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

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Abstract

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 nonlinear 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 nonsignificant 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 2001-2014. 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 hyperlipidemia. Future studies using multicenter MI registries at different climatic, demographic, and socioeconomic settings are warranted to confirm our findings.

Conclusions 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.

Key Words 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 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 nonlinear 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 nonfatal MI cases from January 1, 1987 to December 31, 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-hour 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, hyperlipidemia, and pre-existing cardiovascular diseases (angina, coronary heart disease, hypertension, and stroke) to identify potentially vulnerable subgroups. For nonfatal events, additional information was available on education level (primary school, high school, and university), smoking status (smoker, ex-smoker, and nonsmoker), 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-hour 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-hour 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 nonlinear 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 five 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 2001-2014) 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 cutoffs could avoid the small sample size at extreme temperatures and were consistent with a previous multi-country 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 nonfatal 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 (SD) age was 62.5 (9.3) years and 73% were men (*Table 1*). Of all these events, 14,133 were nonfatal 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 2001-2014. Of all events, the proportion of people living in the city significantly decreased from 1987-2000 to 2001-2015, living alone increased, as did the proportion of men, the prevalence of diabetes mellitus, hyperlipidemia, and pre-existing cardiovascular diseases. Of nonfatal 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.

The daily mean temperature slightly increased from 1987-2000 to 2001-2014 (*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 MI

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, nonsignificant 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 two days (lag 0-1) (see Supplementary material online, *Figure S2-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 versus the MMIT) were found in 2001-2014 for total, nonfatal, recurrent, and NSTEMI events (*Table 3*). Compared with 1987-2000, heat-related MI risks in 2001-2014 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 2001-2014. The heat-related MI risks significantly increased in people with diabetes mellitus from 0.81 (95% CI: 0.58, 1.14) in 1987-2000 to 1.33 [95% confidence interval (CI): 1.06, 1.67] in 2001-2014 (Figure 2 and Take home figure). A significant increase in heat-related MI risk from 1987-2000 to 2001-2014 was also observed in people living in rural counties and with hyperlipidemia. In 2001-2014, 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 hyperlipidemia [1.23 (95% CI: 1.03, 1.46)]. Both cold-related and heat-related MI risks increased for current smokers from 1987-2000 to 2001-2014 (see Supplementary material online, *Figure S5*).

Sensitivity analyses

Our results were robust when we used different cutoffs (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, *Table 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, *Figure 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 2001-2014 compared to 1987-2000 for recurrent and NSTEMI events. Cold-related MI risks nonsignificantly 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 2001-2014 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 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 (2001-2014), we found a significant association between heat and MI occurrence, with significant increases in the risk of total, nonfatal, recurrent, and NSTEMI events. The detection of a heat effect may be partially because of the nonlinearity 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 nonsignificant heat effect, especially when the cold effect dominates the temperature-MI association. In a time-series analysis based on the England and Wales Myocardial Ischemia 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 nonlinear 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 2001-2014. 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 hyperlipidemia 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 2001-2014. Therefore, changes in underlying drivers from climatic, metabolic, and socio-economic 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 hyperlipidemia, which had higher heat effects than the rest of the population. While adverse heat effects have been well documented in urban areas, emerging evidence suggest that people living in nonurban 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 hyperlipidemia (57.2% vs. 49.2%) and pre-existing cardiovascular diseases (79.6% vs. 72.7%) in 2001-2014. The lower socioeconomic status and higher prevalence of pre-existing chronic diseases in 2001-2014 may result in a higher vulnerability to heat in rural residents. A global scale meta-regression analysis found that diabetes incidence in the U.S. 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 hyperlipidemia 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 nonsignificant heat effect on cardiovascular morbidity than those findings related to mortality.[4] It could also be because the significant heat effects we observed on nonfatal 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 nonlinear 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 nonfatal events were different. Time of symptom onset was used and validated against the information from the medical records for nonfatal 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 multicenter 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 hyperlipidemia.

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Figures

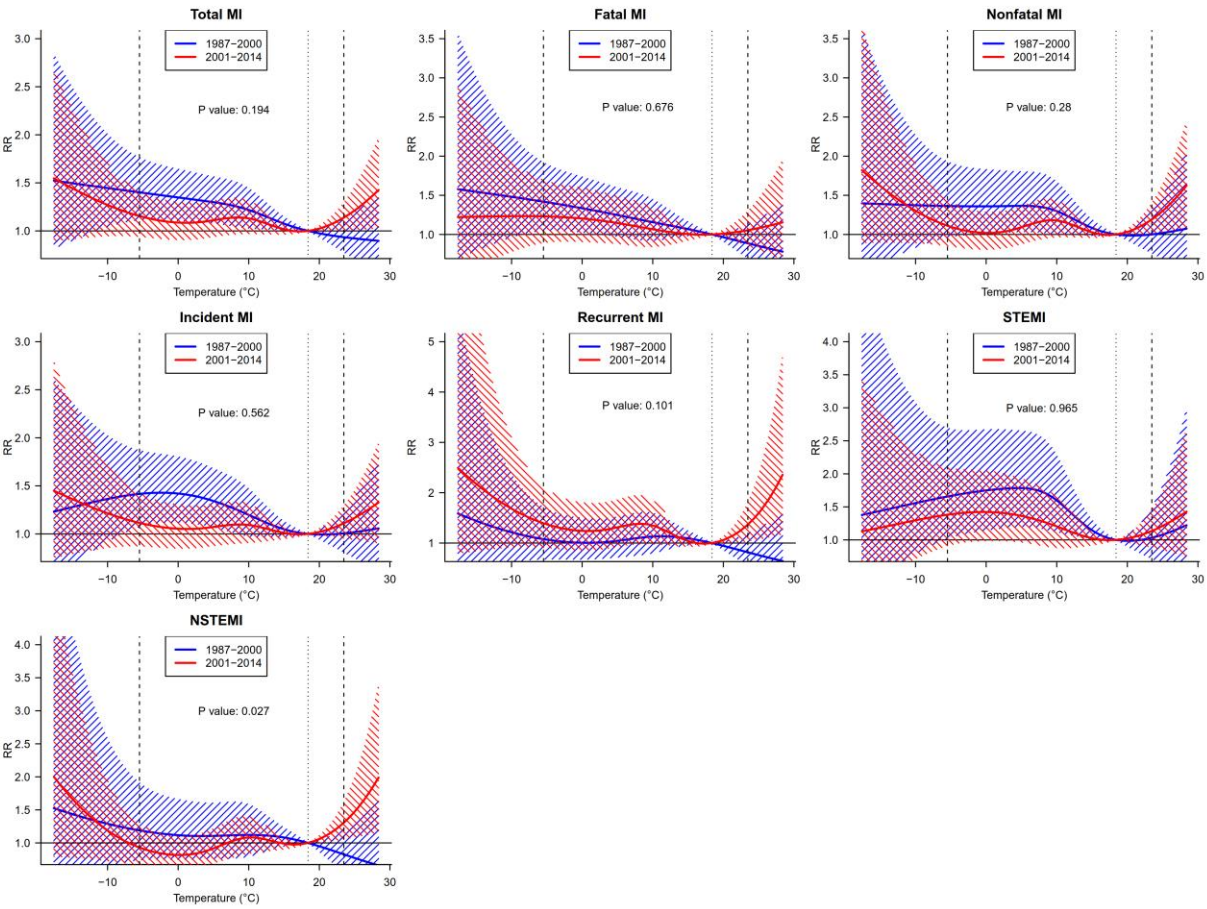


Figure 1. Overall lag-cumulative exposure-response relationships between air temperature and myocardial infarction predicted for 1987-2000 (blue) and 2001-2014 (red) with 95% CI. P value represents the significance test on temporal variation, based on a multivariate Wald test of the reduced coefficients 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).

