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Ambient Air Temperature and Temperature Variability Affecting Blood Pressure – A Repeated-Measures Study in Augsburg, Germany

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Abstract:	Background Ambient air temperature and temperature variability are supposed to influence blood pressure (BP); however, findings are inconsistent. We examined the effects of short-term changes in ambient temperature and temperature variability on systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and pulse pressure (PP) in a repeated-measures study. Methods Repeated BP measurements were available for 3,184 participants from the German population-based Cooperative Health Research in the Region of Augsburg (KORA) S4 survey (1999-2001) and two follow-up examinations (2006–08 and 2013–14). Daily meteorological data were obtained from fixed measurement stations including air temperature and diurnal temperature range (DTR). We used confounder-adjusted additive mixed models to examine immediate (same-day, lag 0), delayed (lag 1 to lag 4), and cumulative (up to lag 0-13) exposure effects. Results Decreases in air temperature were associated with increases in SBP, DBP, and MAP, while we observed no effects for PP at all. For example, a 1°C decrease in the 14-day moving average (lag 0-13) mean air temperature was associated with a 0.54% [95% confidence interval [95%CI]: 0.41%;0.68%] increase in SBP. Furthermore, decreasing DTR was linked to increasing SBP, DBP, and MAP measures. In the sensitivity analyses, results were found to be robust. Examination of exposure-response functions according to season revealed, that associations for summer and winter can be considered linear, while we detected non-linear functions in spring and autumn. Furthermore, exposure-response functions also differed in the three different surveys. Conclusions As BP levels influence the risk of cardiovascular mortality, our results show the importance of considering temperature and its variation as potential risk factors. As ongoing climate change affects temperature variability, it is important to understand how the body adapts to changing ambient temperatures.
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Cover Letter

Ambient Air Temperature and Temperature Variability Affecting Blood Pressure – A Repeated-Measures Study in Augsburg, Germany

Dear Editors,

Please find attached the manuscript „Ambient Air Temperature and Temperature Variability Affecting Blood Pressure – A Repeated-Measures Study in Augsburg, Germany“, submitted for consideration for publication in Science of the Total Environment.

Elevated blood pressure levels are known to play an essential role in the course and progression of cardiovascular and cerebrovascular disease. In addition to familial and lifestyle risk factors, there is increasing evidence that environmental factors such as ambient temperature are important for the pathophysiology of hypertension. As anthropogenic climate change advances and thus increasingly rapid temperature changes occur, it is important to understand how this affects blood pressure - also to preventively address associated, potentially fatal health outcomes such as cardiovascular or cerebrovascular disease.

In our repeated measures study comprising 8,542 observations from 3,184 individuals living in the area of Augsburg/Germany, we investigated short-term effects of ambient temperature and temperature variability on systolic and diastolic blood pressure (SBP, DBP), pulse pressure (PP), and mean arterial pressure (MAP). We considered temperature effects on blood pressure of up to 14 days, covering a time period of 15 years in total.

We found that short-term decreases in ambient temperature were associated with increased blood pressure levels. For example, a 1°C decrease in the 14-day moving average mean air temperature was associated with a 0.54% [95% confidence interval [95%CI]: 0.41%; 0.68%] increase in SBP. We found comparable results for DBP and MAP, while no associations for PP were seen. Furthermore, decreasing diurnal temperature range was linked to increasing SBP, DBP, and MAP. In further analyses we could show that season significantly modified the exposure-response functions. The same applied to the different surveys, indicating that changing climatic conditions might profoundly affect the association between temperature and blood pressure levels.

To summarize, our study investigated the impact of climate change-induced ambient temperature alterations on the human organism to understand how the body responds to these changes. In particular, the influence of temperature variability, as well as the detailed inspection of exposure-response functions, have hardly been investigated so far. Therefore, our study fits within the scopes and aims of Science of the Total Environment, as this study contributes to an improved understanding of the human body's adaptation to environmental changes.

All authors have read and approved the submission of the manuscript; the manuscript has not been published and is not being considered for publication elsewhere. There exists no conflict of any competing financial interest regarding the submitted article. The data and the manuscript are original work.

