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Associations between medium- and long-term exposure to air temperature and epigenetic age acceleration

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ABSTRACT

Climate change poses a serious threat to human health worldwide, while aging populations increase. However, no study has ever investigated the effects of air temperature on epigenetic age acceleration. This study involved 1,725 and 1,877 participants from the population-based KORA F4 (2006–2008) and follow-up FF4 (2013–2014) studies, respectively, conducted in Augsburg, Germany. The difference between epigenetic age and chronological age was referred to as epigenetic age acceleration and reflected by Horvath's epigenetic age acceleration (HorvathAA), Hannum's epigenetic age acceleration (HannumAA), PhenoAge acceleration (PhenoAA), GrimAge acceleration (GrimAA), and Epigenetic Skin and Blood Age acceleration (SkinBloodAA). Daily air temperature was estimated using hybrid spatiotemporal regression-based models. To explore the medium- and long-term effects of air temperature modeled in time and space on epigenetic age acceleration, we applied generalized estimating equations (GEE) with distributed lag non-linear models, and GEE, respectively. We found that high temperature exposure based on the 8-week moving average air temperature (97.5th percentile of temperature compared to median temperature) was associated with increased HorvathAA, HannumAA, GrimAA, and SkinBloodAA: 1.83 (95% CI: 0.29–3.37), 11.71 (95% CI: 8.91–14.50), 2.26 (95% CI: 1.03–3.50), and 5.02 (95% CI: 3.42–6.63) years, respectively. Additionally, we found consistent results with high temperature exposure based on the 4-week moving average air temperature was associated with increased HannumAA, GrimAA, and SkinBloodAA: 9.18 (95% CI: 6.60–11.76), 1.78 (95% CI: 0.66–2.90), and 4.07 (95% CI: 2.56–5.57) years, respectively. For the spatial variation in annual average temperature, a 1 °C increase was associated with an increase in all five measures of epigenetic age acceleration (HorvathAA: 0.41 [95% CI: 0.24–0.57], HannumAA: 2.24 [95% CI: 1.95–2.53], PhenoAA: 0.32 [95% CI: 0.05–0.60], GrimAA: 0.24 [95%: 0.11–0.37], and SkinBloodAA: 1.17 [95% CI: 1.00–1.35] years). In conclusion, our results provide first evidence that medium- and long-term exposures to high air temperature affect increases in epigenetic age acceleration.

1. Introduction

Climate change poses a serious threat to human health worldwide. There is accumulating evidence that higher air temperatures are associated with increased risks for many diseases, especially age-related disease (Chen et al., 2018; Khraishah et al., 2022). The 2021 report of the Lancet Countdown on health and climate change showed that compared to the annual averages of the 1986–2005 baseline, the record temperatures in 2020 were related to a new high of 3.1 billion more person-days of heatwave exposure among people older than 65 years

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(Romanello et al., 2021). A global study found that 37.0% (global range from 20.5% to 76.3%) of warm-season heat-related deaths can be attributed to man-made climate change from 1991 to 2018 based on data from 732 locations in 43 different countries (Vicedo-Cabrera et al., 2021). Furthermore, exposure to high temperature can lead to physiologic dysfunction across some pathways, which possibly includes ageing ones, e.g. cholesterol (Madaniyazi et al., 2020); although this has not been extensively explored.