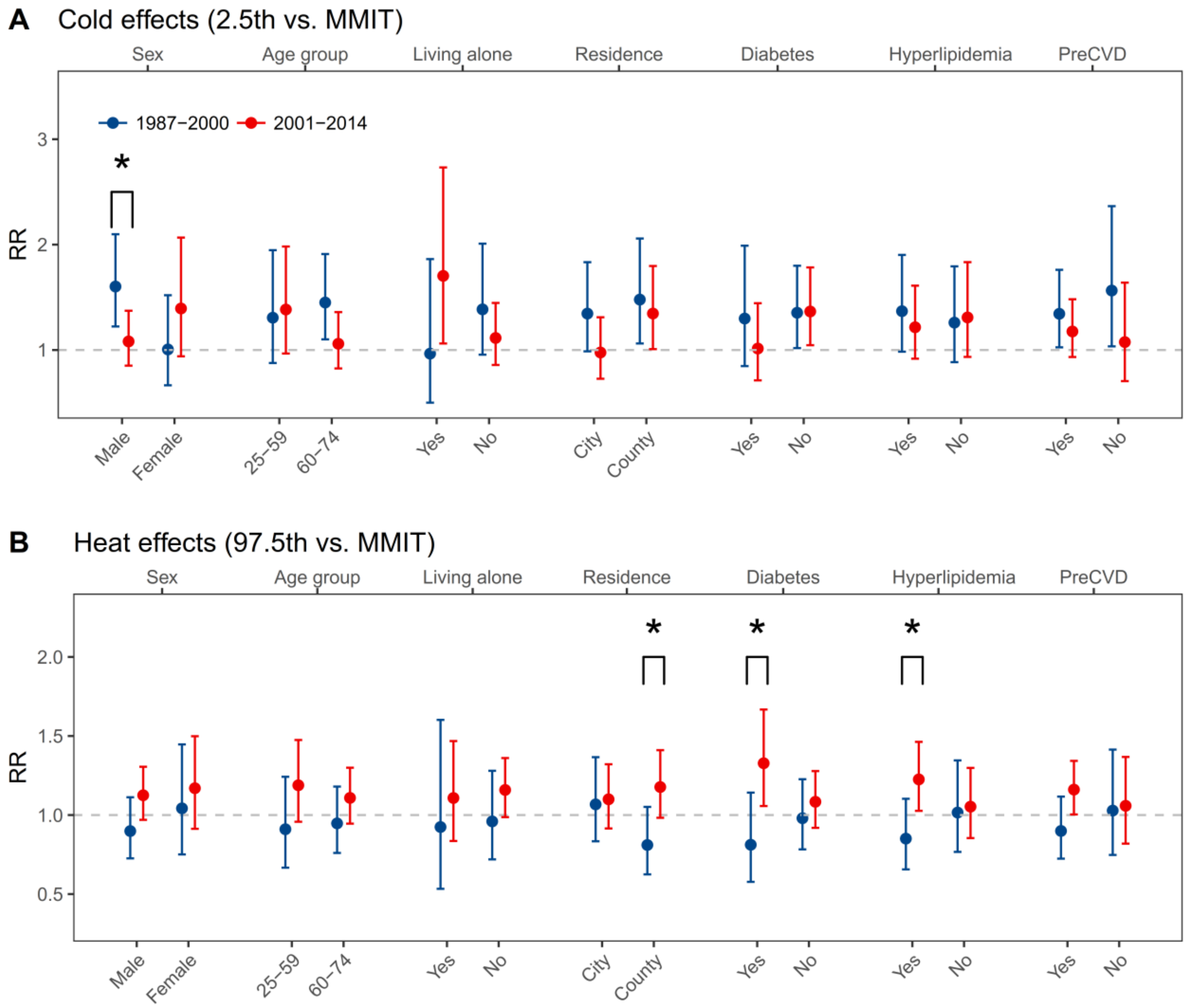
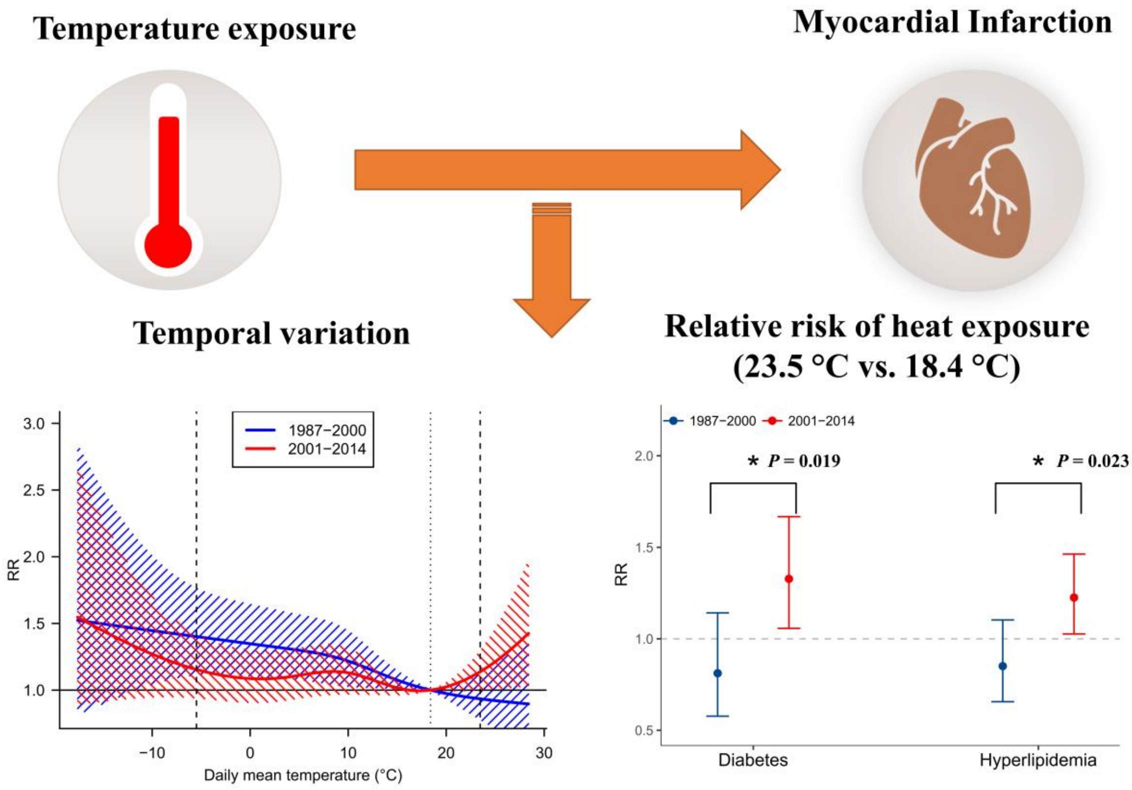


Figure 2. Lag-cumulative relative risk estimates for daily myocardial infarction cases (95% CI) associated with (A) cold exposure (2.5th percentile relative to minimum myocardial infarction temperature (MMIT)) and (B) heat exposure (97.5th percentile relative to MMIT) predicted for 1987-2000 (blue) and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



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

Supplementary Materials

Supplementary Methods

Supplementary Tables

Table S1. Spearman's rank correlation coefficients between daily meteorology and air pollution in Augsburg, Germany during 1987-2014

Table S2. Cumulative RR estimates for daily MI cases (95% CI) associated with heat and cold exposure using different temperature cut-offs

Table S3. Cumulative RR estimates for daily MI cases (95% CI) associated with heat exposure (97.5th percentile relative to MMIT) and cold exposure (2.5 percentile relative to MMIT) using different temperature metrics

Table S4. Cumulative RR estimates for daily MI cases (95% CI) associated with heat exposure (97.5th percentile (23.5 °C) relative to minimum myocardial infarction temperature (MMIT, 18.4 °C)) and cold exposure (2.5th percentile (-5.5 °C) relative to MMIT) during 1992-2014 with and without adjustment for influenza

Table S5. Cumulative RR estimates for daily MI cases (95% CI) associated with heat exposure (97.5th percentile (21.7 °C) relative to minimum myocardial infarction temperature (MMIT, 16.7 °C)) and cold exposure (2.5th percentile (-6.0 °C) relative to MMIT) using the Augsburg airport weather station

Table S6. Cumulative RR estimates for daily MI cases (95% CI) associated with heat exposure (97.5th percentile (23.5 °C) relative to minimum myocardial infarction temperature (MMIT, 18.4 °C)) and cold exposure (2.5th percentile (-5.5 °C) relative to MMIT) with adjustment for percentage of people aged 60 years and above and percentage of foreigners.

Table S7. Cumulative RR estimates for daily MI cases (95% CI) associated with heat exposure (97.5th percentile (23.5 °C) relative to minimum myocardial infarction temperature (MMIT, 18.4 °C)) and cold exposure (2.5th percentile (-5.5 °C) relative to MMIT) using three internal knots for the lag response.

Table S8. Cumulative RR estimates for daily MI cases (95% CI) associated with heat exposure (97.5th percentile (23.5 °C) relative to 75^{th} percentile (16.0 °C)) and cold exposure (2.5th percentile (-5.5 °C) relative to 25^{th} percentile (3.4 °C)).

Table S9. Summary statistics of heat waves and cold spells and the RR estimates (95% CI) for daily cases of MI on heat wave or cold spell days compared with non-heat wave or non-cold spell days in Augsburg, Germany, 1987 to 2014

Supplementary Figures

Figure S1. Overall lag-cumulative exposure-response relationships between air temperature and myocardial infarction throughout the study period with 95% CI. The vertical lines represent the minimum myocardial infarction temperature (dotted) and the 1st and the 99th percentiles of the temperature distribution (dashed).

Figure S2. Lag-response relationships between cold exposure (2.5 percentile relative to MMIT) and MI

Figure S3. Lag-response relationships between heat exposure (97.5 percentile relative to MMIT) and MI

Figure S4. Lag-cumulative relative risk estimates for daily MI cases (95% CI) associated with cold exposure (2.5th percentile (-5.5 °C) relative to MMIT) and heat exposure (97.5th percentile (23.5 °C) relative to MMIT) throughout the study period stratified by subgroups

Figure S5. Lag-cumulative relative risk estimates for daily nonfatal MI cases (95% CI) associated with cold exposure (2.5th percentile relative to minimum myocardial infarction temperature (MMIT)) and heat exposure (97.5th percentile relative to MMIT) predicted for 1987-2000 (blue) and 2001-2014 (red) stratified by education levels, smoking status, and obesity. Asterisks indicate statistical significance for differences in relative risk estimates between 1987-2000 and 2001-2014.

Figure S6. Percent increase (95% CI) in daily MI cases per 10 μg/m^3 increase in air pollutants (PM_{10}, NO_2, and O_3) using different lag days. Lag0 represents the same day of MI occurrence, lag1 to lag4 represent 1 to 4 days before MI occurrence, and the average exposure over 2 days (lag01) and 5 days (lag04)

Figure S7. Modified overall cumulative air temperature-MI associations by PM_{10} with 95% CIs. Blue lines represent for a low air pollution level (concentration below median value) and red lines represent a high air pollution level (concentration above median value). *P* value is the results of significance test between air pollution levels, based on a multivariate Wald test of the reduced coefficients of the temperature effects at low and high air pollution levels

Figure S8. Modified overall cumulative air temperature-MI associations by NO_2 with 95% CIs. Blue lines represent for a low air pollution level (concentration below median value) and red lines represent a high air pollution level (concentration above median value). *P* value is the results of significance test between air pollution levels, based on a multivariate Wald test of the reduced coefficients of the temperature effects at low and high air pollution levels

Figure S9. Modified overall cumulative air temperature-MI associations by O_3 with 95% CIs. Blue lines represent for a low air pollution level (concentration below median value) and red lines represent a high air pollution level (concentration above median value). *P* value is the results of significance test between air pollution levels, based on a multivariate Wald test of the reduced coefficients of the temperature effects at low and high air pollution levels

Figure S10. Percent change (95% CIs) in MI associated with a 1 °C increase in temperature variability on different exposure days in 1987-2000 and 2001-2014. Temperature variability is calculated from the standard deviation of the minimum and maximum temperatures during the exposure days (i.e., lag01, lag02, …, and lag07).

Supplementary Methods

MONICA/KORA MI registry

The MONICA/KORA MI registry was founded in 1984 as part of the WHO MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) project and since 1996 has been continued as part of the KORA (Cooperative Health Research in the Augsburg Region) research program. Since 1984, all cases of MI in eight hospitals in the study area and coronary deaths occurring among residents aged 25 to 74 years old (about 400,000 inhabitants) have been continuously registered in the MONICA/KORA MI registry. Following the MONICA protocol, MI patients who survived at least 24 hours after hospitalization are interviewed about the event, demographic information, co-morbidities, medication, and family history. If a patient survives the 28th day after hospital admission, the MI is identified as nonfatal, otherwise as fatal. Coronary deaths are fatal cases outside the hospital or within the 24-hour after admission to a hospital. All coronary deaths (ICD-9 codes: 410-414) were identified by checking all death certificates through the regional health departments and by information from the last treating physician and/or coroner. For infarction type, bundle branch block was not included in this analysis due to its small sample size (38.6 cases/year).

Over the whole study period, we used a consistent MONICA definition for MI diagnosis.[1] Within the MONICA-defined MI events, additional NSTEMI cases were categorized since 2000 if symptomatic patients had elevated concentrations troponin and no typical ECG changes.[2] Clinical history of diabetes mellitus (yes/no), hyperlipidemia (yes/no), and pre-existing cardiovascular diseases (angina, coronary heart disease, hypertension, and stroke) (yes/no) were obtained from patient interview and chart review during the hospital stay. Self-reported history of diabetes mellitus, hyperlipidemia, and pre-existing cardiovascular diseases were only considered if the chart review confirmed these diseases.[3] More details of the Augsburg MI registry have been described elsewhere.[2, 4]

Meteorological, air pollution, and influenza data

Data on air temperature, relative humidity, barometric pressure, and ozone (O_3) concentrations were obtained from an urban background monitoring station located 7km (Haunstetten, until 2000) and 5km south of the city center (Landesamt-für-Umwelt, from 2001 on). Particulate matter with an aerodynamic diameter <10 µm (PM_{10}) and nitrogen dioxide (NO_2) were continuously measured at an urban background station (Bourges-Platz) located 2km north of the city center. Daily 24-hour average meteorological variables, PM_{10}, NO_2, and daily maximum 8-hour average O_3 concentrations were calculated if at least 75% of the hourly measurements were available. Data on influenza epidemics during 1992 to 2014 were obtained from the German Influenza Working Group (https://influenza.rki.de/).