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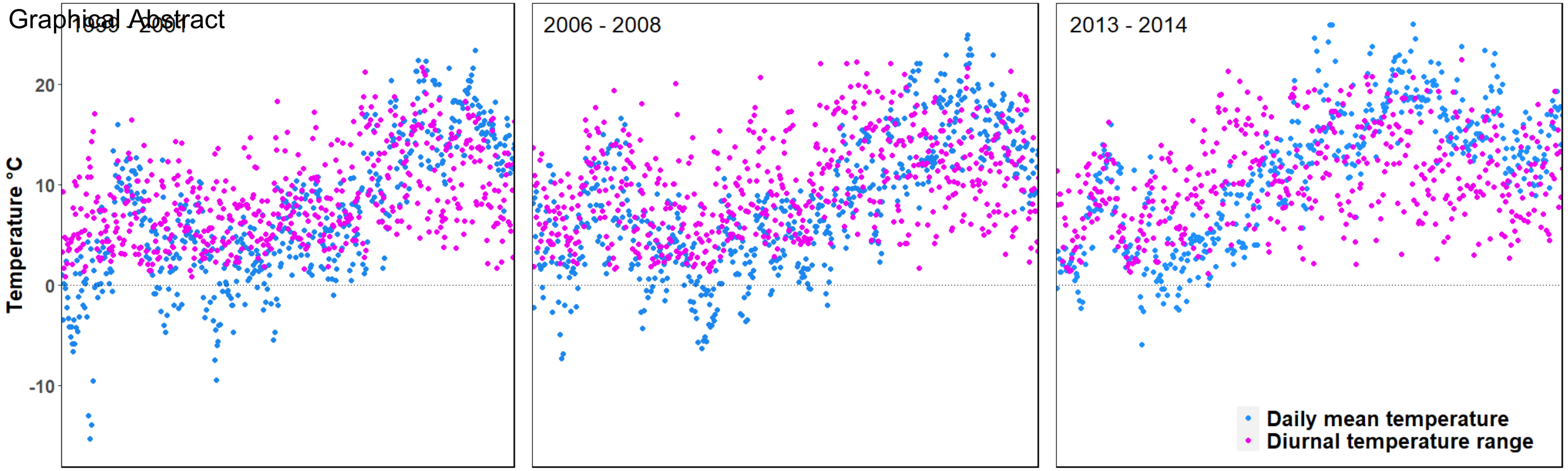
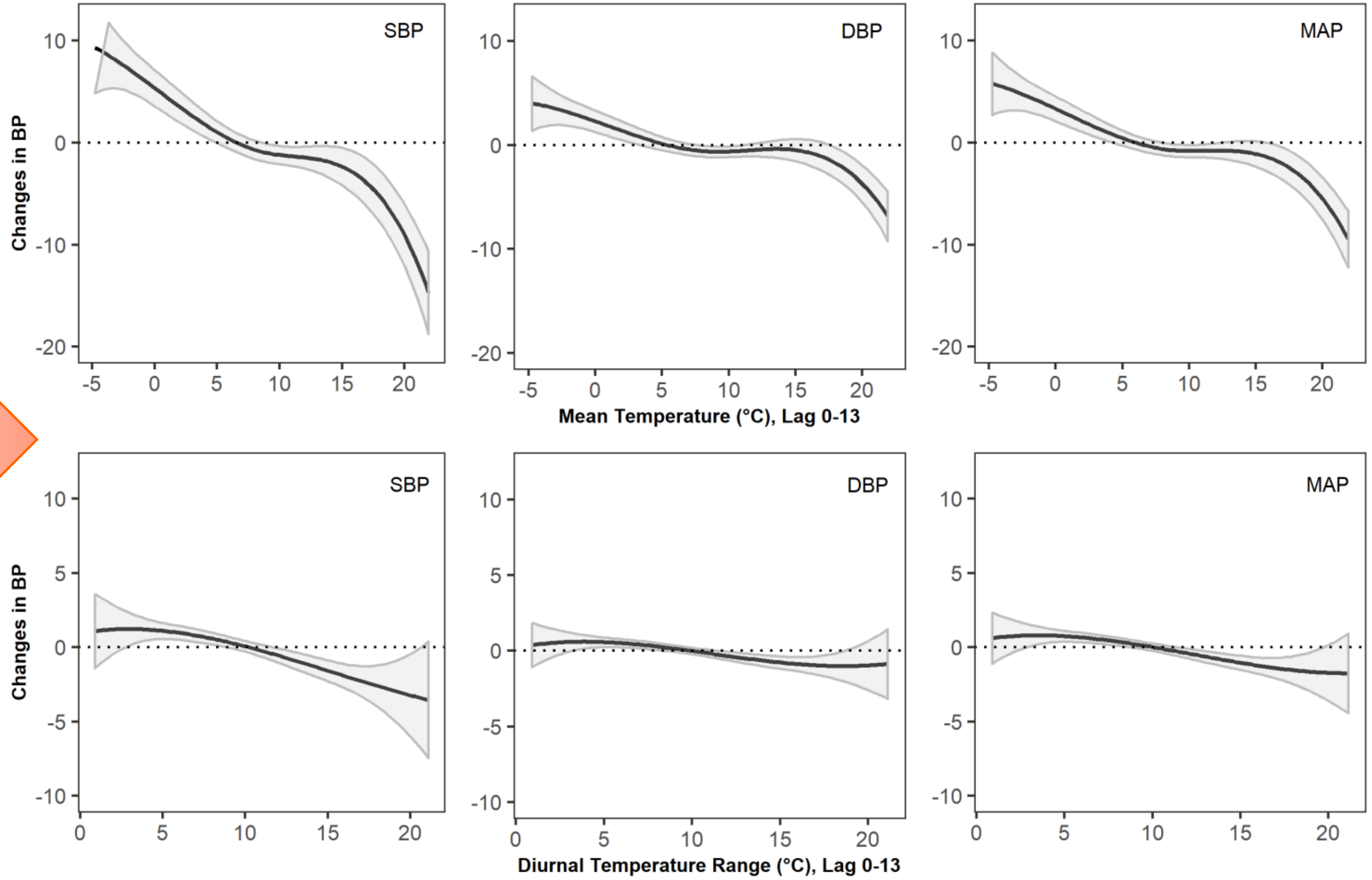
Yours sincerely,

Margarethe Woeckel

Graphical Abstract



Systolic blood pressure
Diastolic blood pressure
Mean arterial pressure



Highlights

- Evidence on how ambient temperature variability affects blood pressure (BP) is scarce.
- Data from a population-based cohort, with repeated measurements taken between 1999-2001, 2006-2008, and 2013-2014.
- Decreasing diurnal temperature range was associated with increased BP.
- Different seasons, as well as the three surveys, affected the shape of the exposure-response functions.
- Changing climatic conditions might profoundly affect the association between temperature and blood pressure levels.

Ambient Air Temperature and Temperature Variability Affecting Blood Pressure – A Repeated-Measures Study in Augsburg, Germany

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Abstract

Background: Ambient air temperature and temperature variability are supposed to influence blood pressure (BP); however, findings are inconsistent. We examined the effects of short-term changes in ambient temperature and temperature variability on systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and pulse pressure (PP) in a repeated-measures study.

Methods: Repeated BP measurements were available for 3,184 participants from the German population-based Cooperative Health Research in the Region of Augsburg (KORA) S4 survey (1999-2001) and two follow-up examinations (2006–08 and 2013–14). Daily meteorological data were obtained from fixed measurement stations including air temperature and diurnal temperature range (DTR). We used confounder-adjusted additive mixed models to examine immediate (same-day, lag 0), delayed (lag 1 to lag 4), and cumulative (up to lag 0-13) exposure effects.

Results: Decreases in air temperature were associated with increases in SBP, DBP, and MAP, while we observed no effects for PP at all. For example, a 1°C decrease in the 14-day moving average (lag 0-13) mean air temperature was associated with a 0.54% [95% confidence interval [95%CI]: 0.41%;0.68%] increase in SBP. Furthermore, decreasing DTR was linked to increasing SBP, DBP, and MAP measures. In the sensitivity analyses, results were found to be robust. Examination of exposure-response functions according to season revealed, that associations for summer and winter can be considered linear, while we detected non-linear functions in spring and autumn. Furthermore, exposure-response functions also differed in the three different surveys.

Conclusions: As BP levels influence the risk of cardiovascular mortality, our results show the importance of considering temperature and its variation as potential risk factors. As ongoing climate change affects temperature variability, it is important to understand how the body adapts to changing ambient temperatures.

Key words: climate change, exposure-response functions, cohort study, cardiovascular morbidity

1. Introduction

Ambient air temperature is known to influence cardiovascular mortality. Low and high daily air temperature levels, as well as temperature variability, have been associated with an increased risk[1-7]. In particular, temperature variability might be an important meteorological indicator, considering that unstable weather patterns are predicted to occur more frequently in the future[5].

One of the leading risk factors for cardiovascular disease and mortality is high blood pressure (BP) levels[8-10]. Short-term increases in BP have been associated with an immediately increasing risk for cardiovascular events[11]. Due to the important role of high BP in cardiovascular morbidity and mortality, it is essential to pay separate attention to the relationship between air temperature and BP. A French study found increasing BP levels among an elderly population when outdoor temperatures declined[12]. Similar results were reported in a population of older men, for which a decrease in air temperature was associated with an increase in DBP[13].

