ESC European Society of Cardiology

European Heart Journal (2019) **0**, 1–9
doi:10.1093/eurheartj/ehz116

Temporal variations in the triggering of myocardial infarction by air temperature in Augsburg, Germany, 1987–2014

Kai Chen[1]*, Susanne Breitner[1,2], Kathrin Wolf[1], Regina Hampel[1], Christa Meisinger[3,4], Margit Heier[1,5], Wolfgang von Scheidt[6], Bernhard Kuch[6,7], Annette Peters[1,2,8], and Alexandra Schneider[1]; for the KORA Study Group[†]

[1]Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany; [2]Institute for Medical Information Processing, Biometry and Epidemiology, Ludwig-Maximilians-Universität München, Marchioninistr. 15, 81377 Munich, Germany; [3]Ludwig-Maximilians-Universität München, UNIKA-T, Neusässer Str. 47, 86156 Augsburg, Germany; [4]Independent Research Group Clinical Epidemiology, Helmholtz Zentrum München–German Research, Center for Environmental Health, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany; [5]MONICA/KORA Myocardial Infarction Registry, Central Hospital of Augsburg, Stenglinstr. 2, 86156 Augsburg, Germany; [6]Department of Internal Medicine I - Cardiology, Central Hospital of Augsburg, Stenglinstr. 2, 86156 Augsburg, Germany; [7]Department of Internal Medicine/Cardiology, Hospital of Nördlingen, Stoffelsberg 4, 86720 Nördlingen, Germany; and [8]Partner-Site Munich, German Research Center for Cardiovascular Research (DZHK), Biedersteiner Straße 29, 80802 Munich, Germany

Received 3 August 2018; revised 17 October 2018; editorial decision 10 January 2019; accepted 18 February 2019

Aims The association between air temperature and mortality has been shown to vary over time, but evidence of temporal changes in the risk of myocardial infarction (MI) is lacking. We aimed to estimate the temporal variations in the association between short-term exposures to air temperature and MI in the area of Augsburg, Germany.

Methods and results Over a 28-years period from 1987 to 2014, a total of 27 310 cases of MI and coronary deaths were recorded. Daily meteorological parameters were measured in the study area. A time-stratified case-crossover analysis with a distributed lag non-linear model was used to estimate the risk of MI associated with air temperature. Subgroup analyses were performed to identify subpopulations with changing susceptibility to air temperature. Results showed a non-significant decline in cold-related MI risks. Heat-related MI relative risk significantly increased from 0.93 [95% confidence interval (CI): 0.78–1.12] in 1987–2000 to 1.14 (95% CI: 1.00–1.29) in 2001–14. The same trend was also observed for recurrent and non-ST-segment elevation MI events. This increasing population susceptibility to heat was more evident in patients with diabetes mellitus and hyperlipidaemia. Future studies using multicentre MI registries at different climatic, demographic, and socioeconomic settings are warranted to confirm our findings.

Conclusion We found evidence of rising population susceptibility to heat-related MI risk from 1987 to 2014, suggesting that exposure to heat should be considered as an environmental trigger of MI, especially under a warming climate.

Keywords Myocardial infarction • Temperature • Temporal variation • Epidemiology

Introduction

Acute myocardial infarction (MI) is a major cause of disability and death worldwide, which can be triggered by short-term exposure to environmental factors such as air temperature.[1,2] Although epidemiological studies have provided evidence that both high and low temperatures (i.e. heat and cold) adversely affect cardiovascular disease by increasing mortality and morbidity,[3,4] the association between air temperature and MI occurrence remains controversial. Most previous studies using registry or similar validated data have reported significant cold effects on MI occurrence,[5–8] whereas only few studies have observed increased risk of MI triggered by heat exposures.[9,10] Under a warming climate, a decline in cold-related MI is expected due to decreased cold days.[2] However, whether climate

* Corresponding author. Tel: +49 89 3187 3697, Fax: +49 89 3187 3380, Email: kai.chen@helmholtz-muenchen.de

† The members of the KORA Study Group are listed in the Acknowledgements.

change will bring benefits from these reduced cold-related MI remains unknown as the heat effects on MI occurrence are less clear.

To project future health impacts of climate change, temporal variations in the association between air temperature and health have become one of the most critical issues.[11,12] Recent studies have reported continuously decreasing heat-related mortality risks over time,[11–13] whereas conflicting trends with either reduction or no change were observed in cold-related mortality risks.[11,14] However, most of these studies have focused on mortality, little is known about the temporal variations in the association between air temperature and MI occurrence.

To address these knowledge gaps, we conducted a time-stratified case-crossover study based on a validated, complete, and detailed registration of all MI and coronary deaths cases in Augsburg, Germany from 1987 to 2014. We used a time-varying distributed lag non-linear model (DLNM)[12] to examine the temporal variations in the association between short-term temperature exposure and occurrence of MI. Subgroup analyses were performed to identify subpopulations with increased susceptibility to air temperatures.

Methods

Study population

This study was based on data from the MONICA/KORA MI registry, a population-based MI registry in Augsburg, Germany. The study area includes the city of Augsburg and the two adjacent rural counties of Augsburg and Aichach-Friedberg. Details of this registry are given in Supplementary material online, *Methods*. In the present study, we used all recorded fatal and non-fatal MI cases from 1 January 1987 to 31 December 2014. We further stratified the MI events by admission type (incident and recurrent events)[15] and infarction type [ST-segment elevation MI (STEMI) and non-ST-segment elevation MI (NSTEMI) for survivors of 24-h hospital stay]. For each event, information was extracted on sex, age groups (25–64 and 65–74 years old), place of residence (city and counties), living alone, history of diabetes mellitus, hyperlipidaemia, and pre-existing cardiovascular diseases (angina, coronary heart disease, hypertension, and stroke) to identify potentially vulnerable subgroups. For non-fatal events, additional information was available on education level (primary school, high school, and university), smoking status (smoker, ex-smoker, and non-smoker), and obesity (body mass index >30 kg/m^2). This study was approved by the ethics committee of Bavarian Chamber of Physicians and performed in accordance with the Declaration of Helsinki.