A further aspect to consider is that the average age of the population is increasing globally. The world's population aged 60 years and more is estimated to increase to more than 2 billion by 2050 (Chatterji et al., 2015); which brings unprecedented challenges. Therefore, a better understanding of the effects of non-optimal environmental conditions on aging is crucial (Peters et al., 2021). Epigenetic age predictors, also defined as epigenetic clocks or DNA methylation ages, are emerging robust biomarkers of biological aging and have been suggested as novel DNA methylation-based biomarkers for the aging process in humans (Simpson and Chandra, 2021). Epigenetic age predictors are based on methylation levels of genome-wide selected CpG sites and are coupled with regression models to compute an estimate of biological age (Noroozi et al., 2021). There are two generations of epigenetic age predictors. The first-generation clocks, Horvath's epigenetic age and Hannum's epigenetic age, were developed to predict chronological age in 2013 and are the most widely used clocks (Horvath, 2013; Hannum et al., 2013). The next-generation clocks, which evolved to combine aging-related features (physiological or cellular aging) to define composite epigenetic age metrics, including PhenoAge and GrimAge, were subsequently developed to better capture changes in biological aging, and predict lifespan and healthspan (Levine et al., 2018; Lu et al., 2019). Furthermore, Horvath et al. developed another novel epigenetic age predictor, the Epigenetic Skin and Blood Age, which has been shown to provide more accurate estimates of chronological age when applied to blood-derived samples compared to the original Horvath' and Hannum' epigenetic age predictors (Horvath et al., 2018).

Epigenetic age acceleration is defined as the discrepancy between DNA methylation-based biological age and chronological age. A positive epigenetic age acceleration value indicates accelerated epigenetic aging, while a negative value of epigenetic age acceleration indicates decelerated epigenetic aging (Noroozi et al., 2021). Epigenetic age acceleration has been associated with increased risks of chronic diseases, such cardiovascular disease, diabetes, and mortality (Wang et al., 2021; Perna et al., 2016; Simpson and Chandra, 2021; Oblak et al., 2021). Previous studies have shown that epigenetic age acceleration is influenced by lifestyle and environmental factors (Oblak et al., 2021); including tobacco smoking (Wu et al., 2019); and air pollution (Ward-Caviness et al., 2020). These suggest that epigenetic age acceleration may capture perturbations in biological processes triggered by environmental exposures, which can then lead to adverse health outcomes. So far, no study has yet investigated the effects of air temperature on epigenetic age acceleration.

Therefore, the goal of this population-based study was to investigate the impact of medium- and long-term air temperature exposure (temporal-spatial variation of 4-week and 8-week averages of air temperature and the spatial variation of annual average air temperature) on epigenetic age acceleration using a longitudinal study design. The 4-week and 8-week exposure windows allow for the examination of temperature exposures over a period of several weeks, which aligns with the timescales of physiological and biological responses to changing temperature conditions. By focusing on these medium-term exposures, we aimed to investigate the delayed responses and adaptation mechanisms of individuals to shifting temperature patterns, which are often manifested over weeks rather than days or years. Moreover, the annual average temperature provides a representative measure of the long-term climatic conditions experienced by individuals. This enables us to assess the sustained exposure to temperature over an extended period, which may have a more pronounced impact on human health and aging processes. Importantly, it also captures sustained changes in temperature associated with climate change over time.

2. Materials and methods

2.1. Study population

This study was based on data from the Cooperative Health Research in the Region of Augsburg (KORA) studies F4 (2006–2008) and FF4 (2013–2014). Both studies were follow-up examinations of the population-based KORA S4 study (1999–2001) conducted in the city of Augsburg, Southern Germany, and two adjacent counties (Holle et al., 2005). Participants underwent physical examinations and standardized interviews assessing sociodemographic characteristics and medical history. Detailed information on the KORA cohort design, measurement, and data collection have been described elsewhere (Holle et al., 2005; Rathmann et al., 2009; Wawro et al., 2020). The present study included 1,725 participants from KORA F4 and 1,877 participants from KORA FF4, who underwent genome-wide DNA methylation measurements using the Illumina 450 K Infinium Methylation BeadChip for KORA F4 and Infinium MethylationEPIC BeadChip for KORA FF4.

The study was approved by the ethics board of the Bavarian Chamber of Physicians (Munich, Germany) in adherence to the declaration of Helsinki. All participants gave written informed consent.