While there have been several studies investigating the effects of air temperature[12-16], little is known about how temperature variability affects BP. A longitudinal study in Seoul, Korea, did not find an association between diurnal temperature range (DTR) and SBP or DBP[17]. By contrast, a large Chinese study showed increased SBP and PP for an increasing DTR, but a negative linear correlation between DTR and DBP[18], while a Chinese prospective cohort study found increasing BP levels with increasing DTR[19]. Facing more extreme and faster temperature changes in the course of climate change[20], it is crucial to improve the understanding of how BP reacts to that.

We investigated the acute impact of ambient air temperature and temperature variability on BP levels in a repeated measurements study in the Augsburg Region, Germany. We obtained data from 3,184 participants of a population-based cohort, with two repeated measurements taken over the course of three time periods, 1999-2001, 2006-2008, and 2013-2014.

2. Methods

2.1. Study Population: Data were obtained from the population-based German Cooperative Health Research in the Region of Augsburg (KORA) cohort study conducted in the city of Augsburg and two adjacent counties (Augsburg and Aichach-Friedberg). For the baseline examination (S4) in 1999-2001, 4,261 participants aged 24-75 with German citizenship were recruited. The first follow-up (F4) was conducted from 2006 to 2008 with 3,080 participants; the second follow-up (FF4) in 2013-2014 with 2,279 participants. The study design and population of the S4, F4, and FF4 surveys have been described elsewhere[21, 22].

All participants gave written informed consent, and all study methods were approved by the Ethics Committee of the Bavarian Chamber of Physicians, Munich.

2.2. Blood Pressure Measurements: Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a validated automatic device (OMRON HEM 705-CP). Three independent measurements were taken on the right arm at a 3-min interval after at least 5 minutes in a sitting position. Measurements were taken identically in S4, F4, and FF4 to make them comparable. The average reading of the second and third measurements was considered for the analyses. Pulse pressure (PP) was calculated as the difference between SBP and DBP. Mean arterial pressure (MAP) was calculated as 1/3 SBP + 2/3 DBP.

2.3. Environmental Measurements: Daily meteorological data were obtained from the German Weather Service (monitoring site located at the Augsburg airport), the Bavarian Environment Agency (located in the Augsburg urban area), and a fixed monitoring site located 1km southeast of the city center of Augsburg[23]. Data included mean, minimum, and maximum air temperature, relative humidity, and barometric pressure and were highly correlated between sites (Spearman correlation coefficients were > 0.95 for all parameters). There were no missing values for meteorological data obtained from the German Weather Service. Given the high correlation between the sites, we used data from only this source for our analyses.

Diurnal temperature range (DTR) was calculated as the difference between the maximum and minimum temperatures on the same day.

Daily data for ozone and nitrogen dioxide (NO_2) were obtained from the monitoring network of the Bavarian Environment Agency. Daily mean concentrations for particulate matter with an aerodynamic diameter less than 2.5 µm (PM2.5) and ultrafine particles (particles with a diameter ≤ 100 nm, UFP) were obtained from a single monitoring station and considered as representative for the urban background in Augsburg[23]. Due to measurement inconsistencies, we included air pollution only for the years 2005 – 2014.

2.4. Covariate Assessment: Anthropometric measures were taken at the KORA study center. Information about health status, smoking status, alcohol consumption, and medication was assessed by questionnaires. Waist-to-hip ratio (WHR): waist circumference [cm]/hip circumference [cm]. The definition regarding the intake of antihypertensive medication was taken from the recommendations of the German Society for Hypertension and Prevention [24]. The smoking status: regular; irregular; former; or never. Physical activity: very active: regularly > 2h/week; moderate active: regularly 1h/week; little active: irregularly 1h/week; non-active: no activity; during the whole year. Socioeconomic status: low: income per month <625€; medium-low: 625€ to <1250€; medium: 1250€ to <1875€; medium-high: 1875€ to <2500€; high: ≥2500€.

2.5. Statistical Analyses: For our analysis, we included all participants from the baseline examination with at least one follow-up visit. Descriptive analyses were performed for participant characteristics as well as for meteorological and air pollution data. Analysis of variance (ANOVA) was used to compare seasonal differences of SBP, DBP, MAP, and PP; Spearman’s rank correlation coefficient was used to compare the different meteorological measurement sites as well as to calculate correlations between ambient temperature and air pollutants.

We used additive mixed models with random participant intercepts to assess the effect of ambient temperature (daily mean, minimum, maximum temperature, and diurnal temperature range) on repeated measurements of SBP, DBP, MAP, and PP. The confounder model was chosen a priori and was identical for all outcomes. It included season, time trend, day of the week, relative humidity with the same lag as air temperature, barometric pressure with the same lag as air temperature, age, sex, WHR, physical activity, smoking status, alcohol consumption (g/day), socioeconomic status, intake of antihypertensive medication (yes vs. no), and intake of statins (yes vs. no). Air temperature was included as a linear term. Immediate (current day, lag 0), delayed (lag 1 up to lag 4), and cumulative (mean of lags 0 and 1, mean of lags 0 to 4, mean of lags 0 to 6, and mean of lags 0 to 13) associations between air temperature and BP metrics were investigated.

We assessed potential effect modification by including an interaction term between air temperature metrics and the effect modifier. The following effect modifiers were taken into account: (1) season (winter (22. December - 21. March) vs. spring (22. March - 21. June) vs. summer (22. June - 21. September) vs. autumn (22. September - 21. December)), (2) sex (female vs. male), (3) waist-to-hip ratio WHR (females: normal <1 vs. high ≥1; males: normal <0.85 vs. high ≥0.85), (4) antihypertensive medication intake (yes vs. no), (5) age (<60 years vs. 60-74 years vs. >74 years), (6) smoking status (regular vs. irregular vs. former vs. never). P-values < 0.05 were considered statistically significant; all reported values were two-tailed.

Statistical analyses were performed using R version R 4.2.1 (The R Foundation for Statistical Computing, Vienna, Austria).

2.6. Sensitivity Analyses: To test the robustness of our results, we performed the following sensitivity analyses: (1) We visually checked the exposure-response functions between air temperature and BP metrics for deviations from linearity. This was done by replacing the linear air temperature term with penalized splines. Degrees of freedom were chosen according to the AIC. (2) We additionally inspected exposure-response functions according to season and for each survey separately. (3) We used distributed-lag non-linear models [25] instead to assess the association between mean air temperature or DTR and BP (Supplement S13). (4) Confounder selection by maximizing the adjusted R^2. Season and day of the year were forced into each model. We included continuous confounders linearly or smoothly as penalized splines (P-splines) depending on the R^2 value. In the case of smooth effects, degrees of freedom were chosen according to R^2. (5) Instead of mean air temperature, we included mean apparent temperature as the exposure variable. (6) We additionally adjusted for $PM_{2.5}$, UFP, NO_2, and ozone with the same lag as the analyzed temperature lag. (7) As BP levels are lower after treatment with antihypertensive drugs, we considered the effect of antihypertensive medication[26]. Hence, we artificially increased BP levels in treated individuals. First, raw residuals were calculated by subtracting the mean BP from the observed BP. In treated individuals, the raw residuals were adjusted by calculating an average of the original value and all larger residuals. The treatment-adjusted BP levels were then calculated by the observed value minus the raw residual plus the adjusted residual. BP levels of untreated individuals remained unchanged. Afterward, we re-calculated the air temperature effects using the treatment-adjusted SBP, DBP, MAP, and PP levels