Exposure data

Daily 24-h average meteorological variables (air temperature, relative humidity, and barometric pressure), particulate matter with an aerodynamic diameter <10 μm (PM_{10}), nitrogen dioxide (NO_2), and daily maximum 8-h average O_3 concentrations were obtained from monitoring stations in Augsburg. Details are given in Supplementary material online, *Methods*.

Statistical analyses

We applied a time-stratified case-crossover design with a conditional Poisson regression model[16] to study the association between air temperature and daily cases of MI and coronary deaths. For each individual, the exposure on the day of MI occurrence ('case' day) was compared with exposures on days at the same day of the week during the same month ('control' day). We further controlled for current day relative humidity and barometric pressure as linear terms and changing number of residents over the years (i.e. adjusting log-transformed population as an 'offset'). To quantify both cold and heat effects on MI,[1] we used the DLNM to characterize the temperature term as a cross-basis matrix, which can flexibly evaluate the complex non-linear and delayed temperature-health dependencies.[17] We applied natural cubic splines with 4 degrees of freedom (df) for temperature exposure–response and a natural cubic spline for the lag-response with an intercept and two internal knots placed at equally spaced values in the log scale. The lag-response relationship represents a new dimension in addition to the usual exposure–response relationship, which estimates the distribution of immediate and delayed effects that cumulate across the lag period of exposure.[17] Temperature effects on short-term MI risk are reported within 5 days in previous studies,[2] we extended the lag period to 10 days to account for potential short-term harvesting effect. For all groups of MI events, we used the temperature between the first and the 99th percentile of the temperature distribution that yielded the minimum risk on total MI events over the whole study period as the reference temperature [hereafter referred to as minimum MI temperature (MMIT)]. We calculated MMIT by scanning through the exposure–response curve estimated from the model to find the temperature value that minimized MI risk.

To model the time-varying association between temperature and MI, we estimated the temperature-MI associations for two sub-periods (1987–2000 and 2001–14) separately. We assessed the temporal variation in temperature-MI associations by comparing the exposure–response curves in each sub-period and tested the statistical significance using a multivariate Wald test.[12] We also calculated the heat effect as lag-cumulative MI risk at the 97.5th percentile relative to MMIT and cold effect as lag-cumulative MI risk at the 2.5th percentile relative to MMIT. These cut-offs could avoid the small sample size at extreme temperatures and were consistent with a previous multicountry study on mortality.[17]

In addition, we conducted stratification analyses for heat and cold effects on total MI events to examine effect modification by sex, age groups, place of residence, living alone, history of hypertension, and diabetes mellitus. We further assessed effect modification by education level, smoking status, and obesity for non-fatal MI events.

To examine the robustness of the results, we conducted sensitivity analyses with regard to different modelling assumptions and confounding adjustments (see Supplementary material online, *Methods*). All analyses were performed with R software, version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided *P*-value <0.05 was considered statistical significant.

Results

Study population and exposure characteristics

Overall, there were 27 310 coronary events recorded between 1987 and 2014, mean (standard deviation) age was 62.5 (9.3) years and 73% were men (*Table 1*). Of all these events, 14 133 were non-fatal MIs and 13 177 were fatal MIs and coronary deaths. Over the 28-year period, the proportion of NSTEMI substantially increased from 20.0% in 1987–2000 to 34.2% in 2001–14. Of all events, the proportion of people living in the city significantly decreased from 1987–2000 to 2001–15, living alone increased, as did the proportion of men, the prevalence of diabetes mellitus, hyperlipidaemia, and pre-existing cardiovascular diseases. Of non-fatal MIs, education levels and the prevalence of obesity increased, whereas current smoking decreased from the early 14-year period to the late 14-year period.

Table 1 Summary statistics of myocardial infarction cases in Augsburg, Germany from 1987 to 2014

	Overall period	1987–2000	2001–2014	*P*-value[a]
No. of cases				
Total MI	27 310	13 770	13 540	
Fatal MI	13 177	7848	5329	
Non-fatal MI	14 133	5922	8211	
Incident MI	18 917	9353	9564	
Recurrent MI	5731	2995	2736	
STEMI	6193	2899	3294	
NSTEMI	7386	2757	4629	
Characteristics of total events				
Men (%)	73	71.2	74.9	<0.001[b]
Age (years), mean (SD)	62.5 (9.3)	62.7 (9.1)	62.3 (9.4)	0.003[c]
Residence in the city (%)	51	53.2	48.8	<0.001[b]
Living alone (%)	10.5	5.5	15.7	<0.001[b]
Diabetes (%)	29.9	27.4	32.5	<0.001[b]
Hyperlipidaemia (%)	51.5	48.0	55.0	<0.001[b]
Pre-CVD (%)	75.4	72.5	78.3	<0.001[b]
Characteristics of non-fatal events				
Education level (%)				<0.001[b]
Low (primary school)	58.1	56.5	59.2	
Medium (high school)	14.3	12.3	15.7	
High (university)	8.1	5.8	9.8	
Unknown	19.5	25.4	15.3	
Obesity (%)	21.6	15	26.4	<0.001[b]
Smoking (%)				<0.001[b]
Smoker	36.3	36.7	36	
Ex-smoker	29.3	27.1	30.9	
Non-smoker	28.5	31.4	26.4	
Unknown	5.9	4.8	6.7	

NSTEMI, non-ST-segment elevation MI; pre-CVD, pre-existing cardiovascular diseases, including angina, coronary heart disease, hypertension, and stroke; STEMI, ST-segment elevation MI.
[a]Comparing the period 1987–2000 with 2001–14.
[b]Pearson's χ^2 test.
[c]Wilcoxon rank-sum test.

The daily mean temperature slightly increased from 1987–2000 to 2001–14 (*Table 2*). Daily mean temperature was highly positively correlated with other temperature metrics, moderately correlated with relative humidity and O_3, but not correlated with barometric pressure or PM_{10} or NO_2 (see Supplementary material online, *Table S1*).

