Triggering of myocardial infarction by heat exposure is modified by medication intake [Letter]

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Triggering of myocardial infarction by heat exposure is modified by medication intake

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Acute myocardial infarction (MI) can be triggered by heat exposure, but it remains unknown whether patients taking certain cardiovascular medications have elevated vulnerability. Based on a validated and complete registration of all 2,494 MI cases in Augsburg, Germany, during warm seasons (May to September) from 2001 to 2014, here we show that heat-related non-fatal MI risk was elevated among users of anti-platelet medication and beta-receptor blockers, respectively, but not among non-users, with significant differences between users and non-users. We also found that these effect modifications were stronger among younger patients (25–59 years), who had a lower prevalence of pre-existing coronary heart disease (CHD, a potential confounder by indication), than among older patients (60–74 years), who had a higher prevalence of pre-existing CHD. Users of these medications may be more vulnerable than non-users to non-fatal MI risk due to heat exposure. Further research is needed to disentangle effect modification by medication use from effect modification by pre-existing CHD.

Acute MI is a leading cause of death and morbidity globally. MI can be triggered by short-term exposure to environmental factors, such as particulate matter (PM) air pollution and low temperatures (that is, cold)[2,3]. Emerging evidence shows that short-term exposure to heat could also trigger the onset of MI[1]. Heat may lead to vasodilation and increased surface blood circulation, resulting in hemoconcentration and thrombosis promotion, or to local and systemic inflammation, leading to endothelial dysfunction[4,5]. Although there are plausible physiological mechanisms whereby medication use can lead to higher vulnerability to heat exposure (for example, impaired sweat production or skin vasodilation, reduced thirst perception or reduced renal function)[6,7], epidemiological evidence on the effect of medication use on heat-related MI occurrence is scarce[8]. Identifying vulnerable subpopulations based on medication intake is critically needed to reduce the burden of heat-related MI in a warming climate.

We examined whether medication use before hospitalization modifies the association between extreme heat exposure on the day of MI onset and risk of MI occurrence, using data from the MONICA/KORA MI registry in the region of Augsburg, Germany, during warm seasons (May to September) in 2001–2014. Previously, using this validated, complete and detailed registration of all MI cases for patients 25–74 years of age, we found that exposure to both cold and heat could trigger the onset of MI[1,3] and that the

Table 1 | Characteristics of survivors of MI with complete information on medication intake before the event in Augsburg, Germany, during the warm seasons (May to September) from 2001 to 2014, by age (*n* (%))

Characteristic	All ages (*n* = 2,494)	25–59 years (*n* = 976)	60–74 years (*n* = 1,518)
Male	1,905 (76.4)	803 (82.3)	1,102 (72.6)
History			
Diabetes	780 (31.3)	231 (23.7)	549 (36.2)
Hypertension	1,937 (77.7)	660 (67.6)	1,277 (84.1)
CHD	690 (27.7)	184 (18.9)	506 (33.3)
Medication intake before the event			
Anti-platelet medication			
Yes	799(32.0)	196 (20.1)	603 (39.7)
No	1,695 (68.0)	780 (79.9)	915 (60.3)
ACE inhibitors			
Yes	628 (25.2)	176 (18.0)	452 (29.8)
No	1,866 (74.8)	800 (82.0)	1,066 (70.2)
Beta-receptor blockers			
Yes	928 (37.2)	266 (27.3)	662 (43.6)
No	1,566 (62.8)	710 (72.7)	856 (56.4)
Calcium channel blockers			
Yes	397 (15.9)	93 (9.5)	304 (20.0)
No	2,097 (84.1)	883 (90.5)	1,214 (80.0)
Diuretics			
Yes	584 (23.4)	122 (12.5)	462 (30.4)
No	1,910 (76.6)	854 (87.5)	1,056 (69.6)
Statins			
Yes	589 (23.6)	160 (16.4)	429 (28.3)
No	1,905 (76.4)	816 (83.6)	1,089 (71.7)