3. Results

3.1. Study population and exposure measures: For our analyses, we included 3,184 individuals from baseline survey S4, 3,079 participants from the first follow-up F4, and 2,279 from the second follow-up FF4 with no missing values in BP measurements (S4-F4-FF4: 2150 participants with both follow-up visits; S4-F4: 3065 participants with only the first follow-up visit; S4-FF4: 2269 participants with only the second follow-up visit). Table 1 shows the characteristics of the study population. SBP, DBP, MAP, and PP did not significantly differ during seasons (ANOVA in Supplement S1). Furthermore, mean BP levels decreased from wave to wave, with the highest levels being measured in baseline examination S4. A possible explanation for this finding might be that healthier participants were more likely to participate in the later follow-up visits.

Descriptive statistics of meteorological variables, air pollution measurements, and the corresponding correlation coefficients are provided in Table 2 and Table S2. Over the whole study period, we observed a mean daily mean temperature of 8.5°C, and a mean DTR of 9.6°C. Daily mean temperature and DTR were moderately positively correlated (Spearman Rank Correlation Coefficient = 0.51), and correlations between temperature variables and relative humidity were all negative (weak to moderate).

3.2. Effects of air temperature on blood pressure: Figure 1 presents the associations between mean air temperature and SBP, DBP, MAP, and PP (a corresponding table is provided in Supplement Table S3; minimum and maximum temperature effects are provided in Table S4). Temperature effects are presented as percent change (and 95%-confidence intervals [95%CI]) of the mean outcome per 1°C degree decrease in air temperature. A decrease in daily mean air temperature was associated with increased

SBP, DBP, and MAP. We observed immediate, delayed and cumulative effects. The strongest temperature effects were observed for the 14-day moving average (lag 0-13) - a 1°C decrease was associated with a 0.54% [95%CI: 0.41%;0.68%] increase in SBP. For DBP and MAP, we observed a 0.42% [95%CI: 0.30%;0.55%] and 0.48% [95%CI: 0.35%;0.60%] increase, respectively.

For DTR (Figure 2, Table S5), we also observed associations for immediate, delayed, and cumulative effects; a 1°C decrease in the 14-day moving average of DTR was associated with a 0.21% [95%CI: 0.14%;0.29%] increase in SBP. Similar effects were detected for DBP and MAP; we observed a 0.17% [95%CI: 0.10%;0.24%] and 0.19% [95%CI: 0.12%;0.26%] increase, respectively.

For PP, we did not observe any significant effects at all.

3.3. Effect modification of temperature effects: Since we observed the strongest temperature effects for lag 0-13, effect modifications were calculated for this cumulative lag (Figure 3), and for comparison for cumulative lag 0-1. Supplement Tables S6-S7 and Figure S8 present the temperature effects (mean temperature and DTR) on SBP, DBP, and MAP by season, sex, WHR, antihypertensive medication, age, and smoking status. Temperature effects on SBP, DBP, and MAP were modified by season. We observed significant effects of mean temperature during summer and winter compared to spring and autumn. For DTR, the interactive effect for winter was significant compared to other seasons. Intake of antihypertensive medication only modified results for DTR, while sex, WHR, age, or smoking did not modify the results.

3.4. Sensitivity analyses: Results of the sensitivity analyses are shown in Figure 4 and the Supplement (Figures S9-S13 and Table S14). Based on the visual inspection of the overall exposure-response functions using smooth terms for air temperature (Figure S9), we concluded that exposure-response functions could be considered linear. However, the linearity assumption is affected by season (Figure 4 and Figure S10), particularly for daily mean temperature. While associations for summer and winter can be considered linear, we detected non-linear exposure-response functions for spring and autumn (Figure 4). The visual inspection of the exposure-response functions according to the different surveys revealed that associations differed for DTR in F4, compared to S4 and FF4 (Figure S12). When we used DLNM to assess the association between temperature and BP, we observed significant effects for all exposure-outcome combinations except lag 0-1 for SBP and MAP (Supplement S13). After selecting the confounder model for SBP, DBP, and MAP, air temperature effects remained nearly unchanged (Table S14). The effects for using apparent temperature instead of air temperature as an exposure variable were not significant anymore. Adjustment for air pollution and inclusion of treatment effects of antihypertensive medication did not change the observed temperature effects.

4. Discussion

This repeated-measures study investigated the association between ambient air temperature or temperature variability and different BP metrics. A decrease in mean air temperature was associated with an increase in SBP, DBP, and MAP, whereas we did not see any significant changes in PP. Regarding temperature variability, we saw increased SBP, DBP, and MAP for a decreasing DTR.

The inverse association between air temperature and SBP or DBP found in our study is consistent with previous studies and has already been reported in detail[12-16]. We observed the inverse associations for all lags with the strongest effects for the 14-day moving average temperature. Whereas most previous studies of acute temperature effects and BP have examined shorter periods of up to 7 days, we provide evidence that the observed effects are even more pronounced when more extended periods of up to 14 days are considered.

Decreasing temperatures activate the sympathetic nervous system, leading to increased heart rates and endothelial-mediated higher vascular resistance, both resulting in increasing BP[27, 28].

As MAP is a predictor for cardiovascular disease in general[29, 30] and is considered a relevant contributor to increasing ischemic stroke risk[31], it is important also to take temperature effects on MAP into account. In a web-based cohort, increasing MAP measurements were found per a decrease in hourly ambient temperature[16]. Similar results were reported in a study with hourly measurements[32]. This association can be explained due to the compound structure of MAP and similar effects of temperature on SBP and DBP.

There are a few studies investigating the influence of temperature variability represented by DTR on cardiovascular mortality[3-7, 33], but little is known about how temperature variability affects BP. A longitudinal study did not find significant associations between DTR and SBP or DBP[17]. A Chinese study showed an increase in SBP and PP for an increasing DTR. However, this study also found an increased DBP for a decreasing DTR[18]. This is only partly consistent with our findings, as we saw a decrease in DTR being associated with an increase in DBP, but also in SBP and MAP. Opposing to our results, a cohort study showed increasing BP measures being associated with an increasing diurnal temperature range of up to 5 days and hourly temperature variation[19]. However, as we have looked at more extended periods of up to 14 days, with the effects being more pronounced at longer time lags, the results might be only partly comparable. Furthermore, as far as we know, this is the first study outside Asia to investigate this association.