Time-varying association of temperature and myocardial infarction

Over the entire 28-year period, significant increasing MI risks were found at low temperatures below the MMIT (18.4°C) for total, fatal, incident, and STEMI events (*Table 3* and Supplementary material online, *Figure S1*). In contrast, non-significant increasing MI risk was found at high temperatures above the MMIT except for fatal events. The lag-response relationships showed that cold effects in most MI groups were within five days (lag 0–4), whereas heat effects immediately appeared on first 2 days (lag 0–1) (see Supplementary material online, *Figures S2* and *S3*).

Temporal variation in temperature-MI associations showed a consistent rising heat effect on all groups of MIs, with strong evidence of a difference in the exposure–response curves observed in NSTEMI events ($P = 0.03$) (*Figure 1*). Significant heat effects (97.5th percentile vs. the MMIT) were found in 2001–14 for total, non-fatal, recurrent, and NSTEMI events (*Table 3*). Compared with 1987–2000, heat-related MI risks in 2001–14 were significantly higher for recurrent and NSTEMI events. No significant changes in cold effects were found from 1987 to 2014, though MI risk estimates generally decreased except for recurrent events.

Subgroup analyses

Throughout the overall study period, we did not find evidence for effect modification by individual characteristics (all $P > 0.05$; see Supplementary material online, *Figure S4*). The cold-related MI risks significantly decreased in male from 1987–2000 to 2001–14. The heat-related MI risks significantly increased in people with diabetes mellitus from 0.81 [95% confidence interval (CI) 0.58–1.14] in

Table 2 Summary statistics of daily meteorology and air pollution in Augsburg, Germany from 1987 to 2014

	Overall period (1987–2014)			1987–2000			2001–2014		
	Mean (SD)	Percentile		Mean (SD)	Percentile		Mean (SD)	Percentile	
		2.5th	97.5th		2.5th	97.5th		2.5th	97.5th
Mean temperature (°C)	9.6 (8.1)	-5.5	23.5	9.6 (7.9)	-5.3	22.8	9.7 (8.2)	-5.7	24.0
Minimum temperature (°C)	5.1 (7.1)	-9.8	16.7	5.3 (6.9)	-9.1	16.5	4.9 (7.2)	-10.2	16.8
Maximum temperature (°C)	14.8 (9.9)	-2.5	32.6	14.5 (9.7)	-2.6	32.1	15.1 (10.1)	-2.3	33.1
Apparent temperature (°C)	7.0 (8.1)	-8.2	20.9	6.9 (7.9)	-8.0	20.3	7.0 (8.3)	-8.4	21.4
Relative humidity (%)	75.7 (12.2)	51.9	95.0	76.6 (12.4)	52.2	95.5	74.8 (12.0)	51.4	93.8
Barometric pressure (hPa)	1018.4 (7.8)	1001.0	1032.7	1018.6 (8.4)	1000.0	1033.8	1018.2 (7.2)	1002.0	1031.3
PM_{10} ($\mu g/m^3$)	31.9 (20.6)	7.3	83.4	36.3 (22.2)	8.6	89.5	26.5 (17.0)	6.5	69.1
NO_2 ($\mu g/m^3$)	34.6 (14.2)	12.7	65.4	36.1 (15.0)	13.1	67.2	33.2 (13.3)	12.5	62.9
O_3 ($\mu g/m^3$)	65.4 (35.4)	5.1	138.2	60.3 (36.2)	3.5	137.3	70.3 (33.8)	8.3	139.6

NO_2, nitrogen dioxide; O_3, ozone; PM_{10}, particulate matter with an aerodynamic diameter <10 μm.

Table 3 Lag-cumulative RR estimates for daily myocardial infarction cases (95% confidence interval) associated with heat exposure [97.5th percentile (23.5°C) relative to minimum myocardial infarction temperature (18.4°C)] and cold exposure [2.5th percentile (−5.5°C) relative to minimum myocardial infarction temperature]

Group	Period	Cold effects		Heat effects	
		RR[a]	*P* value[b]	RR[a]	*P* value[b]
Total MI	1987–2014	1.26 (1.08–1.47)		1.07 (0.96–1.18)	0.08
	1987–2000	1.40 (1.11–1.76)	0.22	0.93 (0.78–1.12)	
	2001–14	1.15 (0.94–1.42)		1.14 (1.00–1.29)	
Fatal MI	1987–2014	1.33 (1.06–1.65)		0.98 (0.84–1.15)	0.29
	1987–2000	1.42 (1.05–1.92)	0.53	0.89 (0.70–1.13)	
	2001–14	1.23 (0.89–1.70)		1.05 (0.86–1.30)	
Non-fatal MI	1987–2014	1.20 (0.97–1.48)		1.14 (0.99–1.31)	0.28
	1987–2000	1.36 (0.96–1.93)	0.36	1.00 (0.76–1.32)	
	2001–14	1.11 (0.85–1.45)		1.19 (1.01–1.40)	
Incident MI	1987–2014	1.24 (1.04–1.49)		1.07 (0.95–1.22)	0.47
	1987–2000	1.42 (1.07–1.87)	0.20	1.01 (0.81–1.25)	
	2001–14	1.11 (0.87–1.42)		1.11 (0.95–1.29)	
Recurrent MI	1987–2014	1.24 (0.91–1.69)		1.13 (0.91–1.41)	0.03
	1987–2000	1.08 (0.68–1.71)	0.42	0.82 (0.56–1.19)	
	2001–14	1.39 (0.91–2.13)		1.37 (1.04–1.80)	
STEMI	1987–2014	1.52 (1.11–2.07)		1.11 (0.90–1.36)	0.67
	1987–2000	1.66 (1.02–2.69)	0.58	1.03 (0.71–1.49)	
	2001–14	1.38 (0.91–2.10)		1.14 (0.89–1.46)	
NSTEMI	1987–2014	0.99 (0.76–1.31)		1.19 (0.99–1.43)	
	1987–2000	1.19 (0.74–1.91)	0.41	0.83 (0.56–1.21)	0.04
	2001–14	0.93 (0.66–1.31)		1.31 (1.06–1.61)	

NSTEMI, non-ST-segment elevation MI; RR, relative risk; STEMI, ST-segment elevation MI.
[a]Conditional Poisson regression adjusted for relative humidity, barometric pressure, and population.
[b]Significance test on temporal variation, based on difference between RR estimates in 1987–2000 and 2001–14.