Statistical analyses

We applied a time-stratified case-crossover design, which is a type of self-matched case-control study in which each individual serves as his or her own control.[5] 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). This approach thus controls for long-term time-trends, seasonality, day of the week, and confounders that do not vary within a month, such as time-invariant individual-level characteristics (e.g., occupation, socioeconomic status, and pre-existing cardiovascular disease). To estimate the temperature effects on the occurrence of MIs, we used a conditional Poisson regression model, which is a flexible alternative to conditional logistic models and allows for over-dispersion in daily cases of MIs.[6]

We tested the statistical significance of the difference in relative risk (RR) between the two sub-periods by calculating the z score as $(\hat{E}_1 - \hat{E}_2)/\sqrt{(S\hat{E}_1)^2 + (S\hat{E}_2)^2}$, where $\hat{E}_1$ and $\hat{E}_2$ are the natural logarithms of RR estimates, and $S\hat{E}_1$ and $S\hat{E}_2$ are their respective standard errors calculated from the widths of 95% CIs. We tested the statistical significance of difference in RR estimates between the two sub-periods for each subgroup of a potential effect modifier. To test the statistical significance between exposure-response curves in each sub-period, we used a multivariate Wald test based on the reduced coefficients of the cross-basis matrix for temperature in each sub-period.[7]

Sensitivity analysis

To examine the robustness of the results, we conducted several sensitivity analyses with regard to: (1) using different cutoffs (1st/99th and 5th/95th) for heat and cold exposures; (2) using alternative daily temperature metrics (maximum, minimum, and apparent temperature); (3) further adjusting for influenza epidemics; (4) investigating potential effect modification of air pollutants on the temperature-MI associations by including an interaction term between the temperature cross-basis matrix and an air pollutant strata indicator as described by Chen et al.;[8] (5) exploring whether extreme temperature events (i.e., heat waves and cold spells) were also associated with the occurrence of MI; (6) using continuously measured meteorological data from the Augsburg airport weather station; (7) further adjusting for changing percentages of people aged ≥ 60 years and foreigners; (8) examining the effects of temperature variability (both intra-day and inter-day changes) on MI occurrence; (9) using equal ranges for cold (2.5th percentile vs. 25th percentile) and heat (97.5th percentile vs. 75th percentile) exposures; and (10) using three internal knots placed at equally spaced values in the log scale for the lag-response.

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Table S1. Spearman's rank correlation coefficients between daily meteorology and air pollution in Augsburg, Germany during 1987-2014

	Tmean	Tmin	Tmax	Tapp	RH	BP	PM_{10}	NO_2
Tmin (°C)	0.95							
Tmax (°C)	0.97	0.87						
Tapp (°C)	1.00	0.95	0.97					
RH (%)	-0.57	-0.38	-0.65	-0.57				
BP (hPa)	0.03	-0.02	0.06	0.03	-0.13			
PM_{10} (μg/m^3)	-0.07	-0.15	0	-0.07	-0.06	0.26		
NO_2 (μg/m^3)	-0.12	-0.24	-0.02	-0.12	-0.07	0.18	0.69	
O_3 (μg/m^3)	0.70	0.58	0.73	0.70	-0.75	-0.01	-0.07	-0.06

Tmean, mean temperature; Tmin, minimum temperature; Tmax, maximum temperature; Tapp, apparent temperature; RH, relative humidity; BP, barometric pressure; PM_{10}, particulate matter with an aerodynamic diameter <10 μm; NO_2, nitrogen dioxide; O_3, ozone.

Table S2. Cumulative RR estimates for daily MI cases (95% CI) associated with heat and cold exposure using different temperature cut-offs.

Cut-offs	Group	Period	Cold effects RR [a]	Cold effects *p* value [b]	Heat effects RR [a]	Heat effects *p* value [b]
1st/99th percentiles	Total MI	1987-2014	**1.30 (1.08, 1.56)**	0.38	1.11 (0.95, 1.30)	0.09
		1987-2000	**1.43 (1.09, 1.87)**		0.92 (0.71, 1.20)	
		2001-2014	1.21 (0.95, 1.54)		**1.22 (1.01, 1.47)**	
	Fatal MI	1987-2014	**1.34 (1.04, 1.74)**	0.54	0.98 (0.78, 1.23)	0.30
		1987-2000	**1.45 (1.02, 2.08)**		0.85 (0.60, 1.21)	
		2001-2014	1.23 (0.84, 1.81)		1.08 (0.80, 1.47)	
	Nonfatal MI	1987-2014	1.26 (0.98, 1.61)	0.63	1.23 (1.00, 1.51)	0.29
		1987-2000	1.37 (0.90, 2.07)		1.02 (0.69, 1.52)	
		2001-2014	1.2 (0.88, 1.65)		**1.31 (1.03, 1.66)**	
	Incident MI	1987-2014	**1.26 (1.02, 1.57)**	0.42	1.12 (0.93, 1.34)	0.48
		1987-2000	**1.39 (1.00, 1.93)**		1.02 (0.74, 1.40)	
		2001-2014	1.16 (0.87, 1.56)		1.17 (0.94, 1.46)	
	Recurrent MI	1987-2014	1.34 (0.93, 1.95)	0.44	1.22 (0.88, 1.69)	0.03
		1987-2000	1.14 (0.66, 1.99)		0.76 (0.44, 1.30)	
		2001-2014	1.53 (0.92, 2.54)		**1.61 (1.08, 2.42)**	
	STEMI	1987-2014	**1.47 (1.02, 2.13)**	0.64	1.19 (0.88, 1.61)	0.72
		1987-2000	1.61 (0.91, 2.84)		1.08 (0.63, 1.85)	
		2001-2014	1.34 (0.82, 2.20)		1.22 (0.85, 1.75)	
	NSTEMI	1987-2014	1.09 (0.78, 1.50)	0.64	1.30 (0.99, 1.69)	0.04
		1987-2000	1.24 (0.70, 2.19)		0.77 (0.44, 1.34)	
		2001-2014	1.05 (0.70, 1.58)		**1.49 (1.09, 2.03)**	
5th/95th percentiles	Total MI	1987-2014	**1.23 (1.07, 1.42)**	0.15	1.04 (0.97, 1.11)	0.08
		1987-2000	**1.38 (1.12, 1.71)**		0.95 (0.84, 1.07)	
		2001-2014	1.12 (0.93, 1.35)		1.08 (1.00, 1.18)	
	Fatal MI	1987-2014	**1.31 (1.07, 1.60)**	0.54	0.98 (0.89, 1.09)	0.27
		1987-2000	**1.39 (1.05, 1.84)**		0.92 (0.78, 1.08)	
		2001-2014	1.22 (0.91, 1.65)		1.03 (0.90, 1.18)	
	Nonfatal MI	1987-2014	1.17 (0.96, 1.42)	0.22	1.08 (0.99, 1.18)	0.27
		1987-2000	1.36 (0.99, 1.87)		0.99 (0.83, 1.19)	
		2001-2014	1.06 (0.83, 1.35)		**1.11 (1.00, 1.24)**	
	Incident MI	1987-2014	**1.23 (1.04, 1.46)**	0.12	1.04 (0.96, 1.13)	0.45
		1987-2000	**1.43 (1.11, 1.84)**		1.00 (0.86, 1.15)	
		2001-2014	1.08 (0.86, 1.36)		1.07 (0.97, 1.18)	
	Recurrent MI	1987-2014	1.18 (0.88, 1.57)	0.43	1.07 (0.93, 1.24)	0.03
		1987-2000	1.04 (0.68, 1.59)		0.87 (0.68, 1.11)	
		2001-2014	1.31 (0.89, 1.95)		**1.21 (1.01, 1.45)**	
	STEMI	1987-2014	**1.54 (1.15, 2.06)**	0.54	1.06 (0.93, 1.21)	0.62
		1987-2000	**1.69 (1.08, 2.66)**		1.00 (0.79, 1.28)	
		2001-2014	1.41 (0.96, 2.07)		1.08 (0.92, 1.27)	
	NSTEMI	1987-2014	0.94 (0.73, 1.21)	0.29	1.12 (0.99, 1.26)	0.04
		1987-2000	1.16 (0.75, 1.78)		0.88 (0.68, 1.13)	
		2001-2014	0.87 (0.63, 1.19)		**1.19 (1.03, 1.36)**	

STEMI, ST segment elevation MI; NSTEMI, non-ST segment elevation MI.

[a] Conditional Poisson Regression adjusted for relative humidity, barometric pressure, and population.

[b] Significance test on temporal vibration, based on difference between RR estimates in 1987-2000 and 2001-2014.

Table S3. Cumulative RR estimates for daily MI cases (95% CI) associated with heat exposure (97.5th percentile relative to minimum myocardial infarction temperature (MMIT)) and cold exposure (2.5 percentile relative to MMIT) using different temperature metrics