Our effects significantly differed when including an interaction term for season in the effect modification analyses. We observed the strongest effects of mean temperature during summer and winter compared to other seasons, while DTR mainly affects BP during winter months. This result is reflected in our exposure-response functions for the different seasons, where we found a linear relationship for mean temperature only during summer and winter. Compared to other studies, Alperovitch et al. found higher BP values during winter when examining outdoor temperature[12], the same applies to a large Chinese study[15], while Halonen et al. did not find differences among seasons[13].

Interestingly, we also found differing exposure-response functions for the three surveys. The negative linear exposure-response function for mean temperature detected during the baseline (S4, 1999-2001) and the first follow-up (F4, 2006-2008) examination is not present during the second follow-up (FF4, 2013-2014). Temporal variations regarding ambient temperature had already been described before for the Augsburg region when examining the effects on myocardial infarction[34]. Due to increasing mean daily temperatures, from 7.0°C during S4 to 11.4°C during FF4, effects for cold temperatures might play a less important role and could explain the altered exposure-response functions.

Anthropogenic climate change is causing a transformation in temperature variability and stability[20]. It is all the more important to improve the understanding of the corresponding adaptation of cardiovascular markers such as BP. Assessments of meteorological data over the past decades have shown a decrease in DTR, mainly due to a substantial increase in the nighttime minimum temperature[35]. A modeling study predicts a similar development for the coming years, but taking into account extensive regional differences in this respect[36]. This is particularly important considering our results that could show increasing BP levels for decreasing DTR. In the light of the inconsistency of results compared to other studies[17-19], and under reconsideration of the temporal variation in the observed exposure-response functions, further research is needed to better understand and characterize how this relates to BP levels.

Rapid but recurring temperature changes affect the body by requiring an adaptive response each time. This leads to increased blood viscosity, an impaired immune system, and higher BP measures[37, 38]. Given that, temperature variability is assumed to be an independent risk factor for increased mortality[5, 6].

A strength of our study is that our data comprised 8,542 observations from 3,184 individuals in a time range of 15 years. Combined with a strong study design that accounted for repeated measures and included different exposure metrics and covariates, our results are supposed to reflect the exposure-response relationship very well. Furthermore, detailed information on participant characteristics was available, enabling appropriate adjustment for potential confounders. Finally, several sensitivity analyses were performed to test the robustness, including additional adjustments for air pollution and the intake of antihypertensive medication.

Several limitations should also be acknowledged. First, we used air temperature data from fixed monitoring sites rather than personal exposure measurements, which can cause exposure measurement errors. This non-differential error likely biases the estimates downward[39]. Second, this study was performed in a temperate climate; therefore, the results may not be relevant to other populations living in different climatic conditions.

5. Conclusions

Although temperature effects on BP are well known, there has been little information concerning the effects of temperature variability. The present repeated-measures study found that BP metrics were associated with decreasing DTR. As this is the first study to examine this association outside Asia, it provides new evidence on the topic. The same applies to the so far rarely examined temperature effects on MAP. As our study investigates longer time periods of up to 14 days, the results indicate that acute effects of ambient temperature on BP last for a prolonged time - a fact that plays an important role, especially regarding preventive measures.

In the course of climate change, temperature variability is becoming increasingly important. In particular, the body’s adaptive mechanisms need to be better understood. As far as BP is concerned, our study makes an important contribution to this issue.

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Disclosures

None declared

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Table 1: Characteristics of the study population

	Overall Total observations = 8,542	**S4** Participants n = 3,184	**F4** Participants n = 3,079	**FF4** Participants n = 2,279
	Mean *(SD)*	**Mean *(SD)***	**Mean *(SD)***	**Mean *(SD)***
SBP	123.3 *(18.7)*	127.5 *(18.6)*	122.2 *(18.6)*	118.9 *(17.7)*
DBP	76.4 *(10.4)*	80.2 *(10.4)*	75.1 *(10.0)*	72.8 *(9.8)*
PP	71.8 *(10.3)*	72.2 *(10.1)*	72.1 *(10.3)*	70.8 *(10.4)*
MAP	92.0 *(12.4)*	96.0 *(12.3)*	90.8 *(12.0)*	88.2 *(11.5)*
Age	54.5 *(13.8)*	48.8 *(13.3)*	56.1 *(13.2)*	60.3 *(12.3)*
WHR	0.88 *(0.1)*	0.86 *(0.1)*	0.88 *(0.1)*	0.91 *(0.1)*
	n *(%)*	**n *(%)***	**n *(%)***	**n *(%)***
Season				
Winter	2,436 *(28.5)*	989 *(31.1)*	1,010 *(32.8)*	437 *(19.2)*
Spring	1,947 *(22.8)*	673 *(21.1)*	677 *(22.0)*	597 *(26.2)*
Summer	1,569 *(18.4)*	432 *(13.6)*	425 *(13.8)*	712 *(31.2)*
Autumn	2,590 *(30.3)*	1,090 *(34.2)*	967 *(31.4)*	533 *(23.4)*
Sex				
Female	4,424 *(51.8)*	1,654 *(52)*	1,593 *(51.8)*	1,177 *(51.7)*
Male	4,118 *(48.2)*	1,530 *(48)*	1,486 *(48.2)*	1,102 *(48.3)*
Diseases				
Myocardial Infarction	237 *(2.8)*	59 *(1.9)*	99 *(3.2)*	79 *(3.5)*
Stroke	160 *(1.9)*	33 *(1.0)*	64 *(2.1)*	63 *(2.8)*
Medication				
Antihypertensive Medication	2,277 *(26.7)*	523 *(16.4)*	948 *(30.8)*	806 *(35.4)*
Smoking habits				
Regular	1,420 *(16.6)*	639 *(20.1)*	472 *(15.3)*	309 *(13.6)*
Irregular	230 *(2.7)*	108 *(3.4)*	79 *(2.6)*	43 *(1.9)*
Former	3,082 *(36.1)*	1,035 *(32.5)*	1,164 *(37.8)*	883 *(38.8)*
Never	3,807 *(44.6)*	1,402 *(44.0)*	1,361 *(44.3)*	1,044 *(45.8)*
Physical activity				
Very active	2,002 *(23.4)*	660 *(20.7)*	746 *(24.3)*	596 *(26.2)*
Moderate active	2,585 *(30.3)*	952 *(30.0)*	924 *(30.0)*	709 *(31.1)*
Little active	1,303 *(15.3)*	569 *(17.9)*	404 *(13.1)*	330 *(14.5)*
Non-active	2,644 *(31.0)*	998 *(31.4)*	1,002 *(32.6)*	644 *(28.2)*
Socioeconomic Status				
High	1,666 *(19.5)*	616 *(19.4)*	674 *(22.0)*	376 *(16.6)*
Medium-high	1,548 *(18.2)*	556 *(17.5)*	603 *(19.6)*	389 *(17.1)*
Medium	1,983 *(23.3)*	737 *(23.2)*	705 *(23.0)*	541 *(23.8)*
Medium-low	1,761 *(20.7)*	674 *(21.2)*	596 *(19.4)*	491 *(21.6)*
Low	1,560 *(18.3)*	595 *(18.7)*	491 *(16.0)*	474 *(20.9)*

Table 1: SD: standard deviation; SBP: systolic blood pressure in mmHg; DBP: diastolic blood pressure in mmHg; PP: pulse pressure in mmHg; MAP: mean arterial pressure in mmHg; Age in years. WHR: Waist-

to-hip Ratio; Winter: 22. December - 21. March; Spring: 22. March - 21. June; Summer: 22. June - 21. September; Autumn: 22. September - 21. December.