1987–2000 to 1.33 (95% CI 1.06–1.67) in 2001–14 (*Figure 2* and *Take home figure*). A significant increase in heat-related MI risk from 1987–2000 to 2001–14 was also observed in people living in rural counties and with hyperlipidaemia. In 2001–14, significant heat-related MI risks were found in people with pre-existing cardiovascular disease [1.16 (95% CI 1.00–1.34)], as well as people with non-cardiovascular diseases such as diabetes mellitus [1.33 (95% CI 1.06–1.67)] and hyperlipidaemia [1.23 (95% CI 1.03–1.46)]. Both cold-related and

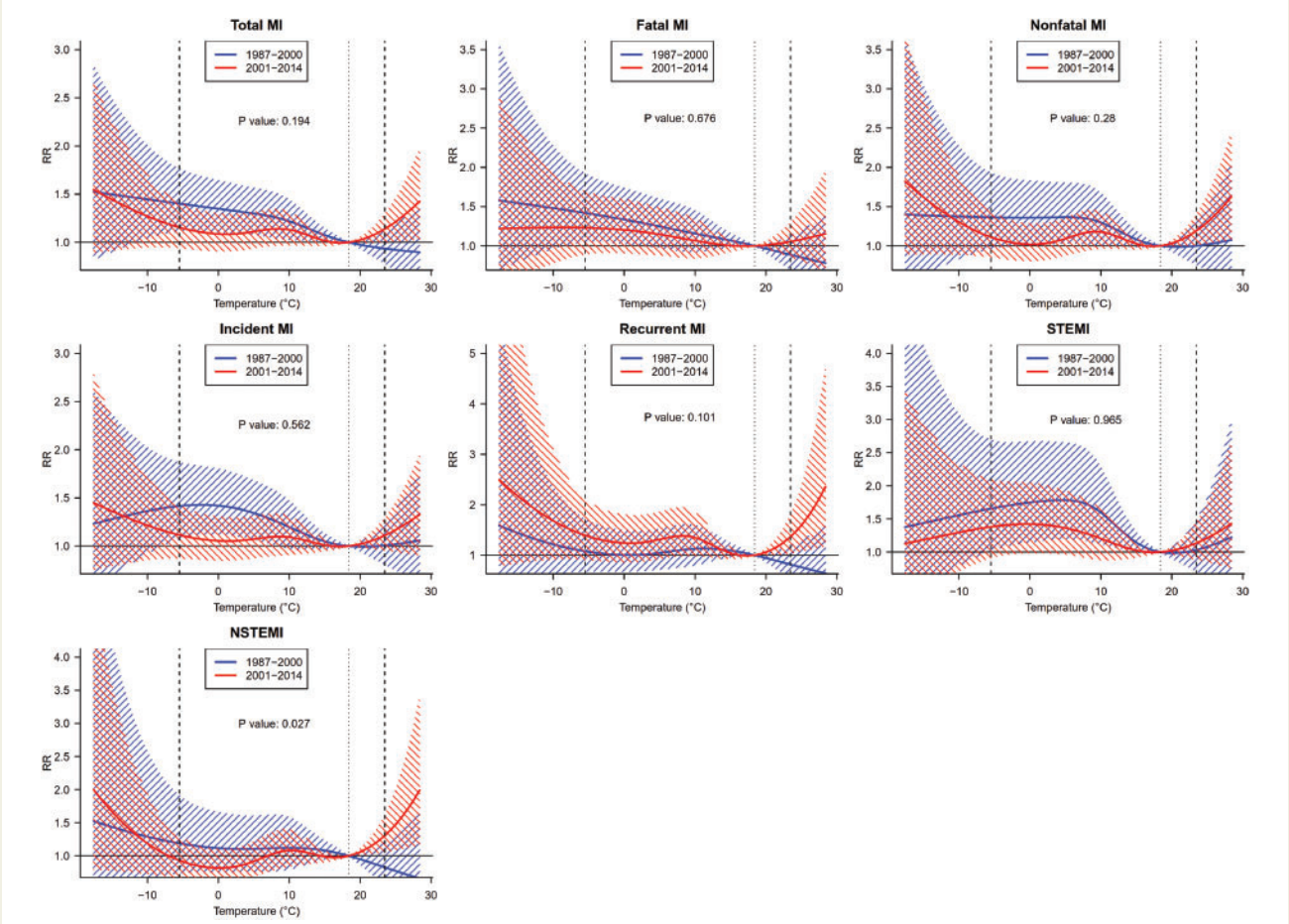


Figure 1 Overall lag-cumulative exposure–response relationships between air temperature and myocardial infarction predicted for 1987–2000 (blue) and 2001–14 (red) with 95% confidence interval. A *P*-value represents the significance test on temporal variation, based on a multivariate Wald test of the reduced coefficients of the interaction terms. The vertical lines represent the minimum myocardial infarction temperature (dotted) and the 1st and the 99th percentiles of the temperature distribution (dashed).

heat-related MI risks increased for current smokers from 1987–2000 to 2001–14 (see Supplementary material online, *Figure S5*).

Sensitivity analyses

Our results were robust when we used different cut-offs (1st/99th and 5th/95th) for heat and cold exposures, when we used different temperature metrics, when we used continuously measured meteorological data, when we additionally adjusted for influenza epidemics and percentages of elderly and foreigners, when we used three internal knots for the lag-response, and when we used equal ranges for cold and heat exposures (see Supplementary material online, *Tables S2–S8*). Moreover, although daily PM_{10}, NO_2, and O_3 were associated with increased MI risks, we did not find significant effect modifications by these air pollutants on the temperature-MI associations, except that a significant effect modification by low PM_{10} levels was noted for cold effects on STEMI events (see Supplementary material online, *Figures S6–S9*). Furthermore, we did not find apparent associations between heat waves, cold spells, and MI events or significant changes in temperature variability-related MI risks over time (see Supplementary material online, *Table S9* and *Figure S10*).