Metric (MMIT)	Group	Period	Cold effects RR [a]	Cold effects *p* value [b]	Heat effects RR [a]	Heat effects *p* value [b]
Tmin (12.9 °C)	Total MI	1987-2014	**1.27 (1.09, 1.48)**	0.32	1.05 (0.94, 1.18)	0.01
		1987-2000	**1.39 (1.10, 1.75)**		0.86 (0.71, 1.05)	
		2001-2014	1.18 (0.97, 1.45)		**1.16 (1.01, 1.34)**	
	Fatal MI	1987-2014	**1.31 (1.05, 1.63)**	0.74	0.98 (0.83, 1.16)	0.26
		1987-2000	**1.36 (1.00, 1.85)**		0.88 (0.67, 1.14)	
		2001-2014	1.26 (0.92, 1.74)		1.07 (0.85, 1.34)	
	Nonfatal MI	1987-2014	1.23 (1.00, 1.52)	0.35	1.11 (0.95, 1.29)	0.03
		1987-2000	1.41 (0.98, 2.01)		0.83 (0.62, 1.12)	
		2001-2014	1.14 (0.88, 1.48)		**1.22 (1.02, 1.45)**	
	Incident MI	1987-2014	**1.26 (1.05, 1.51)**	0.41	1.06 (0.93, 1.22)	0.30
		1987-2000	**1.36 (1.02, 1.80)**		0.96 (0.76, 1.21)	
		2001-2014	1.16 (0.91, 1.48)		1.11 (0.94, 1.31)	
	Recurrent MI	1987-2014	1.30 (0.95, 1.77)	0.62	1.09 (0.85, 1.39)	<0.01
		1987-2000	1.22 (0.76, 1.96)		0.67 (0.45, 0.99)	
		2001-2014	1.43 (0.94, 2.18)		**1.49 (1.10, 2.02)**	
	STEMI	1987-2014	**1.43 (1.05, 1.96)**	0.49	1.09 (0.88, 1.37)	0.21
		1987-2000	1.25 (0.76, 2.04)		0.89 (0.60, 1.31)	
		2001-2014	**1.57 (1.04, 2.36)**		1.20 (0.92, 1.57)	
	NSTEMI	1987-2014	1.06 (0.81, 1.40)	0.09	1.11 (0.91, 1.35)	<0.01
		1987-2000	1.53 (0.94, 2.49)		0.62 (0.41, 0.93)	
		2001-2014	0.91 (0.65, 1.28)		**1.29 (1.03, 1.63)**	
Tmax (26.5 °C)	Total MI	1987-2014	**1.17 (1.01, 1.37)**	0.13	1.02 (0.91, 1.14)	0.46
		1987-2000	**1.36 (1.08, 1.71)**		0.96 (0.80, 1.16)	
		2001-2014	1.06 (0.86, 1.32)		1.05 (0.92, 1.20)	
	Fatal MI	1987-2014	**1.27 (1.02, 1.59)**	0.39	0.96 (0.82, 1.13)	0.98
		1987-2000	**1.42 (1.05, 1.92)**		0.96 (0.75, 1.23)	
		2001-2014	1.16 (0.83, 1.63)		0.95 (0.76, 1.19)	
	Nonfatal MI	1987-2014	1.09 (0.88, 1.35)	0.31	1.07 (0.93, 1.24)	0.39
		1987-2000	1.26 (0.89, 1.79)		0.96 (0.72, 1.28)	
		2001-2014	1.01 (0.76, 1.33)		1.11 (0.94, 1.32)	
	Incident MI	1987-2014	1.19 (0.98, 1.43)	0.12	1.01 (0.89, 1.15)	0.63
		1987-2000	**1.40 (1.06, 1.85)**		0.97 (0.78, 1.22)	
		2001-2014	1.04 (0.81, 1.34)		1.04 (0.89, 1.22)	
	Recurrent MI	1987-2014	1.05 (0.76, 1.45)	0.55	1.10 (0.87, 1.39)	0.29
		1987-2000	0.96 (0.60, 1.53)		0.93 (0.62, 1.37)	
		2001-2014	1.17 (0.75, 1.83)		1.21 (0.90, 1.61)	
	STEMI	1987-2014	1.33 (0.97, 1.83)	0.22	1.08 (0.87, 1.34)	0.90
		1987-2000	**1.66 (1.02, 2.69)**		1.05 (0.71, 1.56)	
		2001-2014	1.10 (0.72, 1.70)		1.08 (0.84, 1.41)	
	NSTEMI	1987-2014	0.92 (0.70, 1.22)	0.80	1.08 (0.89, 1.31)	0.05
		1987-2000	1.01 (0.63, 1.61)		0.76 (0.51, 1.14)	
		2001-2014	0.93 (0.65, 1.33)		1.20 (0.96, 1.50)	
Tappmean (15.8 °C)	Total MI	1987-2014	**1.26 (1.08, 1.47)**	0.22	1.07 (0.96, 1.18)	0.08
		1987-2000	**1.40 (1.11, 1.76)**		0.93 (0.78, 1.12)	
		2001-2014	1.16 (0.94, 1.42)		**1.14 (1.00, 1.29)**	
	Fatal MI	1987-2014	**1.33 (1.07, 1.66)**		0.98 (0.84, 1.15)	

Metric (MMIT)	Group	Period	Cold effects		Heat effects	
			RR [a]	*p* value [b]	RR [a]	*p* value [b]
		1987-2000	**1.42 (1.05, 1.92)**	0.58	0.89 (0.70, 1.13)	0.29
		2001-2014	1.25 (0.91, 1.73)		1.05 (0.86, 1.3)	
	Nonfatal MI	1987-2014	1.19 (0.97, 1.47)		1.14 (0.99, 1.31)	
		1987-2000	1.36 (0.96, 1.93)	0.34	1.00 (0.76, 1.31)	0.27
		2001-2014	1.10 (0.85, 1.44)		**1.19 (1.01, 1.4)**	
	Incident MI	1987-2014	**1.24 (1.03, 1.49)**		1.07 (0.95, 1.22)	
		1987-2000	**1.42 (1.07, 1.87)**	0.19	1.00 (0.81, 1.25)	0.46
		2001-2014	1.10 (0.86, 1.41)		1.11 (0.95, 1.29)	
	Recurrent MI	1987-2014	1.25 (0.91, 1.70)		1.13 (0.91, 1.42)	
		1987-2000	1.08 (0.68, 1.71)	0.40	0.82 (0.56, 1.19)	0.03
		2001-2014	1.41 (0.92, 2.16)		**1.37 (1.04, 1.80)**	
	STEMI	1987-2014	**1.50 (1.09, 2.06)**		1.11 (0.90, 1.36)	
		1987-2000	**1.66 (1.02, 2.69)**	0.55	1.03 (0.71, 1.49)	0.67
		2001-2014	1.36 (0.90, 2.08)		1.14 (0.89, 1.46)	
	NSTEMI	1987-2014	0.99 (0.75, 1.30)		1.19 (0.99, 1.43)	
		1987-2000	1.19 (0.74, 1.91)	0.39	0.82 (0.56, 1.21)	0.04
		2001-2014	0.92 (0.65, 1.30)		**1.31 (1.06, 1.61)**	

STEMI, ST segment elevation MI; NSTEMI, non-ST segment elevation MI.
[a] Conditional Poisson Regression adjusted for relative humidity, barometric pressure, and population.
[b] Significance test on temporal vibration, based on difference between RR estimates in 1987-2000 and 2001-2014.

Table S4. Cumulative RR estimates for daily MI cases (95% CI) associated with heat exposure (97.5th percentile (23.5 °C) relative to minimum myocardial infarction temperature (MMIT, 18.4 °C)) and cold exposure (2.5th percentile (-5.5 °C) relative to MMIT) during 1992-2014 with and without adjustment for influenza [a]

Group	Adjustment for influenza	Cold effects [a]	Heat effects [a]
Total MI	With	**1.19 (1.01, 1.41)**	1.09 (0.96, 1.23)
	Without	**1.20 (1.02, 1.41)**	1.09 (0.96, 1.23)
Fatal MI	With	1.20 (0.94, 1.54)	0.99 (0.81, 1.20)
	Without	1.20 (0.94, 1.52)	0.99 (0.82, 1.20)
Nonfatal MI	With	1.18 (0.94, 1.48)	1.16 (0.99, 1.37)
	Without	1.19 (0.96, 1.49)	1.16 (0.98, 1.37)
Incident MI	With	1.20 (0.98, 1.46)	1.09 (0.93, 1.26)
	Without	1.20 (0.99, 1.46)	1.08 (0.93, 1.26)
Recurrent MI	With	1.23 (0.87, 1.74)	1.21 (0.92, 1.58)
	Without	1.23 (0.87, 1.73)	1.21 (0.92, 1.58)
STEMI	With	**1.52 (1.08, 2.14)**	1.17 (0.92, 1.50)
	Without	**1.54 (1.10, 2.16)**	1.17 (0.92, 1.50)
NSTEMI	With	1.00 (0.75, 1.34)	1.24 (1.00, 1.55)
	Without	1.01 (0.76, 1.35)	1.24 (1.00, 1.55)

STEMI, ST segment elevation MI; NSTEMI, non-ST segment elevation MI.

[a] A weekly doctor's practice index (PI) for each winter season (October to April), representing the relative deviation of the observed acute respiratory activity in comparison to the background level in Germany, was used to denote days with high influenza episodes (PI > 115).

[b] Conditional Poisson Regression adjusted for relative humidity, barometric pressure, and population.

Table S5. Cumulative RR estimates for daily MI cases (95% CI) associated with heat exposure (97.5th percentile (21.7 °C) relative to minimum myocardial infarction temperature (MMIT, 16.7 °C)) and cold exposure (2.5th percentile (-6.0 °C) relative to MMIT) using the Augsburg airport weather station.

Group	Period	Cold effects		Heat effects	
		RR [a]	*p* value [b]	RR [a]	*p* value [b]
Total MI	1987-2014	**1.27 (1.10, 1.47)**	0.14	1.09 (0.97, 1.21)	0.06
	1987-2000	**1.44 (1.16, 1.78)**		0.95 (0.80, 1.13)	
	2001-2014	1.15 (0.94, 1.41)		**1.18 (1.02, 1.36)**	
Fatal MI	1987-2014	**1.33 (1.08, 1.64)**	0.63	1.04 (0.88, 1.22)	0.46
	1987-2000	**1.41 (1.06, 1.87)**		0.97 (0.77, 1.22)	
	2001-2014	1.27 (0.93, 1.74)		1.10 (0.87, 1.38)	
Nonfatal MI	1987-2014	1.22 (1.00, 1.49)	0.15	1.13 (0.97, 1.31)	0.08
	1987-2000	**1.47 (1.06, 2.03)**		0.93 (0.71, 1.20)	
	2001-2014	1.09 (0.84, 1.41)		**1.24 (1.03, 1.48)**	
Incident MI	1987-2014	**1.26 (1.06, 1.50)**	0.12	1.08 (0.95, 1.23)	0.27
	1987-2000	**1.47 (1.13, 1.90)**		0.98 (0.80, 1.21)	
	2001-2014	1.11 (0.87, 1.41)		1.14 (0.96, 1.35)	
Recurrent MI	1987-2014	1.26 (0.93, 1.70)	0.38	1.19 (0.94, 1.50)	0.03
	1987-2000	1.08 (0.70, 1.68)		0.9 (0.63, 1.28)	
	2001-2014	1.42 (0.94, 2.16)		**1.50 (1.10, 2.03)**	
STEMI	1987-2014	**1.51 (1.12, 2.04)**	0.58	1.15 (0.93, 1.44)	0.33
	1987-2000	**1.64 (1.04, 2.59)**		1.00 (0.70, 1.43)	
	2001-2014	1.38 (0.92, 2.07)		1.25 (0.95, 1.65)	
NSTEMI	1987-2014	1.03 (0.79, 1.35)	0.17	1.13 (0.93, 1.38)	0.01
	1987-2000	1.34 (0.86, 2.10)		0.74 (0.52, 1.07)	
	2001-2014	0.91 (0.65, 1.27)		**1.32 (1.05, 1.68)**	

STEMI, ST segment elevation MI; NSTEMI, non-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 2001-2014.