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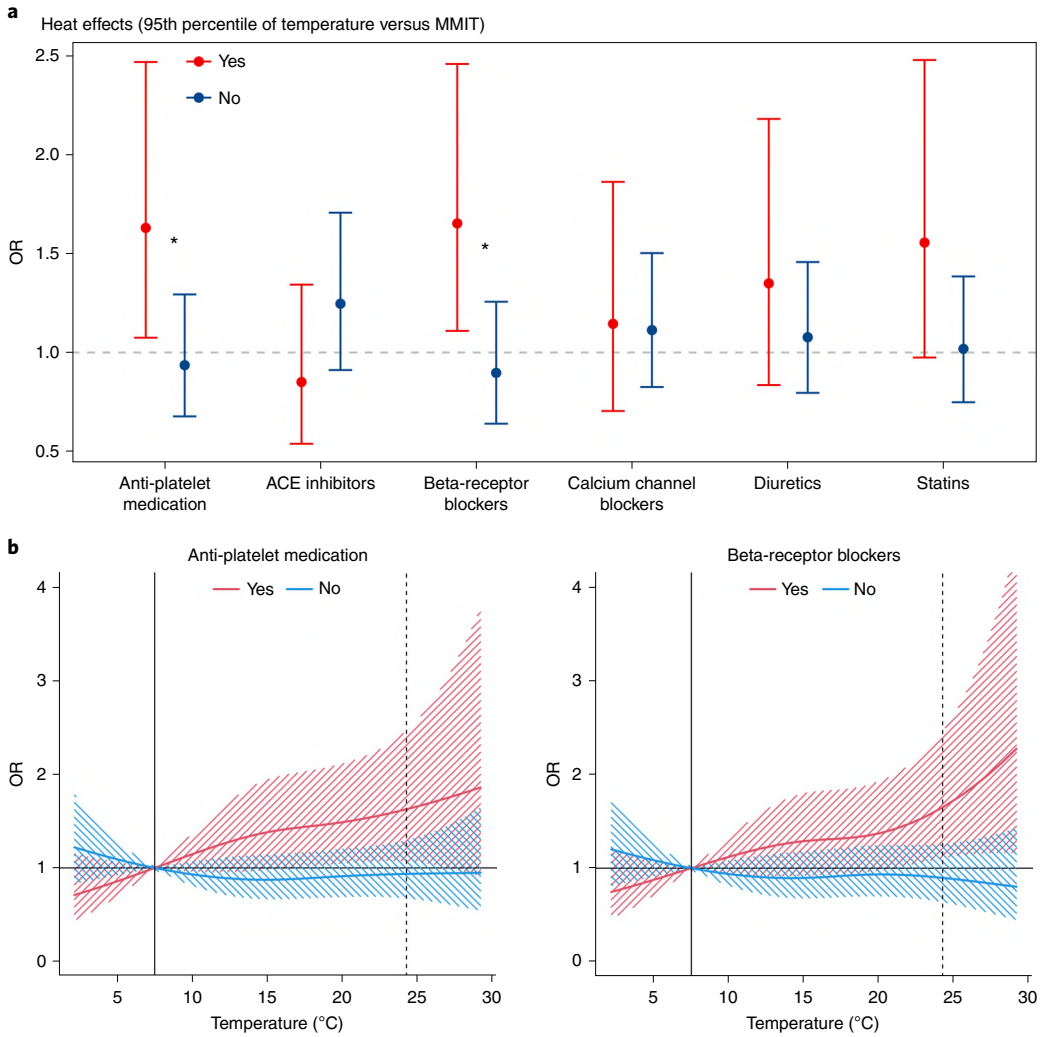

Fig. 1 | Heat-related risks of non-fatal MI stratified by medication intake in Augsburg, Germany, during the warm seasons from 2001 to 2014. a, Effect modification by six medication types with more than 10% of intake frequency among the survivors of MI ($n = 2{,}494$). The OR is for the 95th percentile of temperature (24.2 °C) relative to the MMIT (7.5 °C). Data are presented as point estimates of OR ± 1.96 standard error (that is, 95% CIs). Asterisks indicate statistical significance (two-sided $P = 0.039$ and $P = 0.022$ for anti-platelet and beta-receptor blocker intake, respectively; multiple comparisons were not adjusted) of the differences in risk estimates between users and non-users of a specific medication, based on the Z-score calculated using the coefficients and standard errors for users and non-users. **b**, Exposure-response curves for the temperature–MI relationship stratified by anti-platelet or beta-receptor blocker intake. Solid lines represent the point estimates of OR, and shaded areas represent the 95% CIs. Solid vertical lines are the MMIT, and dashed vertical lines are the 95th percentile of temperature.

burden of heat-related MI will likely increase at 2 °C and 3 °C of global warming[9]. In this study, we used all recorded non-fatal MI cases, defined as surviving the 28th day after hospital admission, with complete information about medication use before the event.

Among all MI occurrences (2,494 cases), 60.9% of patients were 60–74 years old, and more men (76.4%) experienced an MI than women (Table 1). Of all patients with MI, 32.0% used anti-platelet medication, 25.2% used ACE inhibitors, 37.2% used beta-receptor blockers, 15.9% used calcium channel blockers, 23.4% used diuretics and 23.6% used statins before the acute event. Significant heat-related risk for non-fatal MI was observed among users of anti-platelet medication (odds ratio (OR) for the 95th percentile of temperature (24.2 °C) relative to the minimum MI temperature (MMIT) risk (7.5 °C) = 1.63 (95% confidence interval (CI): 1.07, 2.46)) but not among non-users (OR = 0.94 (95% CI: 0.68, 1.29)). Similarly, significant heat-related risk was observed among users of beta-receptor blockers (OR = 1.65 (95% CI: 1.11, 2.45)) but not among non-users (OR = 0.90 (95% CI: 0.64, 1.26)). The OR among anti-platelet medication users was significantly higher than the OR among non-users ($P = 0.04$); the OR among beta-receptor blockers users was significantly higher than the OR among non-users ($P = 0.02$) (Fig. 1a). The exposure-response curves for associations between warm-season temperature and non-fatal MI cases stratified by the intake of anti-platelet medication or beta-receptor blockers are shown in Fig. 1b.

Furthermore, significant heat-related risk was observed among users of both anti-platelet medication and beta-receptor blockers (OR = 1.75 (95% CI: 1.12, 2.73)) but not among non-users of both medications (OR = 0.84 (95% CI: 0.59, 1.19)), with the OR among users significantly higher than the OR among non-users ($P = 0.01$) (Extended Data Fig. 1a). The exposure-response curve for the association between warm-season temperature and non-fatal MI cases stratified by intake/non-intake of both anti-platelet medication and beta-receptor blockers is shown in Extended Data Fig. 1b.