Discussion

In this registry-based time-stratified case-crossover study over 28 years, we found that the heat-related MI risks increased over time, with significantly higher estimates in 2001–14 compared to 1987–2000 for recurrent and NSTEMI events. Cold-related MI risks non-significantly declined throughout the study period. Furthermore, although we found no evidence of effect modification by individual characteristics, people living in counties and with diabetes mellitus had significantly higher heat-related MI risks in 2001–14 compared with 1987–2000. These findings suggest that exposure to heat should be considered as a potentially preventable trigger of MI events under a warming climate.

Throughout the 28-year period, we observed significant cold-induced but not heat-induced increased risk for total MI events, which is consistent with previous studies.[5–8] Our finding of significant

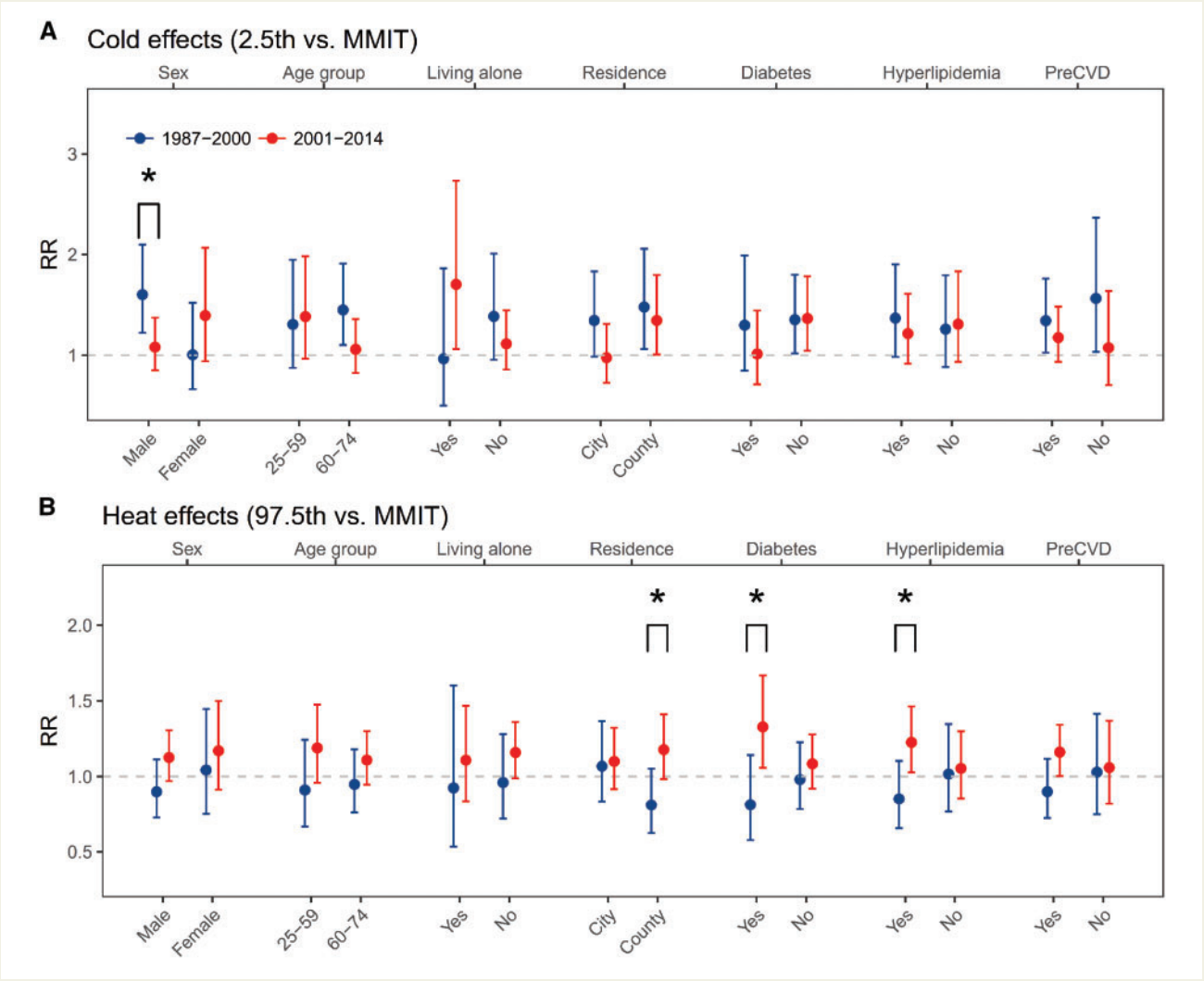
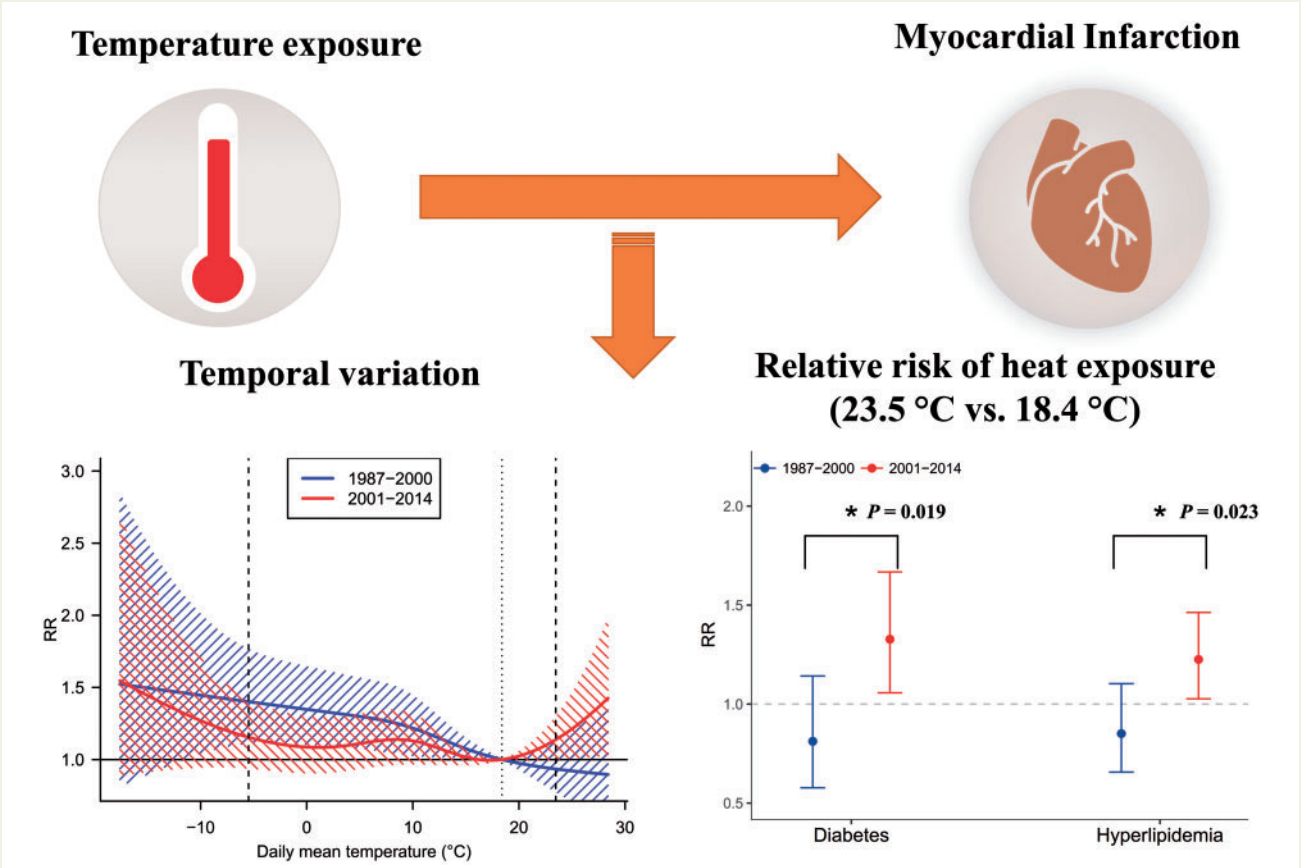