2.2. Exposure assessment

High-resolution (1 × 1 km) daily mean air temperature data were derived for the whole country of Germany using hybrid spatiotemporal regression-based models (Young Virtual Conference and Basel, 2021). These included satellite-based land surface temperature data, ground-based air temperature measurements, and spatial predictors datasets. Three-stage models were trained to achieve air temperature predictions with comprehensive temporal and spatial coverage. The satellite-derived land surface temperature and spatial predictors were modeled as linear mixed effects models with daily random intercepts and slopes using the combinations of days and grid cells where air temperature measurements and satellite-derived land surface temperature were available. A second stage was carried out using the first-stage model to predict air temperature for grid cells with no air temperature measurements but with available satellite-derived land surface temperature data. In cases where neither satellite-derived land surface temperature data nor air temperature measurements were available, the second stage air temperature predictions were regressed against thin-plate spline interpolated air temperature values to achieve full air temperature coverage in the country. The prediction accuracy of our models was quantified using internal and external 10-fold cross-validation. All models performed well ($0.91 \leq R^2 \leq 0.98$), and all models had low errors (1 °C < Root Mean Square Error < 2 °C). In this study, the residential address of each participant was effectively linked to the nearest exposure grid centroid, facilitating the integration of individual participant data with daily exposure data characterized by high spatial resolution (1 × 1 km). This linkage was established through the utilization of pseudonymized participant IDs and exposure grid IDs, thereby ensuring privacy and confidentiality.

We measured the daily concentrations of relative humidity (RH), ozone (O_3), particulate matter with an aerodynamic diameter of ≤ 2.5 μm ($PM_{2.5}$) and nitrogen dioxide (NO_2) by fixed monitoring sites in Augsburg, Germany (Wolf et al., 2015; Chen et al., 2019). RH and O_3 were measured at the official urban background monitoring site located approximately 5 km south of the city center. $PM_{2.5}$ and NO_2 were measured at an urban background monitoring site located approximately 1 km south of the city center, and approximately 2 km north of the city center, respectively. Annual average concentrations of O_3, $PM_{2.5}$ and NO_2 were estimated using land-use regression (LUR) models (Wolf et al., 2017). Briefly, three 2-week measurement campaigns were

conducted at 20 locations in the KORA study area between March 6, 2014, and April 7, 2015. These measurements were taken at each location during the warm, cold, and intermediate seasons. LUR models were then developed by regressing the annual average concentrations measurement at monitoring sites against spatial predictors derived from geographic information systems. Based on the fitted models, we calculated the level of residential exposure for KORA study participants.

2.3. Epigenetic age acceleration

We uploaded normalized DNA methylation data to the online New DNA Methylation Age Calculator (https://dnamage.genetics.ucla.edu/new) according to the recommended guidelines to estimate epigenetic age. Horvath's epigenetic age and Hannum's epigenetic age were calculated using 353 age-related CpGs and 71 age-related CpGs, respectively (Horvath, 2013; Hannum et al., 2013). PhenoAge was developed using 513 phenotypic age-related CpGs; which were DNA methylation surrogate of nine clinical biomarker (alkaline phosphatase, albumin, C-reactive protein, red cell distribution width, creatinine, lymphocyte percent, glucose, mean cell volume, and white blood cell count) (Levine et al., 2018). GrimAge was developed as a function of mortality risk by combining chronological age, sex, and 1030 unique CpGs sites, which were DNA methylation surrogate of cigarette pack-years and DNA methylation surrogates for seven plasma protein markers (growth differentiation factor-15, adrenomedullin, plasminogen activator inhibitor-1, cystatin C, leptin, beta-2-microglobulin, and tissue inhibitor metalloproteinases 1) (Lu et al., 2019). Epigenetic Skin and Blood Age was developed using 391 age-related CpGs (Horvath et al., 2018). In this study, differences between these epigenetic age biomarkers and chronological age (epigenetic age – chronological age) were referred to as epigenetic age acceleration. Therefore, we obtained five epigenetic age acceleration biomarkers: Horvath's epigenetic age acceleration (HorvathAA), Hannum's epigenetic age acceleration (HannumAA), PhenoAge acceleration (PhenoAA), GrimAge acceleration (GrimAA), and Epigenetic Skin and Blood Age acceleration (SkinBloodAA). Details of measures of genome-wide DNA methylation are given in Supplementary material.

2.4. Statistical analysis

We reported the characteristics of participants as mean and standard deviation (SD) for continuous variables and frequencies and percentages for categorical variables.