Compared to the older patients (aged 60–74 years), younger patients (aged 25–59 years) were generally healthier with a lower

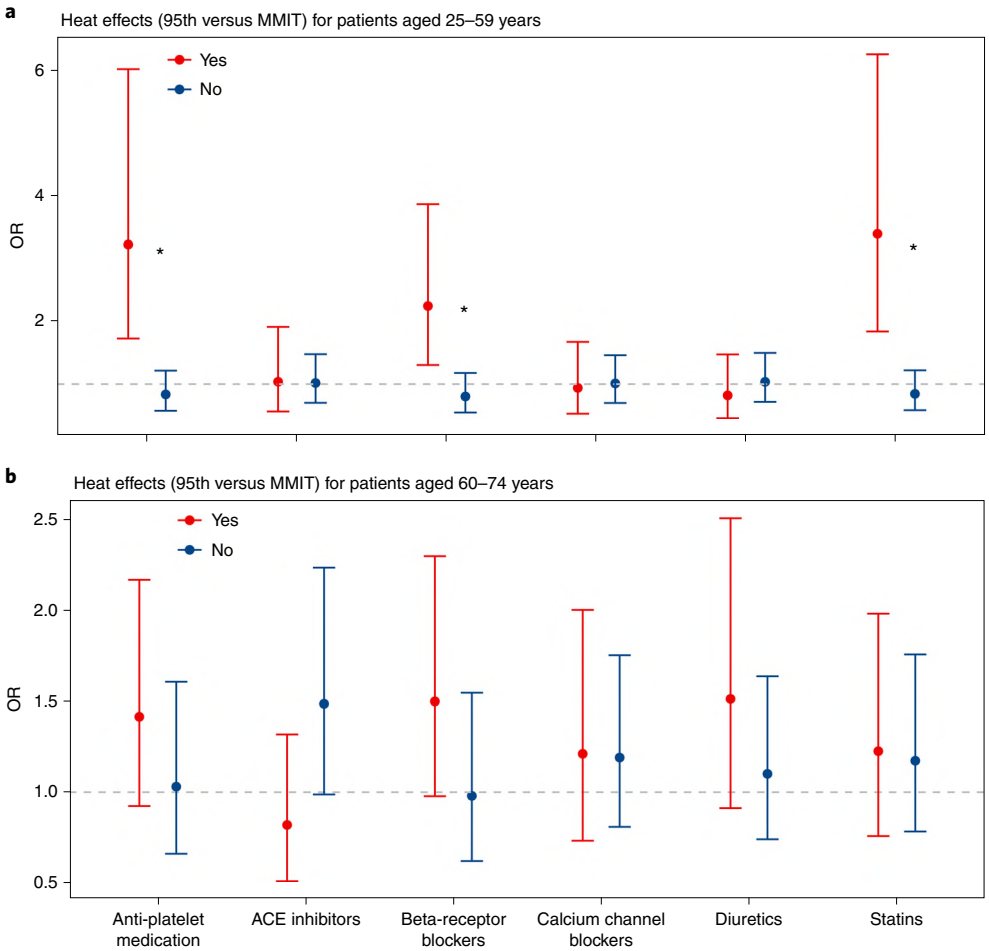

Fig. 2 | Heat-related risks of non-fatal MI stratified by medication intake in two patient age groups in Augsburg, Germany, during the warm seasons from 2001 to 2014. a, Heat effect by medication type for younger patients (25–59 years) ($n=976$). **b**, Heat effect by medication type for older patients (60–74 years) ($n=1,518$). The OR is for the 95th percentile of temperature (24.2 °C) relative to the MMIT (7.5 °C). Data are presented as point estimates of OR ± 1.96 standard error (that is, 95% CIs). Asterisks indicate statistical significance (two-sided $P=0.0003$, $P=0.002$ and $P=0.0001$ for anti-platelet, beta-receptor blocker and statin intake, respectively; multiple comparisons were not adjusted) of the differences in risk estimates between users and non-users of a specific medication, based on the Z-score calculated using the coefficients and standard errors for users and non-users.

prevalence of diabetes (23.7% versus 26.2%), hypertension (67.6% versus 84.1%) and pre-existing CHD (18.9% versus 33.3%) (Table 1). The effect modification by anti-platelet medication and beta-receptor blockers observed in all patients (Fig. 1a) became stronger in the younger patients ($P<0.01$) but weaker in the older patients ($P>0.05$) (Fig. 2). In addition, among younger patients, significant heat-related risk for non-fatal MI was observed among users of statins (OR = 3.39 (95% CI: 1.84, 6.25)) but not among non-users (OR = 0.84 (95% CI: 0.58, 1.22)), with the OR among users significantly higher than the OR among non-users ($P<0.01$).

In separate sensitivity analyses, we (1) used the 97.5th or 90th percentile temperatures to define heat exposure; (2) controlled for relative humidity non-linearly using a natural cubic spline with 3 degrees of freedom (df); (3) additionally adjusted for current day air pollution (inhalable PM or nitrogen dioxide (NO_2)); or (4) used a maximum lag of 3 days (as opposed to the day of onset) to define temperature exposure in a distributed lag non-linear model. These analyses yielded estimates similar to the main analysis (Extended Data Figs. 2 and 3). We did not observe a lagged effect for heat up to 3 days (Extended Data Fig. 4).

