th percentile relative to the MMT, as reported by previous studies [25]. We also explored the cause-specific ERFs excluding the heat wave years 2003 and 2015.

All analyses were performed using R project (version 4.0.3) [36] for statistical computing using the “dlnm [37]” and “mgcv [38]” packages.

3. Results

3.1. Descriptive

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

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

3.2. Overall Results

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

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

3.3. City-specific Results

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

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

4. Discussion

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

Our results on temporal changes in heat-related non-accidental mortality were in contrast to most existing evidence from single-city studies, which showed mostly a decreasing pattern of heat-related mortality risk over time[20, 21, 23, 24, 26, 27, 32]. However, our results were consistent with existing limited evidence from large multi-city[29] and multi-country[18] studies, which found trends in heat-related non-accidental mortality to vary across geographical locations, with increasing risk over time in some cities and countries[18, 29]. For CVD and RD mortality, we observed a constant and an increasing heat-related risk over time, respectively. The results for overall CVD mortality were consistent with a study in China, which also showed stable heat-related RR[9]. Contrastingly, studies conducted in Northeast Asia[19] and the United Kingdom[20] showed a decreasing heat-related mortality risk for CVD and RD deaths over time. A study conducted in Bavaria, Germany, found an increase in the heat-related MI risk over time[25], which was in line with our results also showing an increase in heat-related ischemic heart disease mortality, including MI. We observed similar trends for heart failure.

The results of the 15 German cities for cold-related non-accidental mortality were in line with locations like Canada and Australia, where a stable cold-related RR was observed over time. Similar studies in Sweden showed either dispersed[26] or consistent[24] patterns in cold-attributable non-accidental mortality over the decades. Evidence on cold-related CVD mortality from a multi-city[31] as well a multi-country[19] study has shown increasing sensitivity of CVD deaths towards cold. Similar to these findings, the results of our study also demonstrated a significant increase in the cold effect over time for CVD mortality. In contrast, several single-city studies have shown decreasing trends in cold-related CVD[9, 20]. Our study also found a significant increase in cold-related RR for RD mortality, which was in line with a study exploring this association for overall cardiorespiratory mortality[19] but contrasting to another single-city study which shows a decreasing trend[20].

Several factors play a role in modifying the ERF between air temperature and health outcomes[39]. Among them, improvements in infrastructures, such as housing and air conditioning, socioeconomic changes, and improved health care and services, might decrease the susceptibility to non-optimal temperature exposure. Furthermore, public health interventions that increase the awareness of the health risk associated with exposure to high temperatures might promote behavioural changes, leading to decreased heat-related mortaltiy[40].