We applied generalized estimating equations (GEE) with distributed lag non-linear models (DLNMs) (Gasparrini et al., 2010) and GEE to explore the medium- and long-term effects of air temperature on repeatedly assessed epigenetic age acceleration, respectively. In our analysis, we used all available measures of epigenetic age accelerations, including both repeated and non-repeated measures from the KORA F4 and FF4 cohorts, to maximize statistical power. Repeated measures allow for within-person comparisons over time, while non-repeated measures provide additional data points. To calculate the medium-term exposures to air temperature, we used 4-week and 8-week moving averages of daily air temperature before the blood draw. Moreover, as a surrogate for long-term exposure to air temperature, we used the 365-day moving average of daily air temperature (annual average temperature) before the blood draw. First, we conducted generalized additive mixed models with a spline (four degrees of freedom) to assess deviations of the temperature-response relationship from linearity (supplementary, Figure S1). As there were no significant deviations from linearity for annual average temperature on all markers, the annual average temperature was included linearly in the GEE for these outcomes, and effects were estimated as a 1 °C increase in annual average temperature. However, there were non-linear exposure–response functions of 4-week and 8-week moving averages of temperature and epigenetic age acceleration markers, except for PhenoAA. To make the results more comparable between epigenetic age acceleration biomarkers, we included the medium-term exposure parameters non-linearly in the GEE with DLNMs. For these non-linear models (GEE with DLNMs), a natural cubic spline for the exposure–response function with internal knots (30th and 70th percentile of temperature) was selected. In addition, the median temperature value (9.7 °C) was selected as the reference value. We calculated the high temperature effect as the 97.5th percentile of air temperature distribution (18.5 °C and 18.3 °C for 4-week and 8-week moving averages of temperature, respectively) relative to the median temperature, and the low temperature effect as the 2.5th percentile of air temperature distribution (1.5 °C and 1.4 °C for 4-week and 8-week moving averages of temperature, respectively) relative to the median temperature.

All models were adjusted for *a priori* selected covariates according to previous literature (Kresovich et al., 2021; Zhao et al., ; Oblak et al., 2021) and our own experience: chronological age (years), sex (male, female), education (years), body mass index (BMI, kg/m^2), alcohol consumption (g/day), smoking status (never, former, current), physical activity (low: no exercise at all; medium: occasionally or regularly approximately one hour per week; high: at least two hours per week regularly), season of blood draw (warm: April-September vs. cold: October-March), estimated cell types (monocytes, B Cells, CD4 T cells, CD8 T cells, and natural killer cells). Additionally, to account for potential technical effect, we adjusted for the chip as a covariate in all models. For medium-term temperature effects, we additionally adjusted for day of the week, time trend (natural cubic spline with five degrees of freedom per year), and relative humidity (with the same lag period as the air temperature).

We included an interaction term between air temperature and potential effect modifier in the effect modification analysis. The examined modifiers included sex (male vs. female), obesity (BMI < 30 kg/m^2 vs. ≥ 30 kg/m^2), cardiovascular disease (defined as a history of hypertension, myocardial infarction, angina pectoris, or stroke [yes vs. no]), diabetes (yes vs. no), and areas (urban vs. rural).

We performed several sensitivity analyses to assess the robustness of our results. First, to control for potential confounding from air pollution, we additionally adjusted for O_3, $PM_{2.5}$, and NO_2, separately. Second, we excluded participants who moved throughout the study period to reduce exposure misclassification. Third, instead of epigenetic age acceleration, we used epigenetic age and the residuals computed by linearly regressing chronological age on epigenetic age to explore the air temperature effects. Fourth, we excluded values that deviated beyond 1.5 times the interquartile range from either the lower quartile or the upper quartile to avoid the effects of extreme outliers of outcomes. Fifth, we included only participants with repeated measurements of epigenetic age acceleration (985 participants with 1,970 observations) in the analysis. Sixth, to avoid overestimation, for non-linear exposure–response functions (medium-term effects), the effects were estimated for high temperature as 97.5th percentile of air temperature distribution compared to the 75th percentile (14.5 °C and 14.3 °C for 4-week and 8-week moving averages of temperature, respectively) and for low temperature as 2.5th percentile of air temperature distribution compared to the 25th percentile (4.1 °C and 4.2 °C for 4-week and 8-week moving averages of temperature, respectively). Seventh, we incorporated season into the model as a four-factor category consisting of spring (March - May), summer (June - August), fall (September - November), and winter (December - February), rather than treating season as a dichotomous variable. Finally, 4- and 8-week moving averages of temperature were included as a linear term in the GEE model for PhenoAA.