Very few epidemiological studies have assessed the role of cardiovascular medication use in heat-related MI risk[10]. We found increased heat-related MI risks among users of anti-platelet medication and beta-receptor blockers. In a double-blind, crossover study, the anti-platelet medication aspirin was found to elevate body core temperatures during passive heat stress[11]. During the 2003 European heatwave, patients taking anti-hypertensive medication were found to have an elevated risk for heatstroke[12]. Beta-receptor blockers inhibit skin vasodilation, resulting in reduced heat dissipation through convection and, at the same time, could intensify the blood-pressure-lowering effect of other anti-hypertensive drugs, which then could lead to syncope[13].

A strength of this study is that the case-crossover design controls for pre-existing diseases and other patient characteristics because each case serves as its own control. Although we cannot rule out confounding by indication, in which users of anti-platelet medication or beta-receptor blockers are sicker patients who are inherently more vulnerable to heat-related MI due to their illness and not their medication use, the null results for the other medication types argue against confounding by indication. However, heat-related MI risk was elevated among patients with pre-existing CHD (OR = 2.17 (95% CI: 1.40, 3.38)) but not among patients without pre-existing CHD (OR = 0.88 (95% CI: 0.65, 1.20)) (Extended Data Fig. 5). This difference was highly significant ($P<0.01$), revealing that confounding by indication is a possibility.

An argument against confounding by indication is that the effect modification by both anti-platelet medication and beta-receptor blockers was stronger among younger patients, who had a lower prevalence of pre-existing CHD (Table 1), than among older patients (Fig. 2), who had a higher prevalence of pre-existing CHD, suggesting that pre-existing CHD may not fully confound the effect modification by these two medications. Nevertheless, most patients with pre-existing CHD (84.5%) took either anti-platelet medication or beta-receptor blockers, making it challenging to fully disentangle the effect modification by these two medications from the effect modification by pre-existing CHD. The small sample sizes of subgroups stratified by both medication use and pre-existing CHD status necessitate further research leveraging large registries of patients with MI to separate the effects of medication use from pre-existing CHD.

In summary, we found that patients taking anti-platelet medication or beta-receptor blockers may be more vulnerable than patients not taking these medications to non-fatal MI risk due to heat exposure. Our findings, if confirmed, can help clinicians, patients and public health officials develop targeted strategies to reduce the burden of cardiovascular disease under climate change.

Methods

MONICA/KORA MI registry. We obtained data from the MONICA/KORA MI registry, which recorded all cases of MI occurring among residents aged 25–74 years in the region of Augsburg, Germany, since 1984. This study was restricted to non-fatal cases (defined as patients who survived to at least the 28th day after hospital admission). Information on medication intake was not available for most patients who experienced a fatal MI, whereas about three-quarters of patients who experienced a non-fatal MI were interviewed about their medication intake, along with baseline information, using a standardized questionnaire. History of diabetes, hypertension and CHD were collected from patient interviews and then confirmed by chart review during the hospital stay. Among all MI occurrences (2,494 cases), 60.9% of patients were 60–74 years old, and more men (76.4%) experienced an MI than women. No compensation was provided for study participants. All study participants with a non-fatal MI provided written informed consent. More details of the registry can be found elsewhere[14,15]. This study was approved by the Ethics Committee of the Bavarian Chamber of Physicians.

Meteorological and air pollution data. Daily meteorological data were obtained from an official urban background monitoring site located south of the city center. Daily concentrations of PM with an aerodynamic diameter <10 μm (PM_{10}) and NO_2 were collected from air quality monitoring stations in Augsburg.

Statistical analyses. We applied a time-stratified case-crossover design with conditional Poisson regression to estimate the association between air temperature exposure and non-fatal MI risk. By comparing temperature exposure on the case day with exposures on control days within the same month and the same day of the week, this approach automatically controls for long-term time trends, seasonality, day of the week and time-invariant confounders (for example, pre-existing cardiovascular disease). We investigated temperature exposure on the day of onset using a natural cubic spline with 3 df and further controlled for current-day relative humidity as a linear term and the yearly number of residents as an offset. We calculated the heat effect as MI risk at the 95th percentile of temperature relative to the MMIT risk. We then examined effect modification by intake of six types of medication using stratified analyses (that is, users versus non-users) in all ages and separate age groups (that is, aged 25–59 years and 60–74 years). We tested the statistical significance of the effect modification by calculating the Z-score of difference in risk estimates[9]. Two-sided *P* values less than 0.05 were considered significant. All statistical analyses were conducted with R software (version 4.1.2) using the gnm (version 1.1–1) and dlnm (version 2.4.7) packages.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

All data needed to evaluate the conclusions in the paper are included in the paper. Data were collected within the MONICA/KORA MI registry and cannot be made publicly available because the patient consent did not include such an agreement. However, data may be made available for selected research questions and researchers upon reasonable request to the authors. The timeframe for response to requests from the authors is 4 weeks. Please contact C.M. by email: christine.meisinger@med.uni-augsburg.de. The homepage of the Chair of Epidemiology is http://www.uni-augsburg.de/med/epidemiologie.

Code availability

R code for this analysis is available at https://github.com/CHENlab-Yale/Heat_MI_Medication.

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Author contributions

K.C. and A.S. conceived the study design. K.C. performed the formal analysis, investigation and drafting of the manuscript. R.D., S.B., B.K., C.M. and A.S. contributed to manuscript preparation and editing. R.D., S.B., K.W. and A.S. assisted with the statistical methodology. J.L., T.S., M.H., W.v.S., B.K., C.M. and A.P. contributed to data collection and management. All authors reviewed and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s44161-022-00102-z.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s44161-022-00102-z.