Table 2: Summary statistics and Spearman Rank Correlation Coefficients of daily means of meteorological variables and air pollutants during the three study periods

	Summary Statistics			Spearman Correlation								
	Mean *(SD)*	**Min - Max**	**IQR**	**Min temp**	**Max temp**	**DTR**	**Bar. Press**	**RH**	**$PM_{2.5}$**	**O_3**	**NO_2**	**UFP**
Temp	8.5 *(6.7)*	-15.3 – 26.0	10.2	0.92	0.96	0.51	-0.26	-0.47	-0.26	0.64	-0.24	0.19
Min temp	3.7 *(5.9)*	-20.4 - 17.9	8.4	1	0.81	0.17	-0.28	-0.28	-0.37	0.47	-0.42	0.22
Max temp	13.3 *(8.1)*	-8.6 - 36.9	11.8		1	0.69	-0.22	-0.55	-0.14	0.68	-0.06	0.15
DTR	9.6 *(4.7)*	0.9 – 22.5	7.2			1	-0.04	-0.63	0.20	0.59	0.40	-0.01
Bar. Press	1016 *(8.6)*	989 - 1043	10.9				1	0.05	0.32	-0.21	0.21	-0.15
RH	81.0 *(10.4)*	37.0 - 100.0	14.9					1	0.13	-0.75	0.04	-0.14
$PM_{2.5}$	12.6 *(9.8)*	1.0 - 65.0	12.0						1	-0.18	0.71	-0.16
O_3	60.3 *(32.2)*	2.4 - 176.9	45.7							1	-0.15	0.19
NO_2	31.1 *(11.5)*	10.0 - 77.0	16.0								1	-0.15
UFP	45.2 *(26.0)*	10.0 - 99.0	47.0									1

Table 2: SD: standard deviation; Min: minimum; Max: maximum; IQR: interquartile range; Temp, T: air temperature (°C); Min temp: minimum air temperature (°C); Max temp: maximum air temperature (°C); DTR: diurnal temperature range (°C); Inter temp: Interday temperature difference (°C); Bar. Press: barometric pressure (hPa); RH: relative humidity (%); Air pollution data for the years 2006-2008 and 2013-2014: $PM_{2.5}$: particulate matter with an aerodynamic diameter ≤ 2.5 μm (μg/m^3); O_3: ozone (μg/m^3); NO_2: nitrogen dioxide (μg/m^3); UFP: ultrafine particles (n/cm^3);

Figure 1. Percent change and confidence intervals in mean SBP, DBP, MAP and PP per 1° C decrease in mean ambient temperature.

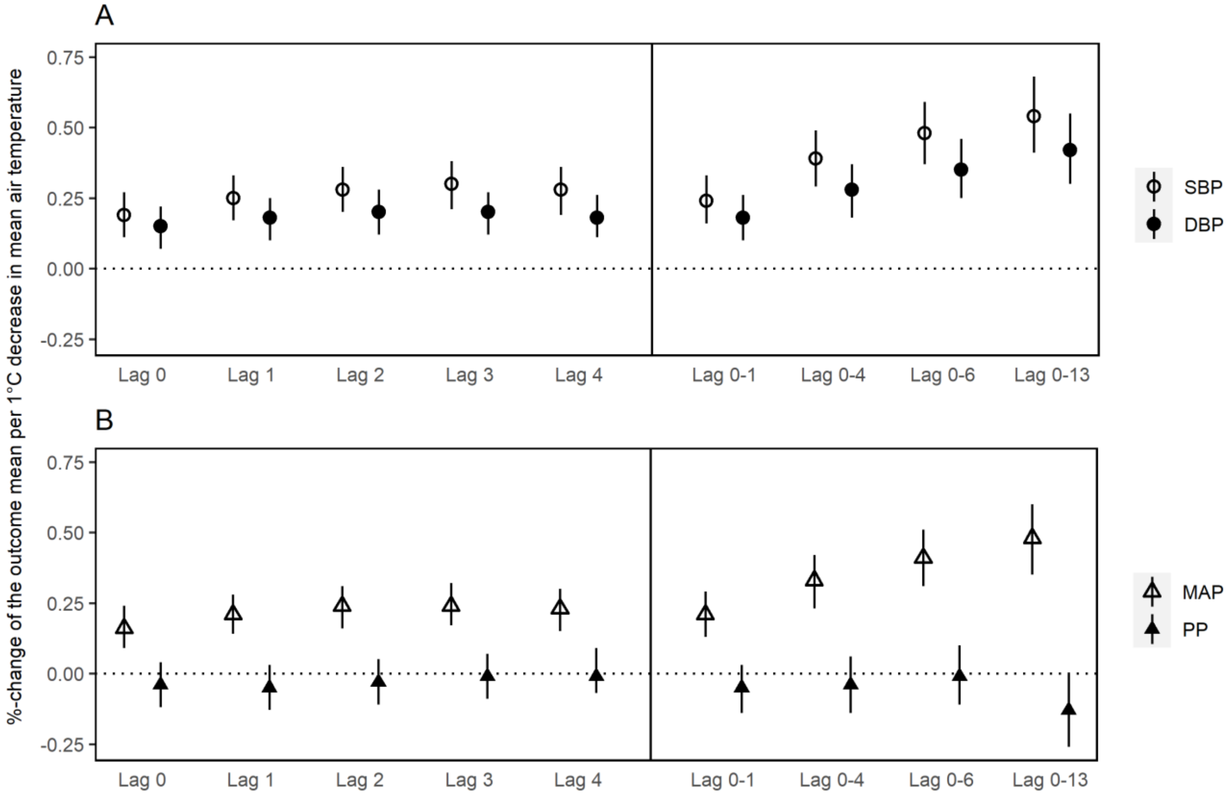

Fig. 1. Percent change and 95% confidence intervals in (A) systolic blood pressure (SBP), diastolic blood pressure (DBP), (B) mean arterial pressure (MAP) and pulse pressure (PP) associated with a 1°C decrease in mean ambient air temperature.