Table S6. Cumulative RR estimates for daily MI cases (95% CI) associated with heat exposure (97.5th percentile (23.5 °C) relative to minimum myocardial infarction temperature (MMIT, 18.4 °C)) and cold exposure (2.5th percentile (-5.5 °C) relative to MMIT) with adjustment for percentage of people aged 60 years and above and percentage of foreigners.

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

STEMI, ST segment elevation MI; NSTEMI, non-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 2001-2014.

Table S7. Cumulative RR estimates for daily MI cases (95% CI) associated with heat exposure (97.5th percentile (23.5 °C) relative to minimum myocardial infarction temperature (MMIT, 18.4 °C)) and cold exposure (2.5th percentile (-5.5 °C) relative to MMIT) using three internal knots for the lag response.

Group	Period	Cold effects		Heat effects	
		RR [a]	*p* value [b]	RR [a]	*p* value [b]
Total MI	1987-2014	**1.25 (1.07, 1.46)**	0.25	1.07 (0.96, 1.19)	0.10
	1987-2000	**1.38 (1.10, 1.75)**		0.94 (0.78, 1.13)	
	2001-2014	1.15 (0.94, 1.42)		1.14 (1.00, 1.29)	
Fatal MI	1987-2014	**1.31 (1.05, 1.63)**	0.58	0.99 (0.84, 1.15)	0.30
	1987-2000	**1.39 (1.03, 1.88)**		0.89 (0.70, 1.14)	
	2001-2014	1.23 (0.89, 1.69)		1.06 (0.86, 1.30)	
Nonfatal MI	1987-2014	1.20 (0.97, 1.48)	0.36	1.14 (0.99, 1.31)	0.32
	1987-2000	1.37 (0.96, 1.94)		1.01 (0.76, 1.33)	
	2001-2014	1.11 (0.85, 1.45)		**1.19 (1.01, 1.40)**	
Incident MI	1987-2014	**1.25 (1.04, 1.50)**	0.24	1.07 (0.94, 1.21)	0.56
	1987-2000	**1.42 (1.07, 1.87)**		1.01 (0.82, 1.26)	
	2001-2014	1.13 (0.88, 1.45)		1.10 (0.94, 1.28)	
Recurrent MI	1987-2014	1.2 (0.87, 1.64)	0.33	1.14 (0.92, 1.43)	0.03
	1987-2000	1.00 (0.63, 1.60)		0.83 (0.57, 1.21)	
	2001-2014	1.38 (0.90, 2.12)		**1.38 (1.04, 1.81)**	
STEMI	1987-2014	**1.48 (1.08, 2.04)**	0.53	1.11 (0.90, 1.37)	0.66
	1987-2000	**1.64 (1.01, 2.67)**		1.03 (0.71, 1.50)	
	2001-2014	1.33 (0.87, 2.03)		1.14 (0.89, 1.47)	
NSTEMI	1987-2014	1.01 (0.77, 1.33)	0.54	1.19 (0.99, 1.43)	0.06
	1987-2000	1.16 (0.72, 1.88)		0.84 (0.57, 1.24)	
	2001-2014	0.96 (0.68, 1.36)		**1.29 (1.05, 1.60)**	

STEMI, ST segment elevation MI; NSTEMI, non-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 2001-2014.

Table S8. Cumulative RR estimates for daily MI cases (95% CI) associated with heat exposure (97.5th percentile (23.5 °C) relative to 75th percentile (16.0 °C)) and cold exposure (2.5th percentile (-5.5 °C) relative to 25th percentile (3.4 °C)).

Group	Period	Cold effects		Heat effects	
		RR [a]	*p* value [b]	RR [a]	*p* value [b]
Total MI	1987-2014	1.06 (0.96, 1.16)	0.92	1.05 (0.93, 1.19)	0.07
	1987-2000	1.07 (0.93, 1.23)		0.89 (0.72, 1.10)	
	2001-2014	1.06 (0.93, 1.20)		1.14 (0.98, 1.32)	
Fatal MI	1987-2014	1.09 (0.95, 1.24)	0.70	0.96 (0.80, 1.15)	0.24
	1987-2000	1.11 (0.93, 1.33)		0.85 (0.64, 1.13)	
	2001-2014	1.05 (0.86, 1.29)		1.06 (0.83, 1.34)	
Nonfatal MI	1987-2014	1.03 (0.90, 1.17)	0.69	1.12 (0.95, 1.32)	0.25
	1987-2000	1.00 (0.80, 1.24)		0.95 (0.69, 1.32)	
	2001-2014	1.06 (0.90, 1.25)		1.19 (0.98, 1.43)	
Incident MI	1987-2014	1.04 (0.93, 1.16)	0.84	1.06 (0.92, 1.23)	0.42
	1987-2000	1.03 (0.87, 1.22)		0.98 (0.76, 1.26)	
	2001-2014	1.05 (0.91, 1.22)		1.11 (0.93, 1.32)	
Recurrent MI	1987-2014	1.08 (0.89, 1.31)	0.84	1.11 (0.85, 1.44)	0.04
	1987-2000	1.06 (0.79, 1.41)		0.76 (0.49, 1.19)	
	2001-2014	1.10 (0.84, 1.43)		1.36 (0.99, 1.88)	
STEMI	1987-2014	0.97 (0.81, 1.18)	0.75	1.07 (0.84, 1.36)	0.53
	1987-2000	0.93 (0.70, 1.24)		0.95 (0.62, 1.47)	
	2001-2014	0.99 (0.77, 1.28)		1.13 (0.84, 1.51)	
NSTEMI	1987-2014	1.06 (0.90, 1.26)	0.99	1.20 (0.97, 1.49)	0.04
	1987-2000	1.08 (0.80, 1.46)		0.78 (0.49, 1.22)	
	2001-2014	1.08 (0.88, 1.34)		**1.34 (1.05, 1.71)**	

STEMI, ST segment elevation MI; NSTEMI, non-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 2001-2014.

Table S9. Summary statistics of heat waves and cold spells and the RR estimates (95% CI) for daily cases of MI on heat wave or cold spell days compared with non-heat wave or non-cold spell days in Augsburg, Germany

Group	Overall period (1987-2014)		1987-2000		2001-2014	
	Heat waves [a]	Cold spells [b]	Heat waves [a]	Cold spells [b]	Heat waves [a]	Cold spells [b]
Summary statistics						
Days per year	18.9	12.1	17.6	10.1	20.1	14.1
Intensity (°C) [c]	15.3	1.4	14.6	0.4	16.0	2.1
RR estimates (95% CI) [d]						
Total MI	0.88 (0.44, 1.77)	1.04 (0.45, 2.39)	0.88 (0.30, 2.56)	0.82 (0.23, 2.91)	0.91 (0.36, 2.31)	1.23 (0.40, 3.76)
Fatal MI	0.79 (0.28, 2.18)	1.23 (0.37, 4.08)	0.71 (0.17, 2.96)	1.31 (0.25, 6.95)	0.89 (0.20, 3.84)	1.10 (0.19, 6.26)
Nonfatal MI	0.97 (0.38, 2.52)	0.88 (0.28, 2.79)	1.16 (0.24, 5.73)	0.42 (0.06, 2.89)	0.92 (0.28, 3.04)	1.33 (0.31, 5.70)
Incident MI	0.70 (0.30, 1.62)	0.90 (0.33, 2.45)	0.86 (0.24, 3.12)	1.04 (0.22, 4.85)	0.65 (0.21, 1.95)	0.76 (0.20, 2.85)
Recurrent MI	1.32 (0.32, 5.50)	2.32 (0.39, 13.72)	0.34 (0.04, 2.93)	0.37 (0.03, 4.77)	3.32 (0.48, 22.90)	14.51 (1.21, 174.67)
STEMI	0.60 (0.15, 2.41)	0.42 (0.08, 2.27)	0.21 (0.03, 1.73)	0.80 (0.06, 11.42)	1.52 (0.23, 10.00)	0.24 (0.03, 2.23)
NSTEMI	1.58 (0.45, 5.54)	1.20 (0.26, 5.47)	8.33 (0.83, 83.42)	1.00 (0.07, 14.17)	0.80 (0.17, 3.68)	1.47 (0.22, 9.61)

STEMI, ST segment elevation MI; NSTEMI, non-ST segment elevation MI.

[a] Heat waves were defined as periods of at least two days with 1) daily maximum apparent temperature > its monthly 90th percentile or 2) daily maximum apparent temperature > its monthly median value and daily minimum temperature > its monthly 90th percentile (based on the method proposed by D'Ippoliti et al.). Reference: D'Ippoliti D, Michelozzi P, Marino C, de'Donato F, Menne B, Katsouyanni K, Kirchmayer U, Analitis A, Medina-Ramón M, Paldy A, Atkinson R, Kovats S, Bisanti L, Schneider A, Lefranc A, Iñiguez C, Perucci CA. The impact of heat waves on mortality in 9 European cities: results from the EuroHEAT project. Environ Health 2010;9(1):37.

[b] Cold spells were defined as periods of at least two days with daily minimum apparent temperature < its monthly 10th percentile.

[c] Intensity was defined as average daily mean temperature during the heat waves or cold spells.

[d] Conditional Poisson regression adjusted for daily mean temperature, relative humidity, barometric pressure, and population.

Figure S1. Overall lag-cumulative exposure-response relationships between air temperature and myocardial infarction throughout the study period with 95% CI. The vertical lines represent the minimum myocardial infarction temperature (dotted) and the 1st and the 99th percentiles of the temperature distribution (dashed).