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

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

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

5. Conclusion

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

Acknowledgement

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

Funding

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

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

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

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

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

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

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

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

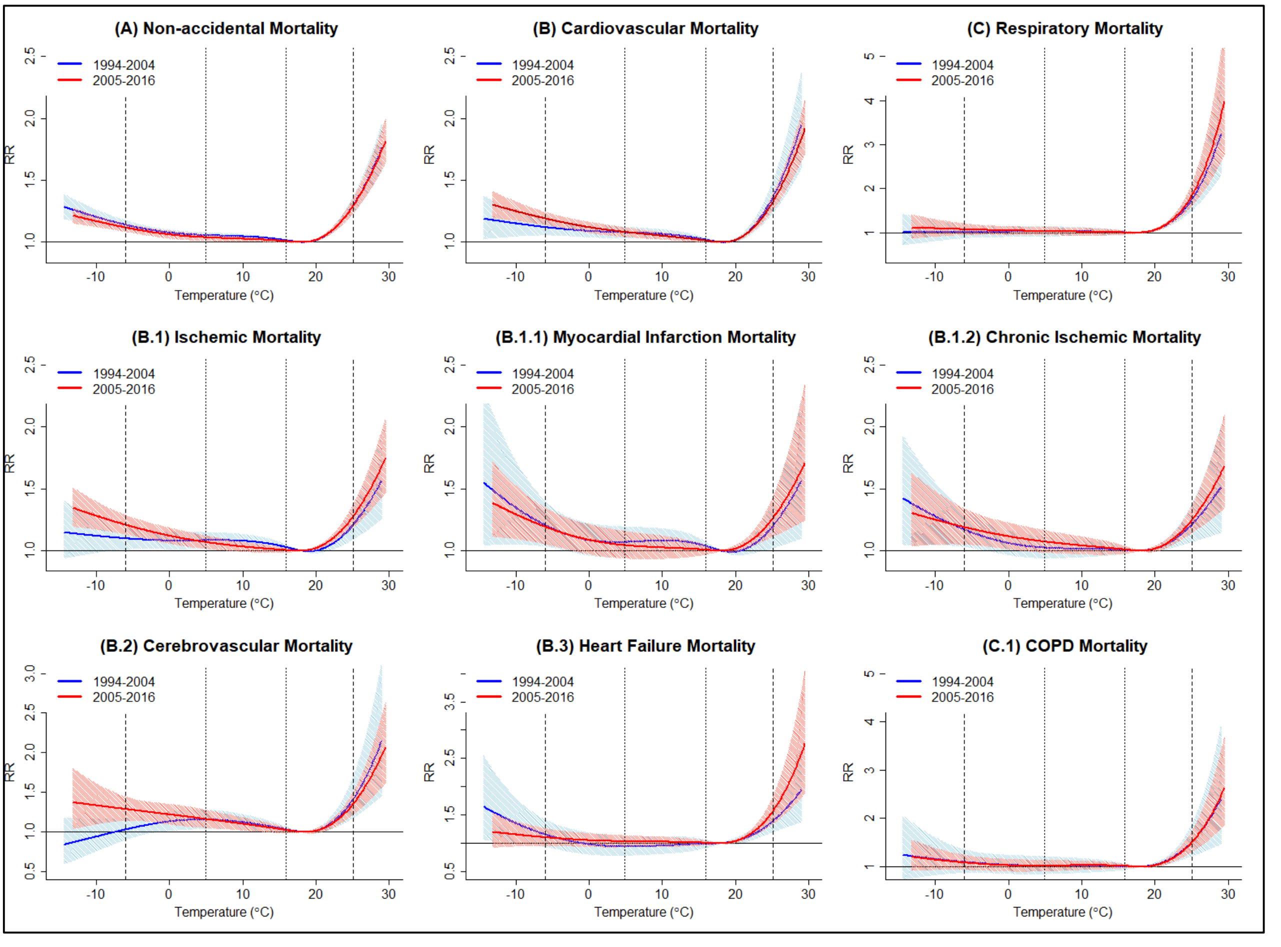

Figure 1: Temporal variation in the lag-cumulative exposure–response relationships between air temperature and cause-specific mortality for 1993–2004 (blue) and 2004–2016 (red) with 95% confidence interval.
[Dotted lines represent the 25th(4.9 °C)and the 75th (15.9 °C) temperature percentiles; dashed lines represent the 1st (-6.0 °C) and the 99th (25.1 °C) temperature percentiles

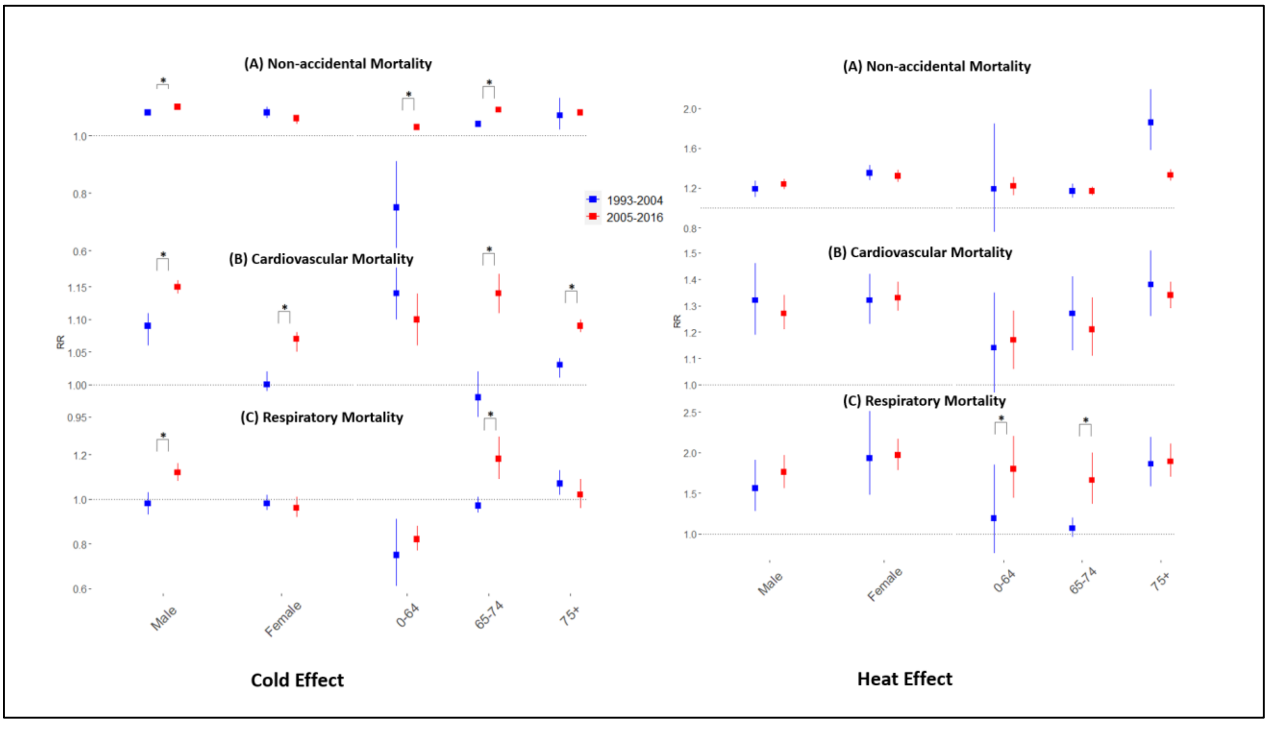

Figure 2: Lag-cumulative RR estimates for daily cause-specific mortality (95% confidence interval) as cold effect [RR at 1st (-6.0 °C) percentile relative to 25th percentile (4.9 °C)] and heat effect [RR at 99th (25.1 °C) percentile relative to 75th (15.9 °C) percentile] for 1993–2004 (blue) and 2005–2016 (red) stratified by subgroups.

[Asterisks indicate statistical significance for differences in relative risk estimates between 1993–2004 and 2005–2016.

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