For the long-term effects (linear associations), we quantified the effect estimates as the change in epigenetic age acceleration per 1 °C increase in air temperature with corresponding 95% confidence intervals (CIs). For the medium-term effects (non-linear associations), the effect estimates indicate changes in epigenetic age acceleration per increase or decrease in air temperature from the median to the 97.5th and 2.5th percentiles, respectively, with 95% (CIs). Additionally, to facilitate

comparisons of the effects across different epigenetic age acceleration markers, we expressed the effect estimates as percent changes relative to the standard deviation (SD). The multiple tests were adjusted using Benjamin-Hochberg false discovery rate (FDR) methods, and adjusted $p < 0.05$ was considered for the significance. All statistical analyses were done with R (version 4.1.2).

3. Results

3.1. Study population, epigenetic age acceleration, and exposure data

There were 3,602 observations from 2,617 participants of KORA F4 (1,725) and FF4 (1,877) included in this analysis. Of these 2,617 participants, 985 (37.6%) completed two examinations. Table 1 presents the characteristics of the study population in KORA F4 and KORA FF4. The mean chronological age was 61.0 years in KORA F4 and 58.6 years in KORA FF4. The mean BMI in KORA F4 and FF4 was 28.1 kg/m^2 and 27.8 kg/m^2, respectively. 48.9% and 47.7% of the participants were male in KORA F4 and FF4, respectively. Of the participants, 31.4% and 27.2% had low physical activity in KORA F4 and FF4, respectively.

The levels of epigenetic age acceleration are presented in Table 2. The mean was −2.3 years, 0.6 years, −9.7 years, −0.2 years, and −2.7 years for HorvathAA, HannumAA, PhenoAA, GrimAA, SkinBloodAA, respectively. There were weak correlations between epigenetic age acceleration biomarkers (r: 0.34–0.44), except for HannumAA and SkinBloodAA (r = 0.81). The levels of epigenetic age acceleration at each examination are presented in Supplementary Table S1.

Table 3 shows the distributions of meteorological variables and air pollutants. The mean of the 4-week moving average temperature was 9.4 °C, the 8-week moving average temperature was 9.5 °C, and the annual average temperature was 9.3 °C for all 3,602 observations. The distributions of meteorological variables and air pollutants at each examination are presented in Supplementary Table S2.

Table 1
Descriptive statistics of participant characteristics and epigenetic age acceleration at each examination.

	KORA F4 (n = 1,725)	KORA FF4 (n = 1,877)
Chronological age (years)	61.0 (8.9)	58.6 (11.6)
Sex (male)	843 (48.9%)	895 (47.7%)
Body mass index (kg/m^2)	28.1 (4.78)	27.8 (5.12)
Education (years)	11.5 (2.64)	12.0 (2.66)
Smoking status		
Never	721 (41.8%)	770 (41.0%)
Former smoker	754 (43.7%)	796 (42.4%)
Current smoker	248 (14.4%)	311 (16.6%)
Physical activity		
Low	542 (31.4%)	511 (27.2%)
Medium	736 (42.7%)	863 (46.0%)
High	445 (25.8%)	503 (26.8%)
Alcohol consumption (g/day)	15.5 (20.5)	14.6 (19.4)
History of diseases		
Cardiovascular diseases (yes)	814 (47.2%)	701 (37.3%)
Diabetes (yes)	158 (9.2%)	162 (8.6%)
Season		
Cold	1147 (66.5%)	785 (41.8%)
Warm	578 (33.5%)	1092 (58.2%)
Areas		
Urban	763 (44.2%)	734 (39.1%)
Rural	959 (55.6%)	1139 (60.7%)
Estimated cell types, %		
CD8 + T lymphocytes	5.9 (6.3)	5.0 (3.8)
CD4 + T lymphocytes	16.3 (6.7)	18.6 (5.9)
Natural killer cells	4.3 (3.1)	6.5 (3.8)
B cells	5.0 (3.0)	5.4 (3.0)
Monocytes	14 (2.8)	7.0 (2.2)