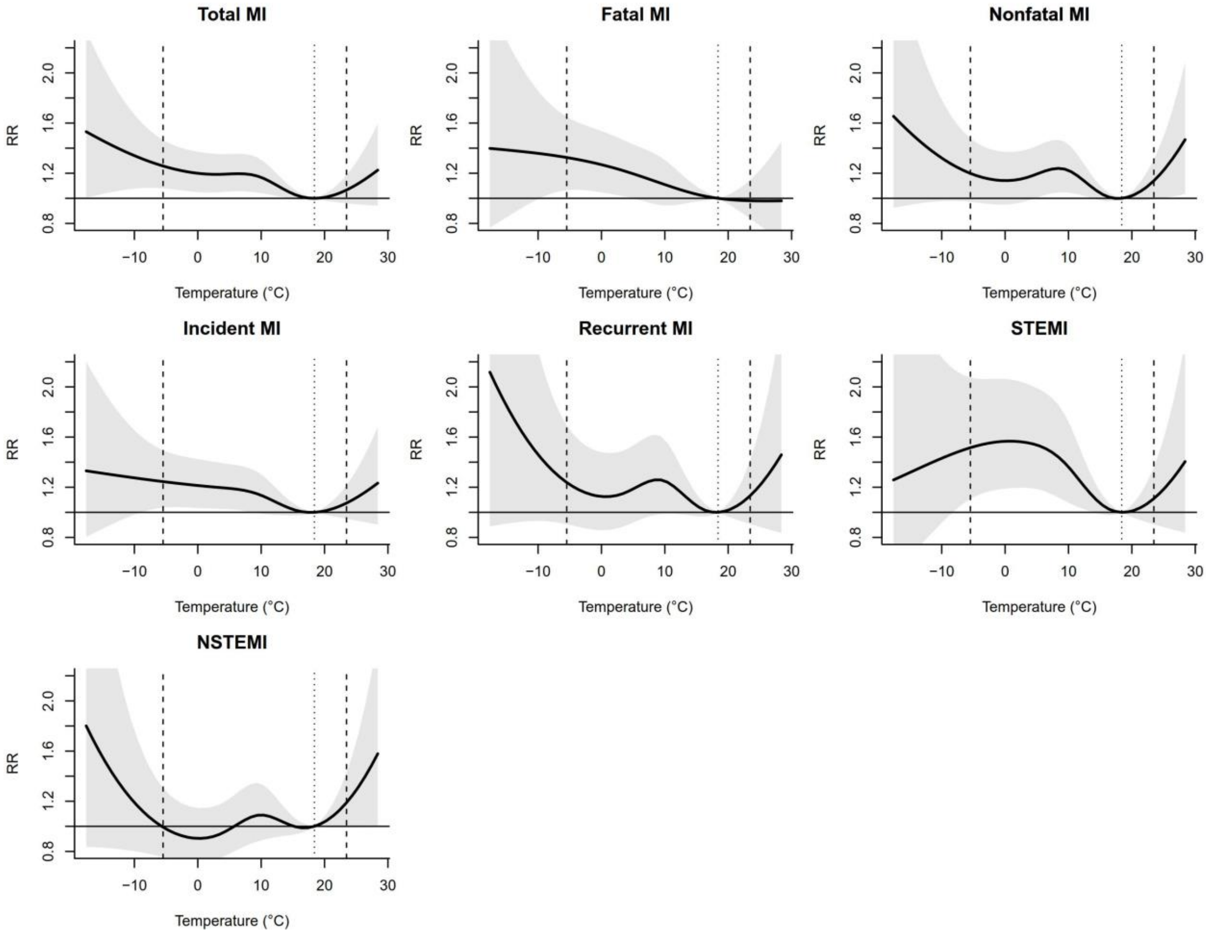

Figure S2. Lag-response relationships between cold exposure (2.5 percentile relative to MMIT) and MI

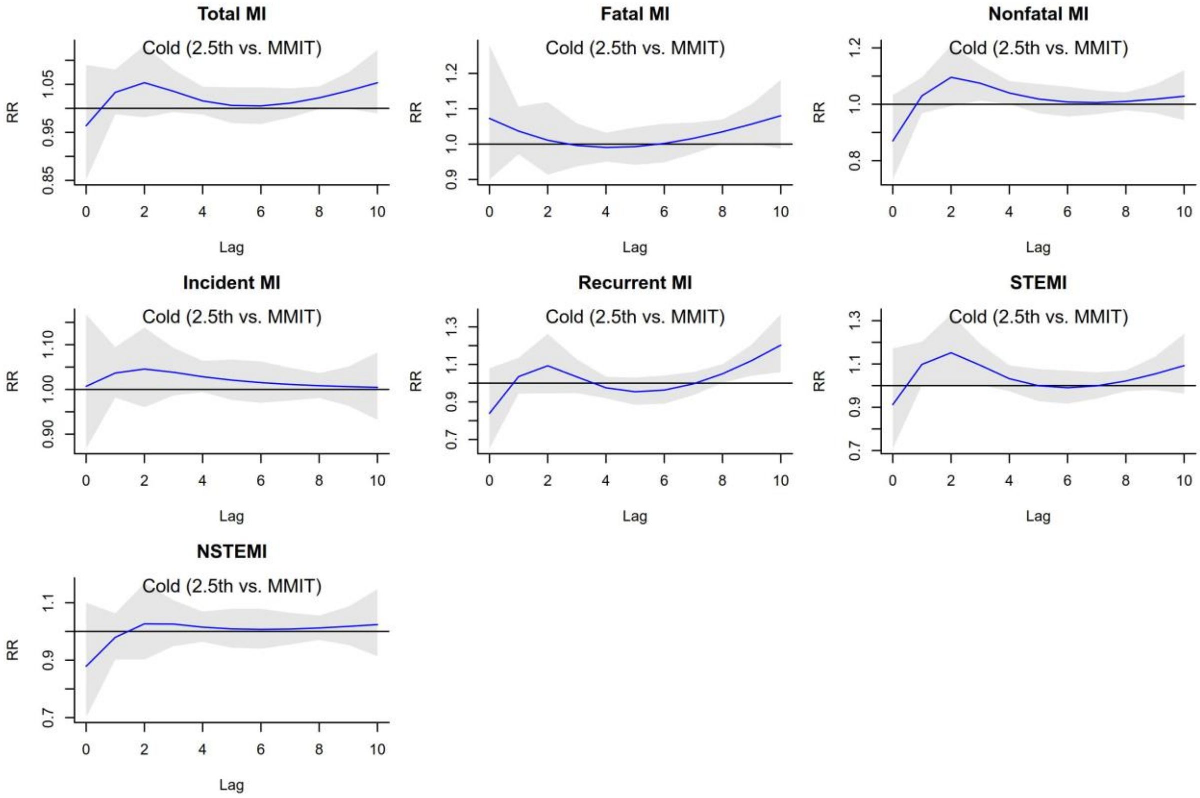

Figure S3. Lag-response relationships between heat exposure (97.5 percentile relative to MMIT) and MI

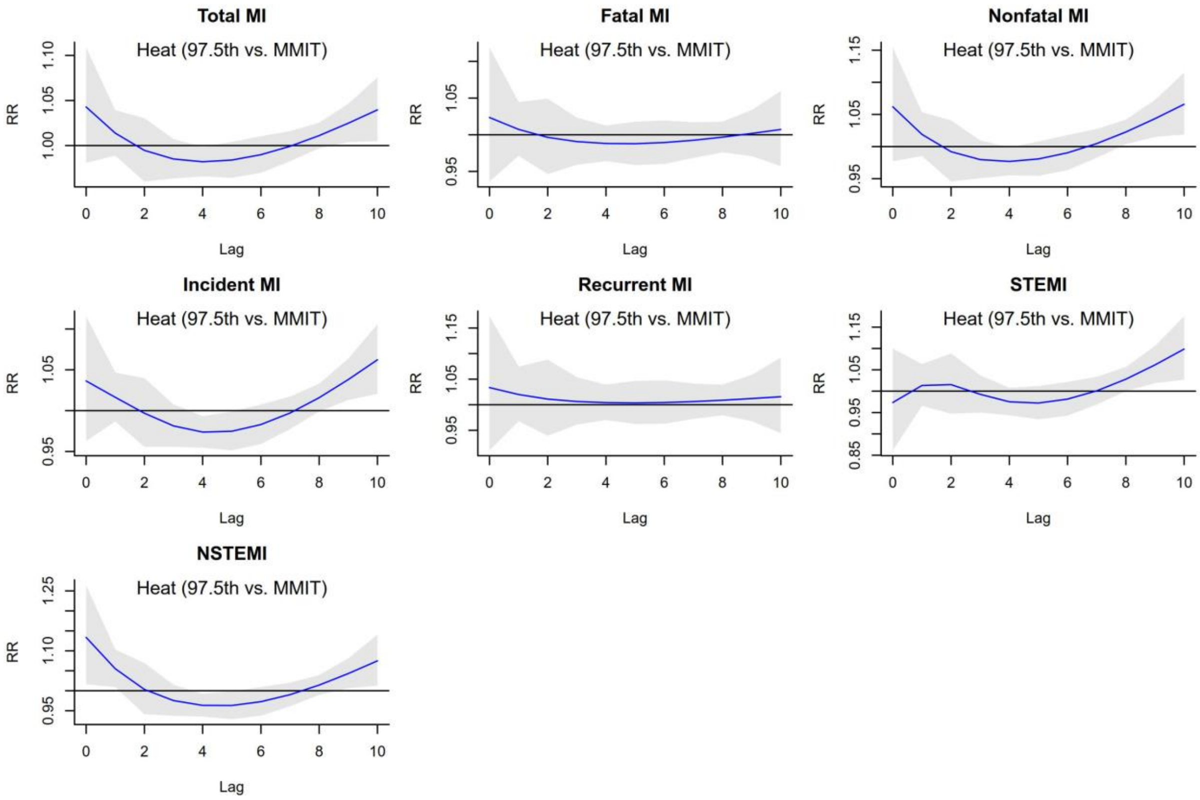

Figure S4. Cumulative relative risk estimates for daily MI cases (95% CI) associated with cold exposure (2.5th percentile relative to MMIT) and heat exposure (97.5th percentile relative to MMIT) throughout the study period stratified by subgroups