Figure 2 Lag-cumulative relative risk estimates for daily myocardial infarction cases (95% confidence interval) associated with (*A*) cold exposure (2.5th percentile relative to minimum myocardial infarction temperature) and (*B*) heat exposure (97.5th percentile relative to minimum myocardial infarction temperature) predicted for 1987–2000 (blue) and 2001–14 (red) stratified by subgroups. Asterisks indicate statistical significance for differences in relative risk estimates between 1987–2000 and 2001–2014.

cold effect on STEMI, together with two recent nationwide registry studies in Japan[18] and Belgium,[19] provides further evidence that exposure to cold may be an important environmental trigger for STEMI.

Similar to a recent systematic review and meta-analysis,[4] no apparent association between heat and MI was detected in this study. However, when restricting the analysis to the late period (2001–14), we found a significant association between heat and MI occurrence, with significant increases in the risk of total, non-fatal, recurrent, and NSTEMI events. The detection of a heat effect may be partially because of the non-linearity of temperature-MI associations we used in this study. Previous time-series studies[5,6,8,18,19] generally used a linear inverse relationship between temperature and MI to estimate cold effect, which may limit their ability to detect a potential, even non-significant heat effect, especially when the cold effect dominates the temperature-MI association. In a time-series analysis based on the England and Wales Myocardial ischaemia National Audit Project database, no heat effect was found when using a linear association at daily timescale,[5] whereas a significant heat effect was found when using a non-linear association at sub-daily timescale.[9] Moreover, Augsburg has a relatively temperate yet warming climate, with the average daily maximum temperature increasing from 14.5°C during 1978–2000 to 15.1°C during 2001–14. There is little residential air conditioning in Augsburg, thus people may become more vulnerable to heat under global warming. In addition, significant increases in MI risk factors such as diabetes mellitus and hyperlipidaemia over time (*Table 1*) may also contribute to the increasing heat-related MI risks. Furthermore, change in socioeconomic status may also modify the heat-related MI over time. For example, the prevalence of people with low-level education, which had the highest heat-related MI risk among education levels, increased from 56.5% to 59.2% from 1987–2000 to 2001–14. Therefore, changes in underlying drivers from



Take home figure Rising population susceptibility to heat effects on MI occurrence, especially among patients with diabetes mellitus and hyperlipidaemia. Asterisks (*) indicate statistical significance for differences in relative risk estimates between 1987–2000 and 2001–2014.

climatic, metabolic, and socioeconomic conditions may contribute to the increasing susceptibility to heat-related MI.

In the late period, we found an increasing population susceptibility to heat-induced MI risks in Augsburg. This trend was more pronounced among people living in rural counties, with diabetes mellitus and hyperlipidaemia, which had higher heat effects than the rest of the population. While adverse heat effects have been well documented in urban areas, emerging evidence suggests that people living in non-urban areas could have similar or even higher heat-related mortality risks.[20] Compared with 1987–2000, rural residents in the Augsburg region had a higher percentage of people with low-level education (61.1% vs. 58.3%), higher prevalence of hyperlipidaemia (57.2% vs. 49.2%) and pre-existing cardiovascular diseases (79.6% vs. 72.7%) in 2001–14. The lower socioeconomic status and higher prevalence of pre-existing chronic diseases in 2001–14 may result in a higher vulnerability to heat in rural residents. A global scale meta-regression analysis found that diabetes incidence in the US and glucose intolerance prevalence worldwide increased with higher air temperature,[21] suggesting patients with diabetes mellitus may be vulnerable to heat. A recent study in Hong Kong also found a significantly stronger heat-related MI risk for diabetic individuals compared with non-diabetic individuals among people <75 years old.[22] This may because people with diabetes have impaired endothelial function and poor skin blood flow, leading to compromised thermoregulation at high temperatures.[23] People with hyperlipidaemia may have high levels of serum low-density lipoprotein when air temperature increases,[24] resulting in a high heat-related MI risk.