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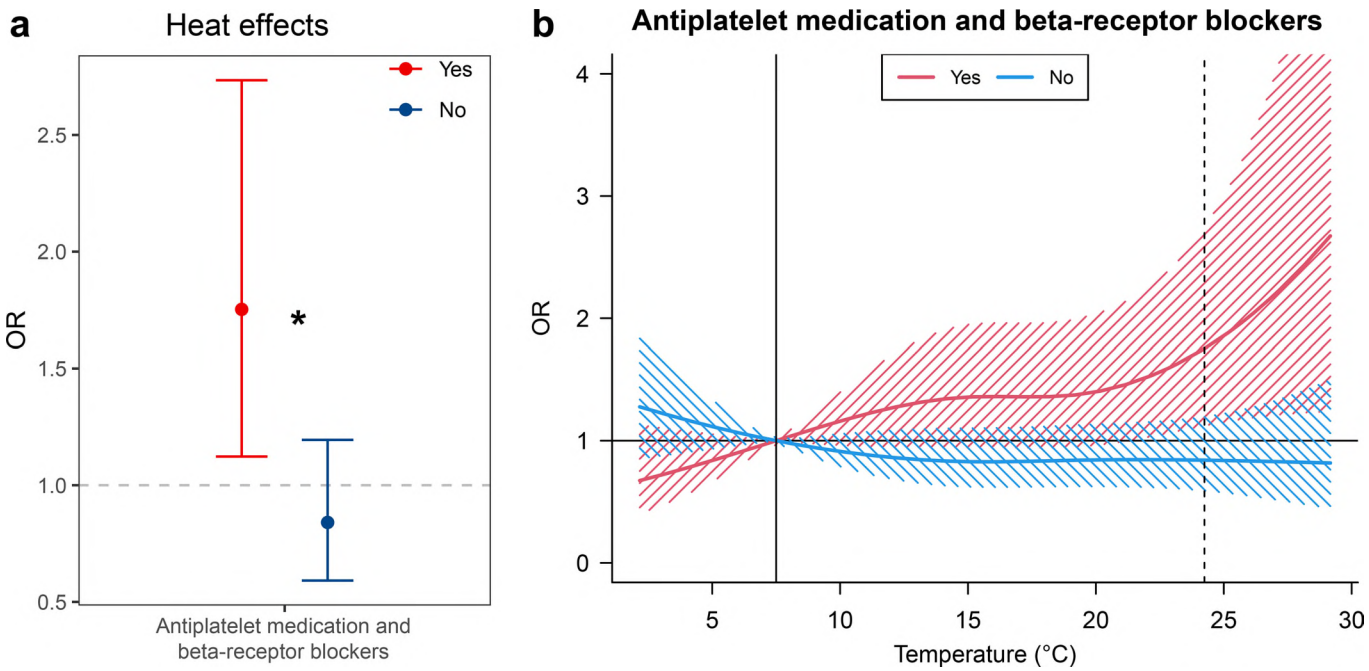