All models were adjusted for season, time trend, day of the week, relative humidity with the same lag as temperature, barometric pressure with the same lag as temperature, age, sex, waist-to-hip ratio, physical activity, smoking status, alcohol consumption, socioeconomic status, use of antihypertensive medication, and use of statins.

Figure 2. Percent change and confidence intervals in mean SBP, DBP, MAP and PP per 1° C decrease in DTR.

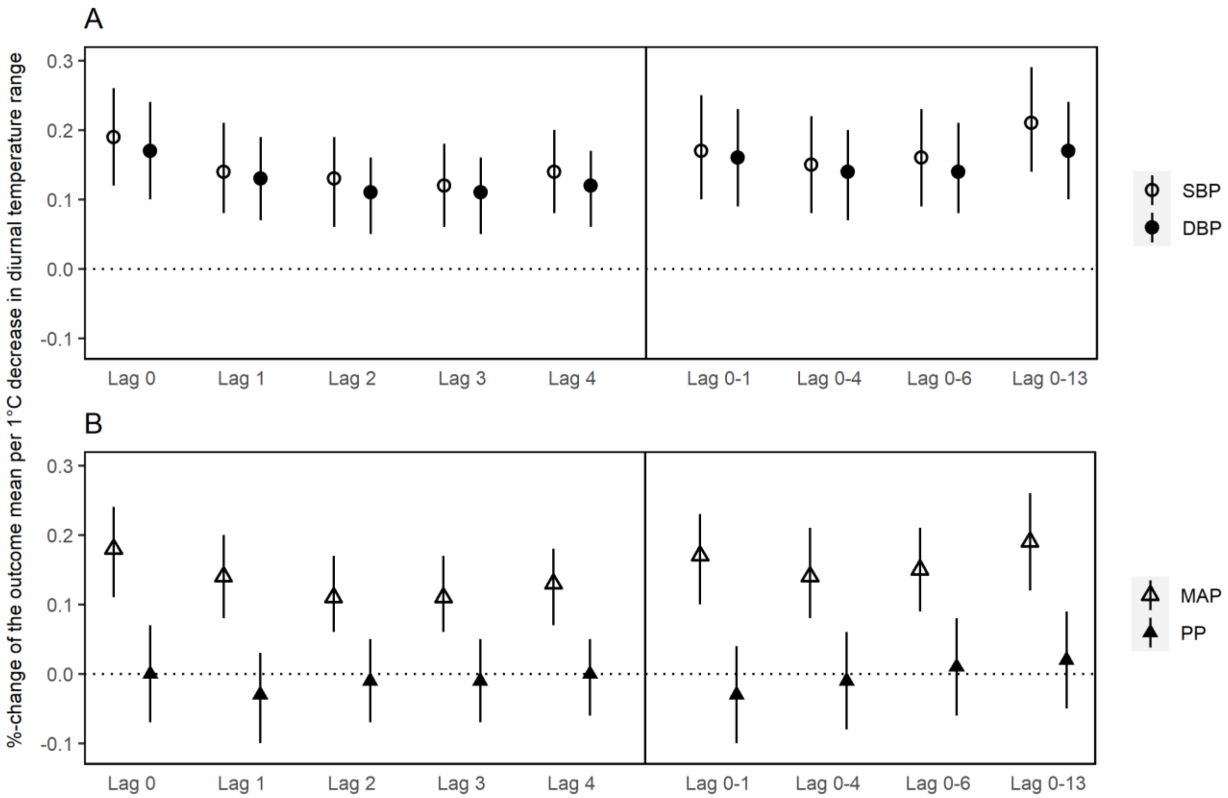

Fig. 2. Percent change and 95% confidence intervals in (A) systolic blood pressure (SBP), diastolic blood pressure (DBP), (B) mean arterial pressure (MAP) and pulse pressure (PP) associated with a 1°C decrease in mean DTR.

All models were adjusted for season, time trend, day of the week, relative humidity with the same lag as temperature, barometric pressure with the same lag as temperature, age, sex, waist-to-hip ratio, physical activity, smoking status, alcohol consumption, socioeconomic status, use of antihypertensive medication, and use of statins.

Figure 3. Percent change and confidence intervals in mean SBP, DBP and MAP per 1° C decrease in mean ambient temperature, stratified by season, sex, waist-to-hip ratio, intake of anti-hypertensive medication, age and smoking.