Over the study period, we did not find a significant decline in cold-related MI risks. Although significant decreases in male and increases in current smokers were noted, contrasting patterns were found for different subgroups (e.g. sex and smoking). Thus, the changing cold effects over time with regard to sex and smoking should be interpreted with caution, calling for replication by future studies. Moreover, we did not find significant changes in the association between short-term temperature variability and MI over time, suggesting a stable short-term impact of temperature variability on MI.

Recently, emerging evidence suggested a temporal decrease in heat-related mortality risks,[11–13] which can be attributed to population adaptation to heat due to certain climate, demographic, and socioeconomic factors (e.g. increasing residential air conditioning).[13] However, to the best of our knowledge, no published epidemiological study to date has examined the temporal changes in temperature-MI associations. Our results revealed increased heat-related MI risks over the last three decades, which was in contrast to the finding of

declining heat-related mortality risks in those mortality studies.[11–13] This inconsistency may be due to the generally smaller and non-significant heat effect on cardiovascular morbidity than those findings related to mortality.[4] It could also be because the significant heat effects we observed on non-fatal and recurrent MIs are not reflected by the mortality studies. Moreover, we did not find significantly declining cold or heat effects on MI in the late warm period, suggesting no signs for population adaptation. Under a warming climate, increasing heat exposures and population susceptibility may lead to more heat-related MI events. Meanwhile, cold impacts may have a small reduction or remain stable,[25,26] leading to a potential net increase in temperature-related MI events in the future.

To prevent heat-related MI, air conditioning adaptation may help but can also exacerbate air pollution-related mortality due to increases in electricity demand.[27] On the other hand, lifestyle interventions for MI such as addressing overweight[28–30] could be a sound way to prevent diabetes mellitus, thus reducing the heat-related MI risks.

Potential mechanisms for air temperature triggering incident coronary events have been proposed to explain the observed cold and heat effects. Low temperatures may lead to a stimulation of cold receptors in the skin and an increase in renal diuresis, which result in elevated blood pressure, acute changes in blood markers of inflammation and coagulation.[2,31] High temperatures may lead to increased surface blood circulation and sweating, which may increase cardiac strain, blood viscosity, plasma cholesterol, and interleukin-6 levels.[32]

The main strength of the present study is the validated, complete, and detailed registration of all MI and coronary deaths cases by the MONICA/KORA MI registry over a 28-year period. Other strengths include the time-stratified case-crossover design that controls for long-term time-trends and seasonality in underlying MI rates, time-invariant confounding, and avoids time-trend bias from the exposure,[33] the application of the time-varying DLNM to characterize the non-linear and delayed temperature-health dependence and its changes over time,[12] and the ability to perform subgroup analyses of the time-varying temperature-MI associations with patient characteristics. Our study also has several limitations. First, our exposure data were obtained from one fixed outdoor monitoring station, which leads to measurement error. However, this measurement error is likely to be random and might result in an underestimation of effect estimates. In addition, the precisions of time of onset for fatal and non-fatal events were different. Time of symptom onset was used and validated against the information from the medical records for non-fatal MI, whereas time of hospital arrival or death was used for fatal MI.[8] Moreover, fewer NSTEMI cases were diagnosed in the first period as troponin was only introduced later, thus the results of NSTEMI should be interpreted with caution. However, although absolute numbers of NSTEMI cases are not comparable, temperature effect estimates should be when using the case-crossover design. Finally, our results are based on a monocentric study in Augsburg, Germany and may not be applicable to other regions with different climatic, demographic, and socioeconomic conditions. Future studies using multicentre MI registries are warranted to confirm our findings.

In conclusion, our study yields evidence of rising population susceptibility to heat effects on MI occurrence, especially among patients with diabetes mellitus and hyperlipidaemia.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

The KORA Study Group consists of A. Peters (speaker), H. Schulz, L. Schwettmann, R. Leidl, M. Heier, K. Strauch, and their co-workers, who are responsible for the design and conduct of the KORA studies.

Funding

This work was supported by the Deutsche Stiftung für Herzforschung (German Foundation of Heart Research) (grant number F/51/15). The KORA research platform and the MONICA Augsburg studies were initiated and financed by the Helmholtz Zentrum München, German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education, Science, Research, and Technology and by the State of Bavaria. Since 2000, the MI data collection has been co-financed by the German Federal Ministry of Health and Social Security to provide population-based MI morbidity data for the official German Health Report (see www.gbe-bund.de).

Conflict of interest: none declared.