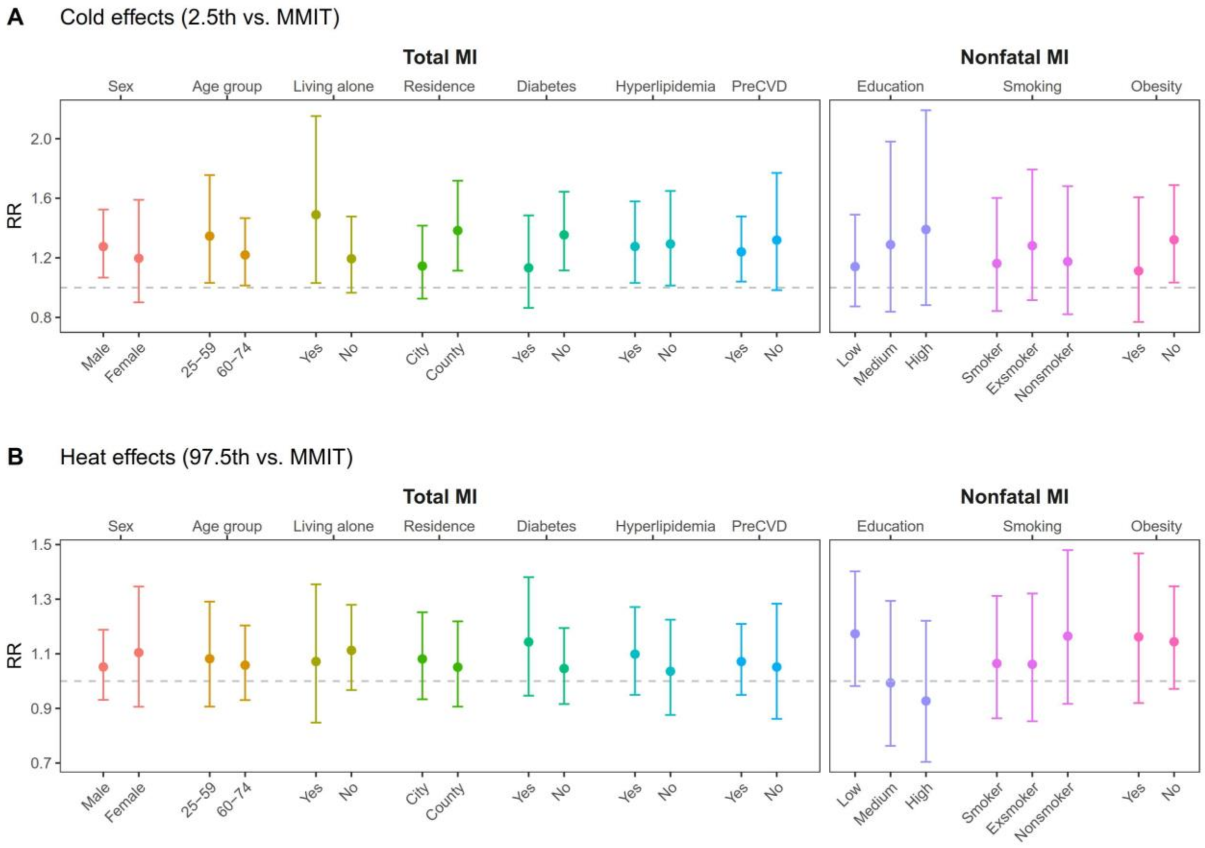

Figure S5. Lag-cumulative relative risk estimates for daily nonfatal MI cases (95% CI) associated with cold exposure (2.5th percentile relative to minimum myocardial infarction temperature (MMIT)) and heat exposure (97.5th percentile relative to MMIT) predicted for 1987-2000 (blue) and 2001-2014 (red) stratified by education levels, smoking status, and obesity. Asterisks indicate statistical significance for differences in relative risk estimates between 1987-2000 and 2001-2014.

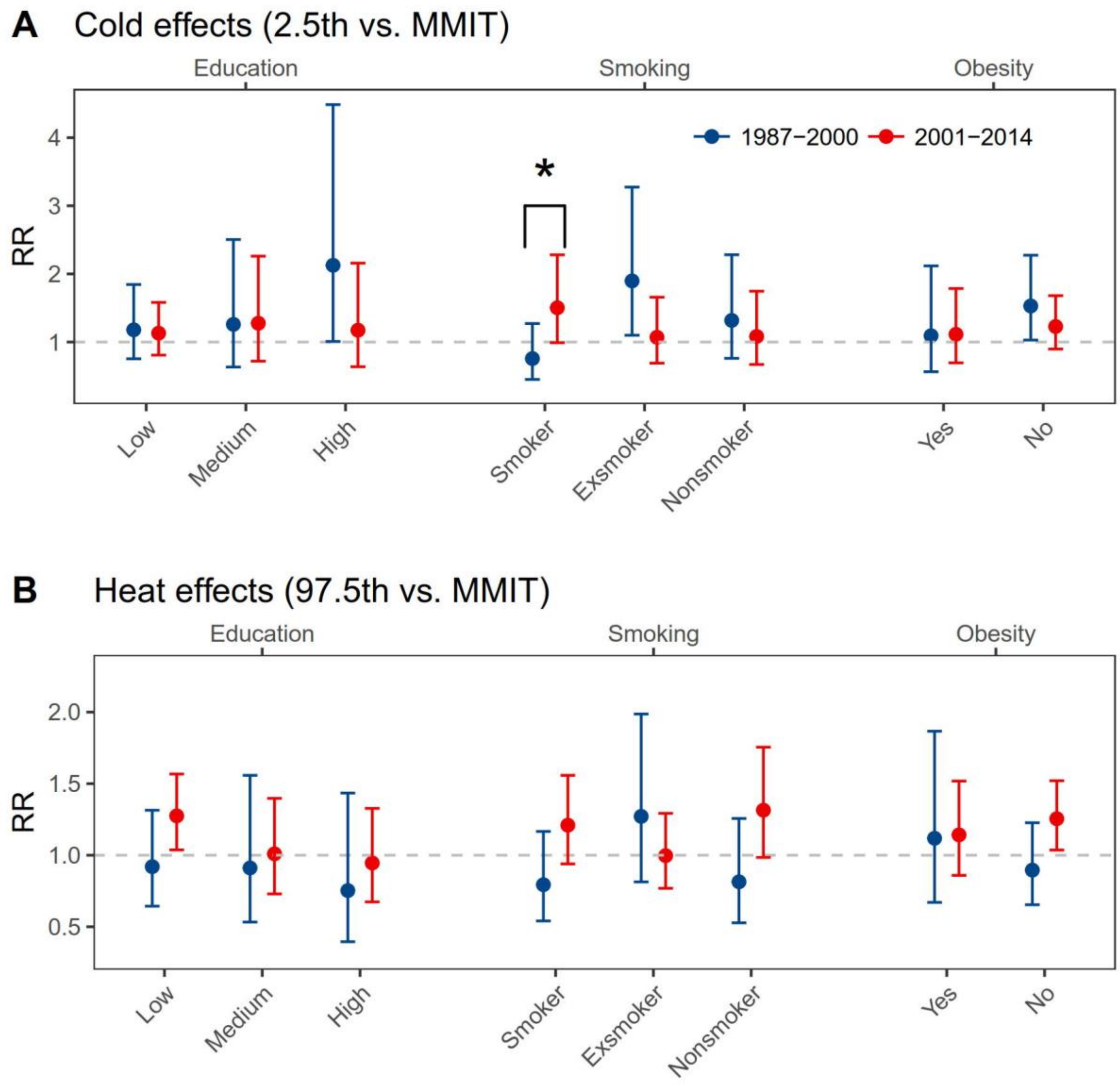

Figure S6. Percent increase (95% CI) in daily MI cases per 10 μg/m³ increase in air pollutants (PM_{10}, NO_2, and O_3) using different lag days. Lag0 represents the same day of MI occurrence, lag1 to lag4 represent 1 to 4 days before MI occurrence, and the average exposure over 2 days (lag01) and 5 days (lag04).

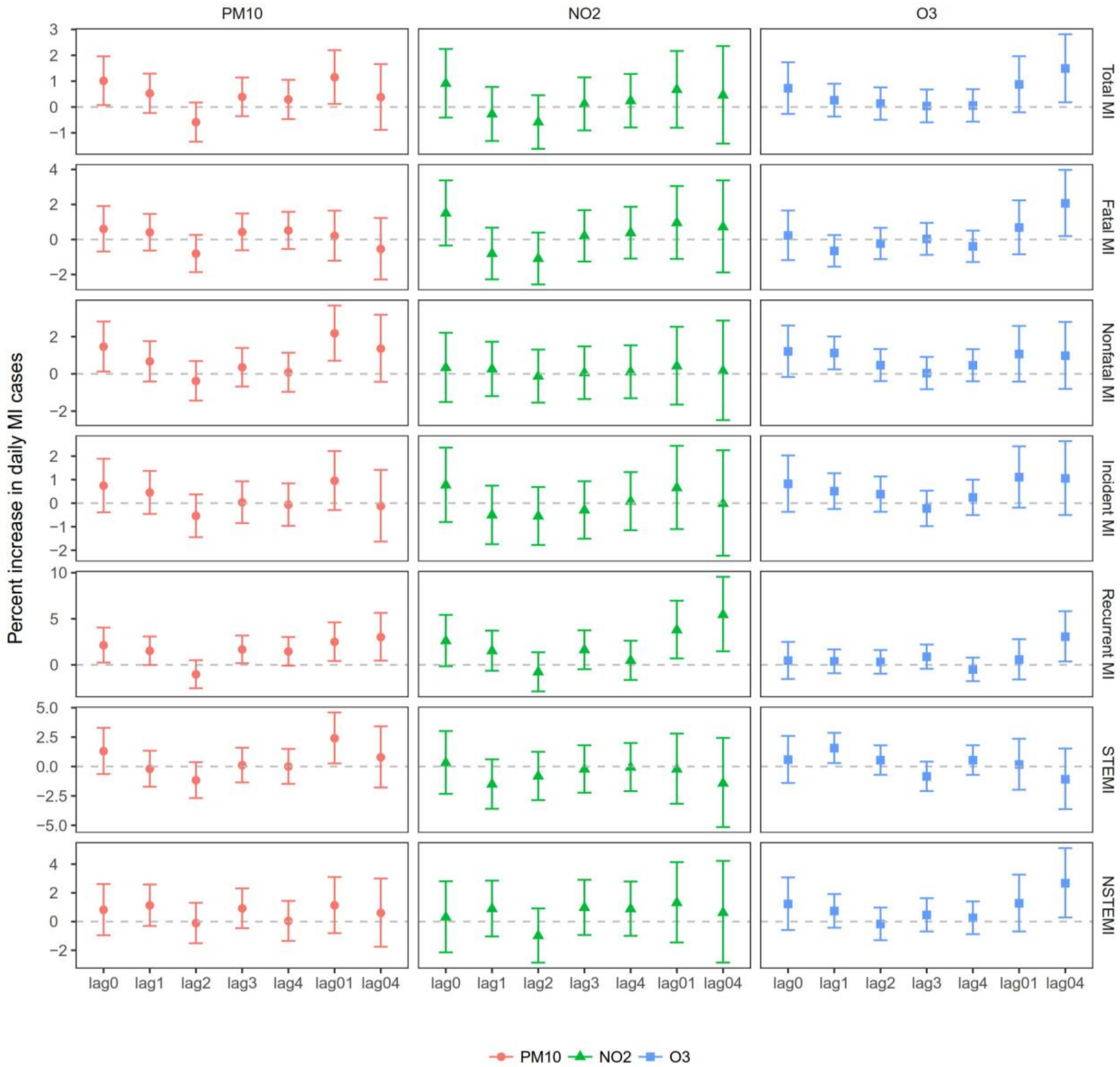

Figure S7. Modified overall cumulative air temperature-MI associations by PM_{10} with 95% CIs. Blue lines represent for a low air pollution level (concentration below median value) and red lines represent a high air pollution level (concentration above median value). *P* value is the results of significance test between air pollution levels, based on a multivariate Wald test of the reduced coefficients of the temperature effects at low and high air pollution levels