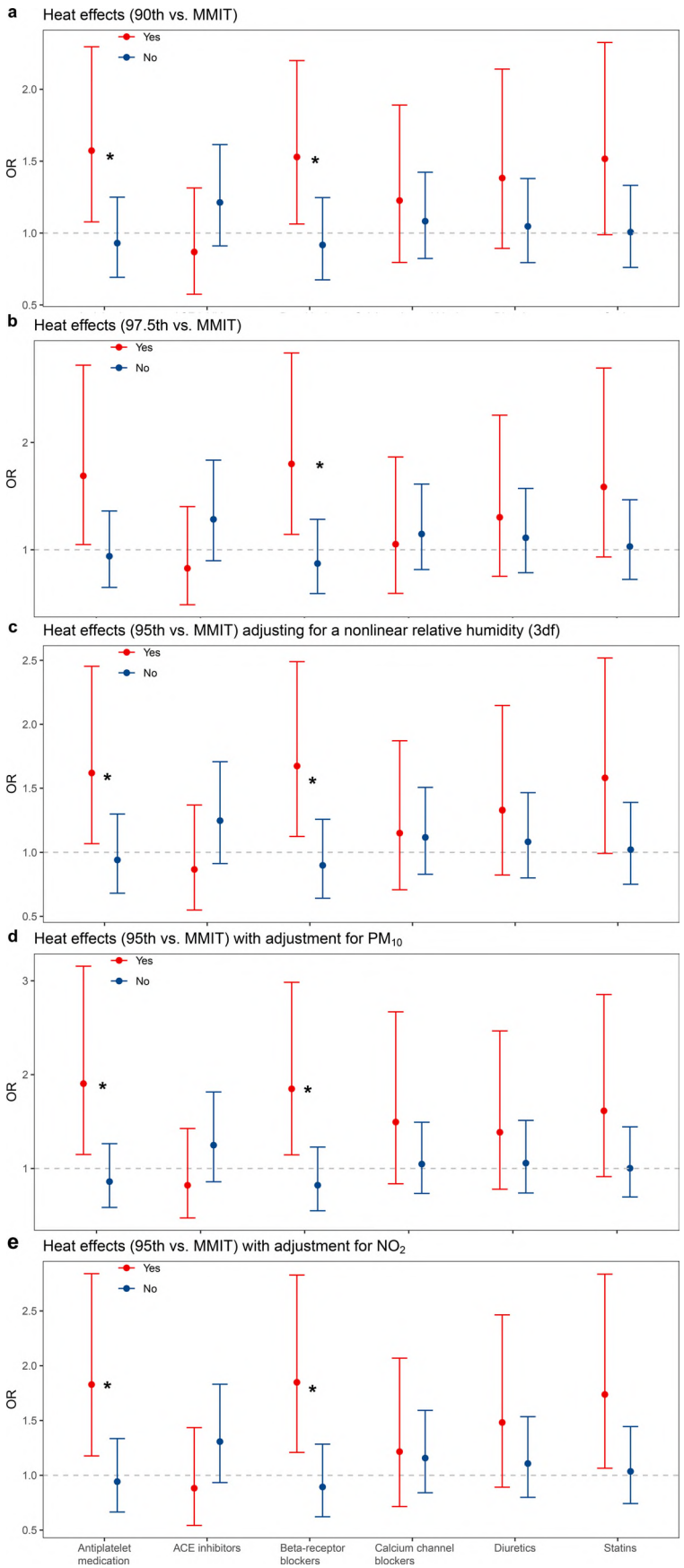
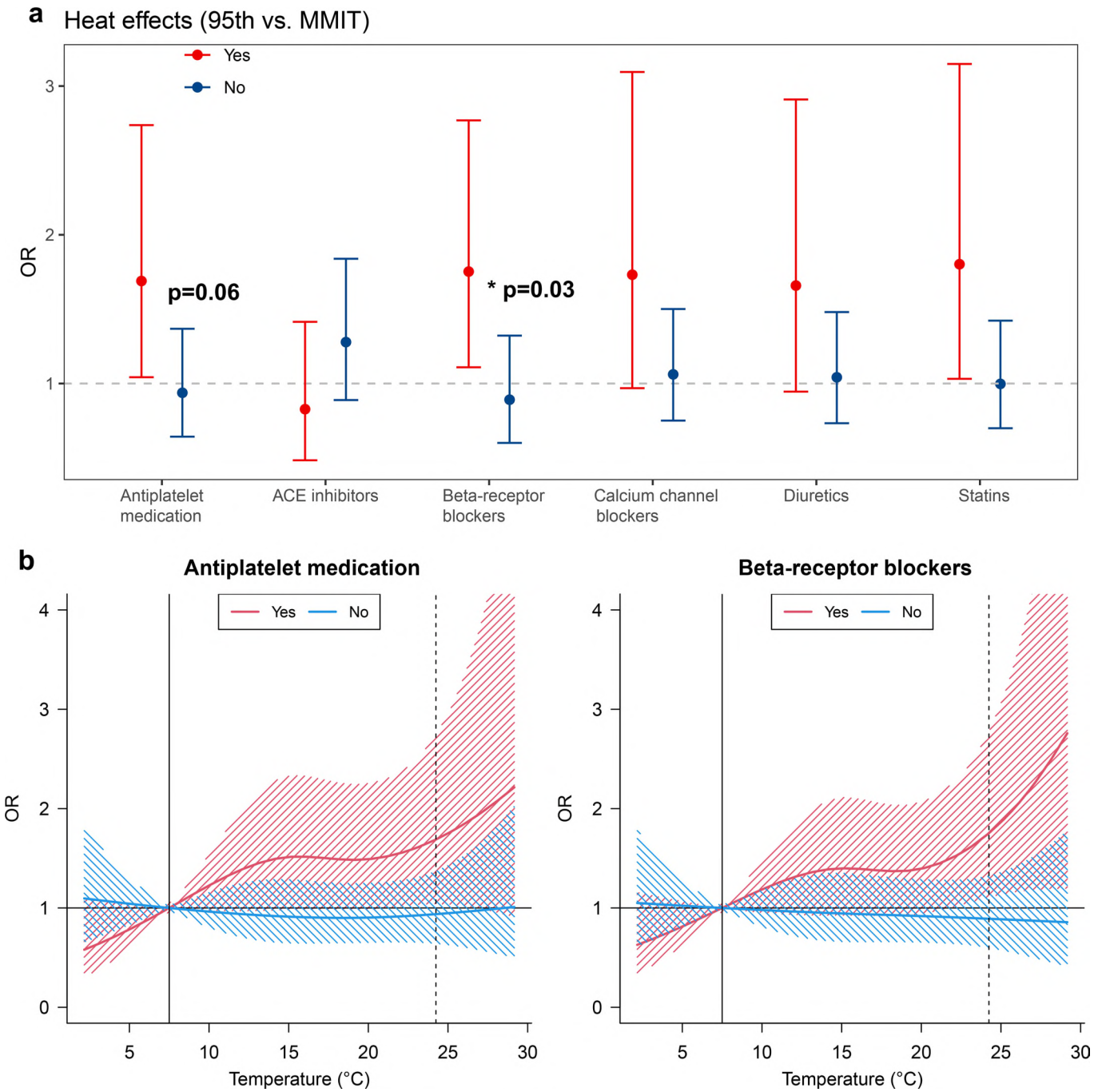