References

1. Bhaskaran K, Hajat S, Haines A, Herrett E, Wilkinson P, Smeeth L. Effects of ambient temperature on the incidence of myocardial infarction. *Heart* 2009;**95**:1760.
2. Claeys MJ, Rajagopalan S, Nawrot TS, Brook RD. Climate and environmental triggers of acute myocardial infarction. *Eur Heart J* 2017;**38**:955–960.
3. Basu R. High ambient temperature and mortality: a review of epidemiologic studies from 2001 to 2008. *Environ Health* 2009;**8**:40.
4. Turner LR, Barnett AG, Connell D, Tong S. Ambient temperature and cardiorespiratory morbidity: a systematic review and meta-analysis. *Epidemiology* 2012;**23**:594–606.
5. Bhaskaran K, Hajat S, Haines A, Herrett E, Wilkinson P, Smeeth L. Short term effects of temperature on risk of myocardial infarction in England and Wales: time series regression analysis of the Myocardial Ischaemia National Audit Project (MINAP) registry. *BMJ* 2010;**341**:c3823.
6. Danet S, Richard F, Montaye M, Beauchant S, Lemaire B, Graux C, Cottel D, Marécaux N, Amouyel P. Unhealthy effects of atmospheric temperature and pressure on the occurrence of myocardial infarction and coronary deaths. *Circulation* 1999;**100**:e1.
7. Wichmann J, Ketzel M, Ellermann T, Loft S. Apparent temperature and acute myocardial infarction hospital admissions in Copenhagen, Denmark: a case-crossover study. *Environ Health* 2012;**11**:19.
8. Wolf K, Schneider A, Breitner S, von Klot S, Meisinger C, Cyrys J, Hymer H, Wichmann H-E, Peters A. Air temperature and the occurrence of myocardial infarction in Augsburg, Germany. *Circulation* 2009;**120**:735–742.
9. Bhaskaran K, Armstrong B, Hajat S, Haines A, Wilkinson P, Smeeth L. Heat and risk of myocardial infarction: hourly level case-crossover analysis of MINAP database. *BMJ* 2012;**345**:e8050.
10. Madrigano J, Mittleman MA, Baccarelli A, Goldberg R, Melly S, von Klot S, Schwartz J. Temperature, myocardial infarction, and mortality: effect modification by individual and area-level characteristics. *Epidemiology* 2013;**24**:439–446.
11. Chung Y, Noh H, Honda Y, Hashizume M, Bell ML, Guo Y-LL, Kim H. Temporal changes in mortality related to extreme temperatures for 15 cities in Northeast Asia: adaptation to heat and maladaptation to cold. *Am J Epidemiol* 2017;**185**:907–913.
12. Gasparrini A, Guo YM, Hashizume M, Kinney PL, Petkova EP, Lavigne E, Zanobetti A, Schwartz JD, Tobias A, Leone M, Tong SL, Honda Y, Kim H, Armstrong BG. Temporal variation in heat-mortality associations: a multicountry study. *Environ Health Perspect* 2015;**123**:1200–1207.
13. Petkova EP, Gasparrini A, Kinney PL. Heat and mortality in New York City since the beginning of the 20th century. *Epidemiology* 2014;**25**:554–560.
14. Yang C, Meng X, Chen R, Cai J, Zhao Z, Wan Y, Kan H. Long-term variations in the association between ambient temperature and daily cardiovascular mortality in Shanghai, China. *Sci Total Environ* 2015;**538**:524–530.

15. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2018;**40**:237–269.
16. Armstrong BG, Gasparrini A, Tobias A. Conditional Poisson models: a flexible alternative to conditional logistic case cross-over analysis. *BMC Med Res Methodol* 2014;**14**:122.
17. Gasparrini A, Guo YM, Hashizume M, Lavigne E, Zanobetti A, Schwartz J, Tobias A, Tong SL, Rocklov J, Forsberg B, Leone M, De Sario M, Bell ML, Guo YLL, Wu CF, Kan H, Yi SM, Coelho M, Saldiva PHN, Honda Y, Kim H, Armstrong B. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *Lancet* 2015;**386**:369–375.
18. Yamaji K, Kohsaka S, Morimoto T, Fujii K, Amano T, Uemura S, Akasaka T, Kadota K, Nakamura M, Kimura T. Relation of ST-segment elevation myocardial infarction to daily ambient temperature and air pollutant levels in a Japanese nationwide percutaneous coronary intervention registry. *Am J Cardiol* 2017;**119**:872–880.
19. Claeys MJ, Coenen S, Colpaert C, Bilcke J, Beutels P, Wouters K, Legrand V, Van Damme P, Vrints C. Environmental triggers of acute myocardial infarction: results of a nationwide multiple-factorial population study. *Acta Cardiologica* 2015;**70**:693–701.
20. Chen K, Zhou L, Chen X, Ma Z, Liu Y, Huang L, Bi J, Kinney P. Urbanization level and vulnerability to heat-related mortality in Jiangsu Province, China. *Environ Health Perspect* 2016;**124**:1863–1869.
21. Blauw LL, Aziz NA, Tannemaat MR, Blauw CA, de Craen AJ, Pijl H, Rensen PCN. Diabetes incidence and glucose intolerance prevalence increase with higher outdoor temperature. *BMJ Open Diabetes Res Care* 2017;**5**:e000317.
22. Lam HCY, Chan JCN, Luk AOY, Chan EYY, Goggins WB. Short-term association between ambient temperature and acute myocardial infarction hospitalizations for diabetes mellitus patients: a time series study. *PLoS Med* 2018;**15**:e1002612.
23. Petrofsky JS. The effect of type-2-diabetes-related vascular endothelial dysfunction on skin physiology and activities of daily living. *J Diabetes Sci Technol* 2011;**5**:657–667.
24. Halonen JI, Zanobetti A, Sparrow D, Vokonas PS, Schwartz J. Outdoor temperature is associated with serum HDL and LDL. *Environ Res* 2011;**111**:281–287.
25. Oudin Åström D, Ebi KL, Vicedo-Cabrera AM, Gasparrini A. Investigating changes in mortality attributable to heat and cold in Stockholm, Sweden. *Int J Biometeorol* 2018;**62**:1777–1780.
26. Patrick LK, Joel S, Mathilde P, Elisaveta P, Alain LT, Sylvia M, Robert V. Winter season mortality: will climate warming bring benefits? *Environ Res Lett* 2015;**10**:064016.
27. Abel DW, Holloway T, Harkey M, Meier P, Ahl D, Limaye VS, Patz JA. Air-quality-related health impacts from climate change and from adaptation of cooling demand for buildings in the eastern United States: an interdisciplinary modeling study. *PLoS Med* 2018;**15**:e1002599.
28. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–177.
29. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC) *Eur Heart J* 2016;**37**:267–315.
30. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney M-T, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen M-L, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S, ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.
31. Schäuble CL, Hampel R, Breitner S, Rückerl R, Phipps R, Diaz-Sanchez D, Devlin RB, Carter JD, Soukup J, Silbajoris R, Dailey L, Koenig W, Cyrys J, Geruschkat U, Belcredi P, Kraus U, Peters A, Schneider AE. Short-term effects of air temperature on blood markers of coagulation and inflammation in potentially susceptible individuals. *Occup Environ Med* 2012;**69**:670.
32. Schneider A, Rückerl R, Breitner S, Wolf K, Peters A. Thermal control, weather, and aging. *Curr Environ Health Rep* 2017;**4**:21–29.
33. Janes H, Sheppard L, Lumley T. Case–crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. *Epidemiology* 2005;**16**:717–726.