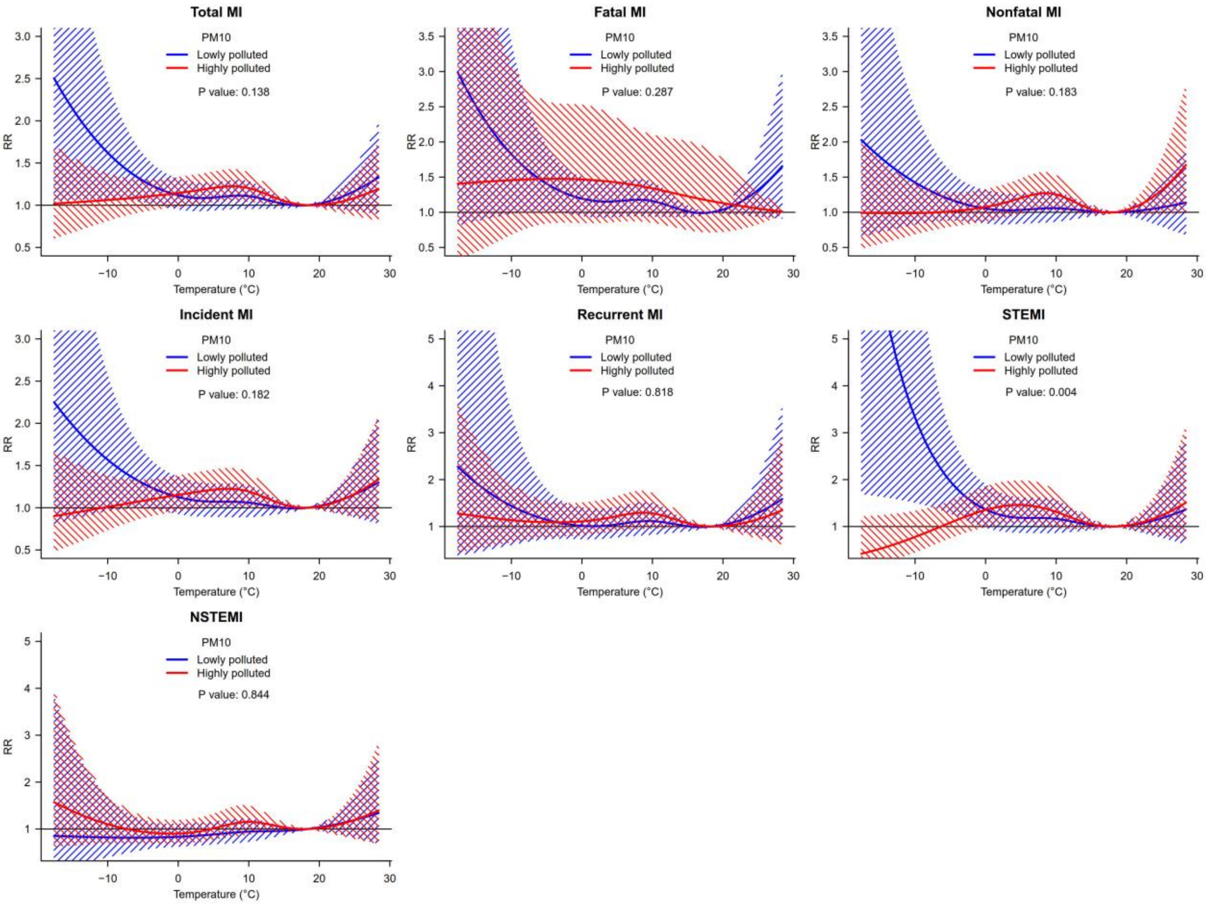

Figure S8. Modified overall cumulative air temperature-MI associations by NO_2 with 95% CIs. Blue lines represent for a low air pollution level (concentration below median value) and red lines represent a high air pollution level (concentration above median value). *P* value is the results of significance test between air pollution levels, based on a multivariate Wald test of the reduced coefficients of the temperature effects at low and high air pollution levels

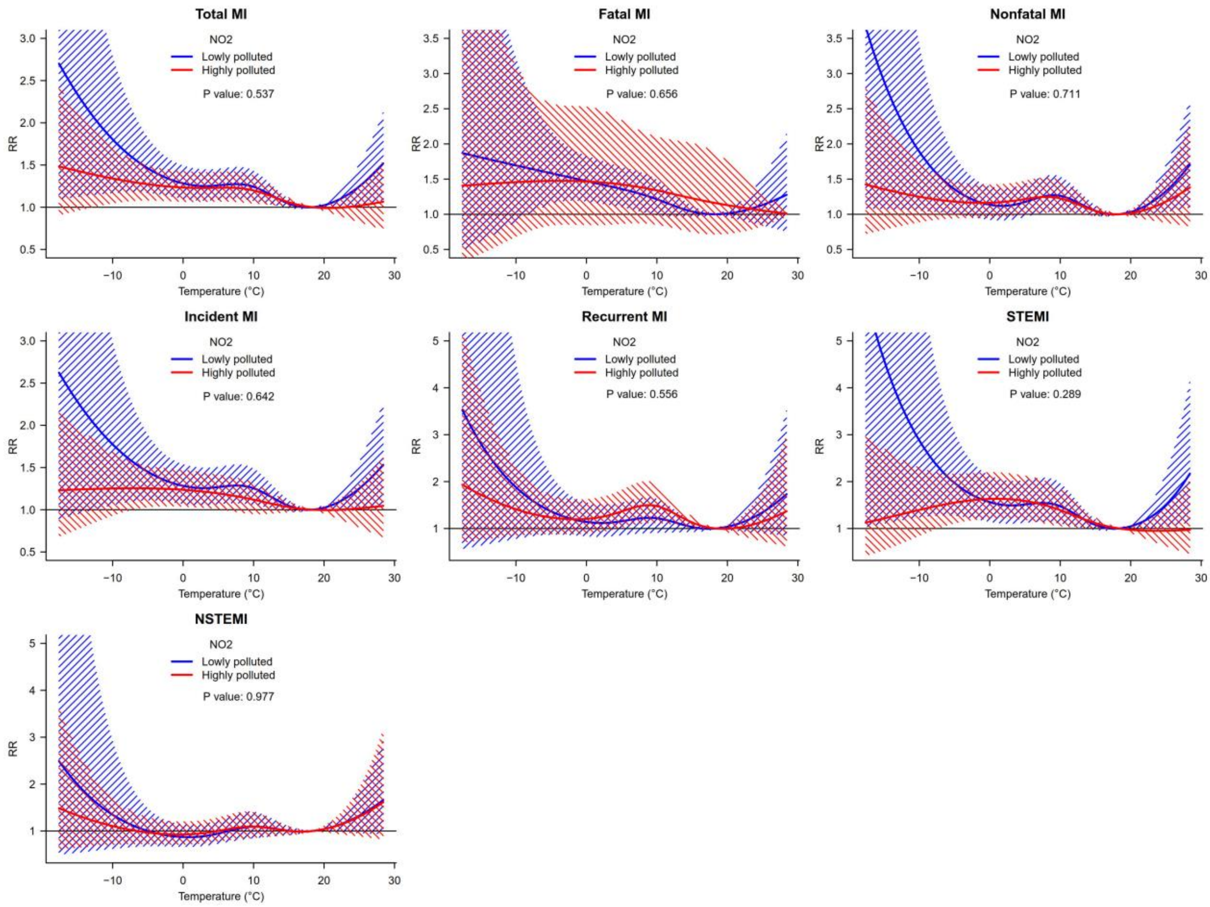

Figure S9. Modified overall cumulative air temperature-MI associations by O_3 with 95% CIs. Blue lines represent for a low air pollution level (concentration below median value) and red lines represent a high air pollution level (concentration above median value). *P* value is the results of significance test between air pollution levels, based on a multivariate Wald test of the reduced coefficients of the temperature effects at low and high air pollution levels

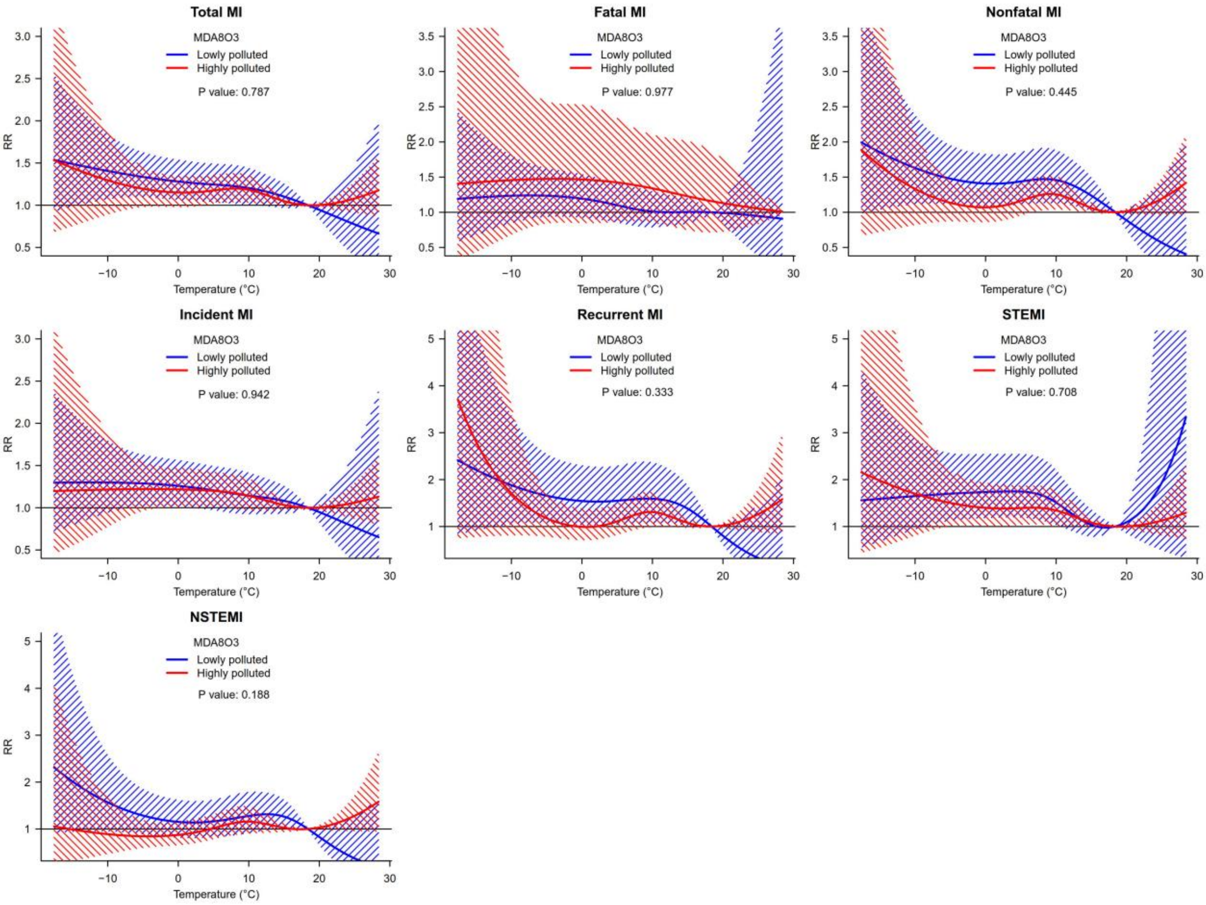

Figure S10. Percent change (95% CIs) in MI associated with a 1 °C increase in temperature variability on different exposure days in 1987-2000 and 2001-2014. Temperature variability is calculated from the standard deviation of the minimum and maximum temperatures during the exposure days (i.e., lag01, lag02, …, and lag07).