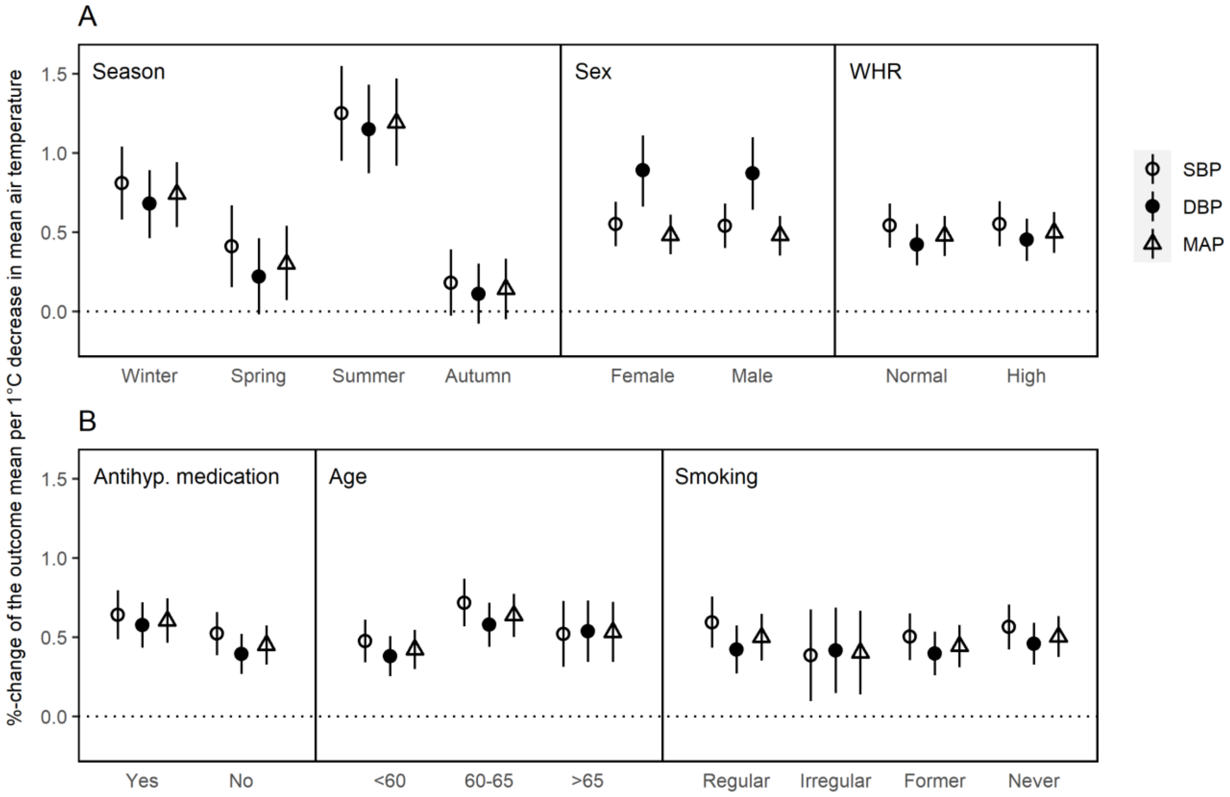

Fig. 3. Percent change and 95% confidence intervals in in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP), associated with a 1°C decrease in mean ambient air temperature in cumulative lag 0-13, taking the following effect modifiers into account: season (winter (22. December - 21. March) vs. spring (22. March - 21. June) vs. summer (22. June - 21. September) vs. autumn (22. September - 21. December)), sex (female vs. male), waist-to-hip ratio WHR (females: normal <1 vs. high ≥1; males: normal <0.85 vs. high ≥0.85), antihypertensive medication intake (yes vs. no), age (<60 years vs. 60-74 years vs. >74 years), smoking status (regular vs. irregular vs. former vs. never).
All models were adjusted for season, time trend, day of the week, relative humidity with the same lag as temperature, barometric pressure with the same lag as temperature, age, sex, waist-to-hip ratio, physical activity, smoking status, alcohol consumption, socioeconomic status, use of antihypertensive medication, and use of statins. The respective effect modifier was excluded from adjustment.

Figure 4. Exposure-response functions for the association between mean ambient temperature and SBP, DBP and MAP for different seasons.

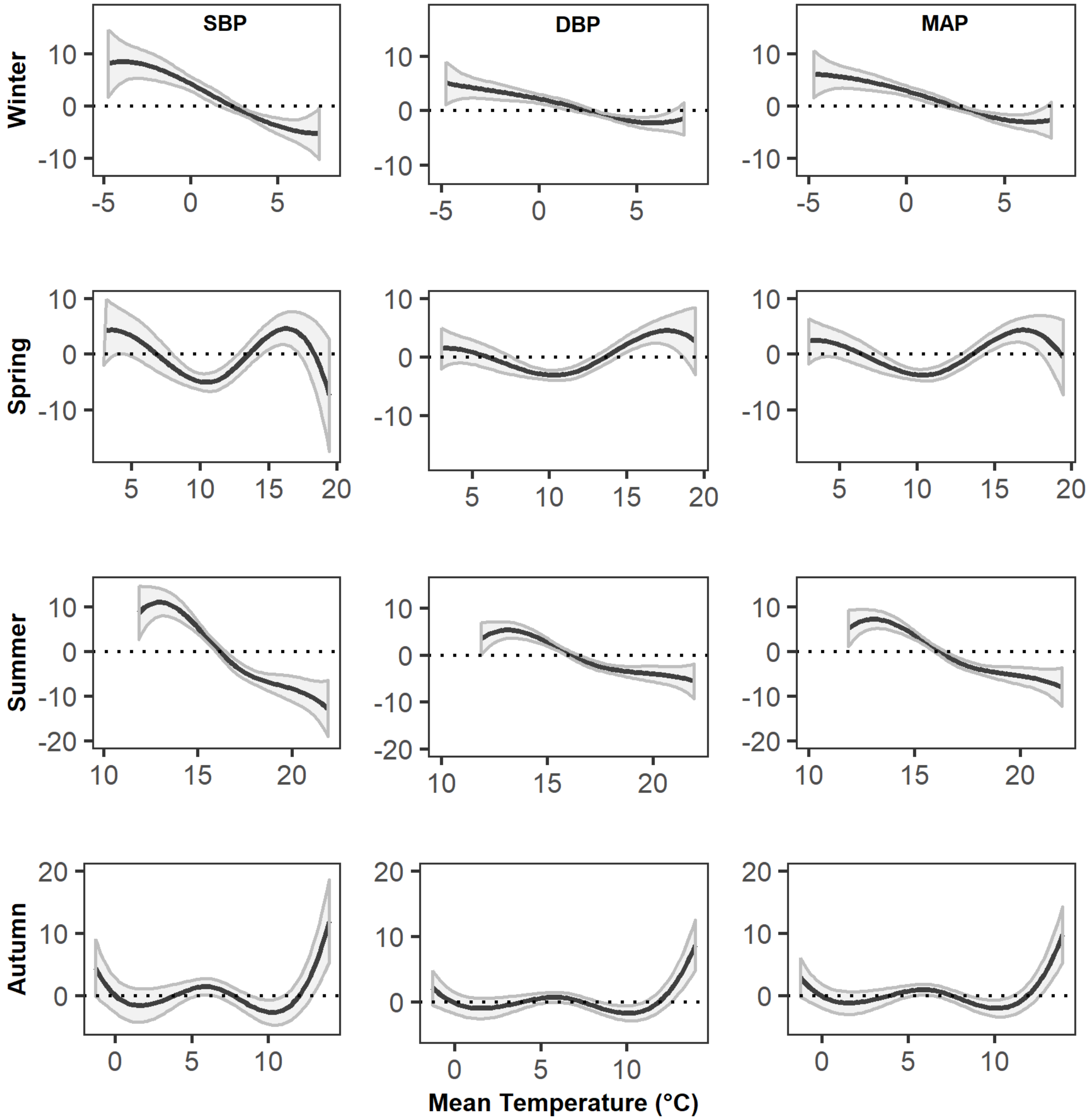

Fig. 4. Exposure-response functions for the association between daily mean temperature in cumulative lag 0-13 with 95% confidence intervals, and changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) on the y-axis, by different seasons. Daily mean temperature (Lag 0-13) was included as penalized spline with 6 degrees of freedom.

All models were adjusted for time trend, day of the week, relative humidity with the same lag as temperature, barometric pressure with the same lag as temperature, age, sex, waist-to-hip ratio, physical activity, smoking status, alcohol consumption, socioeconomic status, use of antihypertensive medication, and use of statins.

Declaration of interests

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

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Authorship Contribution Statement

M.W. Conceptualization, Methodology, Formal Analysis, Validation, Investigation, Writing – Original Draft, Visualization. A.S. Conceptualization, Methodology, Validation, Resources, Writing – Review & Editing, Supervision, Project administration. J.C. Resources, Data Curation, Writing – Review & Editing. K.W. Conceptualization, Resources, Data Curation, Writing – Review & Editing. C. M. Resources, Data Curation, Writing – Review & Editing. M. H. Resources, Data Curation, Writing – Review & Editing. A. P. Conceptualization, Methodology, Resources, Writing – Review & Editing, Supervision. S. B. Conceptualization, Methodology, Formal Analysis, Validation, Investigation, Writing – Original Draft, Writing – Review & Editing, Supervision, Project administration.