Extended Data Fig. 1 | Heat-related risks of non-fatal myocardial infarction (MI) stratified by intake/non-intake of both antiplatelet medication and beta-receptor blockers (both versus neither) in Augsburg, Germany, during the warm seasons from 2001 to 2014. The odds ratio (OR) for heat exposure, which is defined as the 95th percentile of temperature (24.2 °C) relative to the minimum MI risk temperature (7.5 °C) (n = 1,911). Data are presented as point estimates of OR ± 1.96 standard error (that is, 95% confidence intervals). Asterisk indicates statistical significance (two-sided p-value =0.011; multiple comparisons were not adjusted) of the differences in risk estimates between users and non-users, based on the z score calculated using the coefficients and standard errors for users and non-users. Participants taking only one of these medications were excluded from this analysis; (**b**) Exposure-response curves for the temperature-MI relationship stratified by intake/non-intake of both antiplatelet and beta-receptor blockers. Solid lines represent the point estimates of OR; shaded areas represent the 95% confidence intervals. Solid vertical line is the MMIT and dashed vertical line is the 95th percentile of temperature.

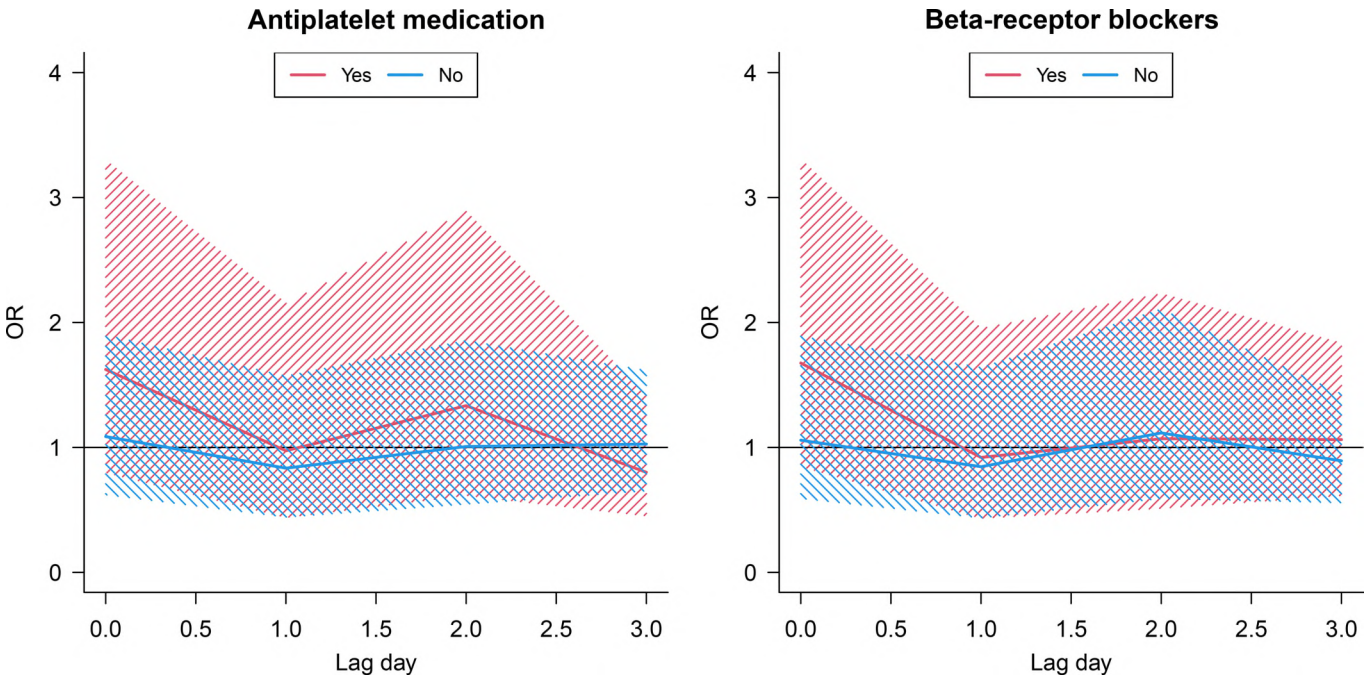


Extended Data Fig. 2 | See next page for caption.

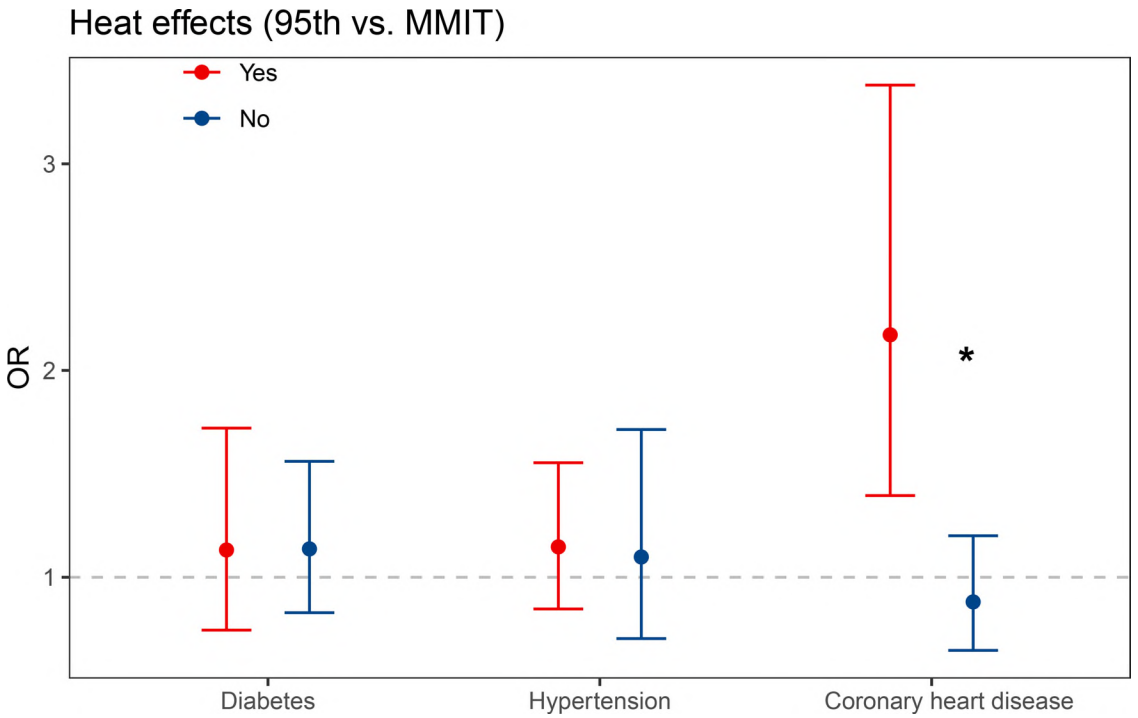
Extended Data Fig. 2 | Sensitivity analysis of heat-related risks of non-fatal myocardial infarction (MI) stratified by medication intake in Augsburg, Germany, during the warm seasons from 2001 to 2014. The odds ratio (OR) is for the 95th percentile of temperature (24.2 °C) relative to the minimum MI risk temperature (MMIT; 7.5 °C). Data are presented as point estimates of OR ± 1.96 standard error (that is, 95% confidence intervals). (**a**) Using the 90th percentile temperature to define heat exposure (n = 2,494). Asterisks indicate statistical significance (two-sided p-value = 0.032 and 0.035 for antiplatelet and beta-receptor blockers intake, respectively; multiple comparisons were not adjusted) of the differences in risk estimates between users and non-users of a specific medication, based on the z score calculated using the coefficients and standard errors for users and non-users. (**b**) Using the 97.5th percentile temperature to define heat exposure (n = 2,494). Asterisks indicate statistical significance (two-sided p-value = 0.017 for beta-receptor blockers intake; multiple comparisons were not adjusted). (**c**) Controlling for relative humidity nonlinearly using a natural cubic spline with 3 degrees of freedom (df) (n = 2,494). Asterisks indicate statistical significance (two-sided p-value = 0.043 and 0.019 for antiplatelet and beta-receptor blockers intake, respectively; multiple comparisons were not adjusted). (**d**) Additionally adjusting for current day PM_{10} (inhalable particulate matter) concentration (n = 1,729). Asterisks indicate statistical significance (two-sided p-value = 0.014 and 0.011 for antiplatelet and beta-receptor blockers intake, respectively; multiple comparisons were not adjusted). (**e**) Additionally adjusting for current day NO_2 (nitrogen dioxide) concentration (n = 2,118). Asterisks indicate statistical significance (two-sided p-value = 0.021 and 0.011 for antiplatelet and beta-receptor blockers intake, respectively; multiple comparisons were not adjusted). The 90th, 95th, and 97.5th represents the 90th, 95th, and 97.5th percentile of temperature, respectively.



Extended Data Fig. 3 | Sensitivity analysis of heat-related risks of non-fatal myocardial infarction (MI) at a maximum lag of 3 days stratified by medication intake in Augsburg, Germany, during the warm seasons from 2001 to 2014. (**a**) Effect modification by six medication types with more than 10% of intake frequency among the MI survivors (n = 2,124). The odds ratio (OR) is for the 95th percentile of temperature (95th; 24.2 °C) relative to the minimum MI risk temperature (MMIT; 7.5 °C). Data are presented as point estimates of OR ± 1.96 standard error (that is, 95% confidence intervals). Two-sided P-value (0.060 and 0.028 for antiplatelet and beta-receptor blockers intake, respectively; multiple comparisons were not adjusted) indicates the statistical significance of the difference in risk estimates between users and non-users of a specific medication, based on the z score calculated using the coefficients and standard errors for users and non-users. (**b**) Exposure-response curves for the temperature-MI relationship stratified by antiplatelet or beta-receptor blockers intake. Solid lines represent the point estimates of OR; shaded areas represent the 95% confidence intervals. Solid vertical lines are the minimum MI temperatures (MMIT; 7.5 °C) and dashed vertical lines are the 95th percentile of temperature (24.2 °C).



Extended Data Fig. 4 | Lag-response curves for heat-related risks of non-fatal myocardial infarction stratified by antiplatelet and beta-receptor blockers intake. The odds ratio (OR) is for the 95th percentile of temperature (24.2 °C) relative to the minimum MI risk temperature (MMIT; 7.5 °C). Solid lines represent the point estimates of OR; shaded areas represent the 95% confidence intervals.



Extended Data Fig. 5 | Heat-related risks of non-fatal myocardial infarction (MI) stratified by history of diabetes, hypertension, or pre-existing coronary heart disease in Augsburg, Germany, during the warm seasons from 2001 to 2014. The odds ratio (OR) is for the 95th percentile of temperature (95th; 24.2 °C) relative to the minimum MI risk temperature (MMIT; 7.5 °C) (n = 2,136). Data are presented as point estimates of OR ± 1.96 standard error (that is, 95% confidence intervals). Asterisk indicates statistical significance (two-sided p-value = 0.001 for patients with pre-existing coronary heart disease; multiple comparisons were not adjusted) of the difference in risk estimates between users and non-users of a specific medication, based on the z score calculated using the coefficients and standard errors for users and non-users.