Note: Data are reported as mean (SD) or n (%). *KORA*: Cooperative Health Research in the Region of Augsburg. *F4*: first follow-up examination of KORA S4. *FF4*: second follow-up examination of KORA S4.

3.2. Effects of air temperature on epigenetic age acceleration

We found significant medium-term effects of high temperature for the 4-week (Fig. 1. A) and the 8-week moving average of air temperature (Fig. 1. B) on HorvathAA, HannumAA, GrimAA, and SkinBloodAA. For an increment in the 4-week moving average air temperature from the median (9.7 °C) to the 97.5th percentile (18.5 °C, high temperature exposure), HannumAA, GrimAA, and SkinBloodAA significantly increased by 9.18 (95% CI: 6.60–11.76), 1.78 (95% CI: 0.66–2.90), and 4.07 (95% CI: 2.56–5.57) years, respectively. HorvathAA showed a borderline significant association (1.36 years, 95% CI: −0.005–2.73). In addition, for an increment in the 8-week moving average air temperature from the median (9.7 °C) to the 97.5th percentile (18.3 °C, high temperature exposure), HorvathAA, HannumAA, GrimAA, and SkinBloodAA significantly increased by 1.83 (95% CI: 0.29–3.37), 11.71 (95% CI: 8.91–14.50), 2.26 (95% CI: 1.03–3.50), and 5.02 (95% CI: 3.42–6.63) years, respectively. No significant effects were found for low temperature for the 4-week or 8-week moving averages.

Regarding the long-term effects of annual average temperature (Fig. 2), we found a 1 °C increase in annual average temperature to be significantly associated with an increase in HorvathAA, HannumAA, PhenoAA, GrimAA, and SkinBloodAA (0.41 [95% CI: 0.24–0.57], 2.24 [95% CI: 1.95–2.53], 0.32 [95% CI: 0.05–0.60], 0.24 [95% CI: 0.11–0.37], and 1.17 [95% CI: 1.00–1.35] years, respectively).

Furthermore, effect estimates expressed as percent changes of the SD of outcomes with 95% CIs are shown in Figure S2 (Supplementary). The effect estimates for potential demographic and lifestyle confounders are presented in Figure S3 (Supplementary).

3.3. Effect modification

Fig. 3 shows that the long-term effects of annual average temperature were slightly stronger for female participants for most of the biomarkers, with a significant difference between women and men for HovathAA and SkinBloodAA only. Also, obese participants showed slightly stronger effects with a significant difference compared to the non-obese participants only for GrimAA. A slight indication of stronger effects could also be found for participants with cardiovascular disease, but none of the biomarkers showed a significant difference compared to participants without cardiovascular disease. Moreover, participants with diabetes demonstrated significantly stronger effects than those without diabetes for HannumAA, PhenoAA, and SkinBloodAA. There were no significant effect modifications for 4- and 8-week moving averages of air temperature (Supplementary Figure S4 and S5). Finally, there were no effect modifications with urban and rural areas, except that participants living in rural areas showed a significantly stronger effect of annual average temperature on HannumAA (data not shown).

3.4. Sensitivity analysis

In general, associations between medium- and long-term exposure to air temperature and epigenetic age acceleration were robust to a series of sensitivity analyses (Supplementary Figures S6 and S7, and Table S3). We found similar effect estimates when additionally adjusting for air pollutants, except for medium-term effects on HannumAA and SkinBloodAA, which was slightly decreased. Secondly, the observed associations remained robust when restricting the analyses to the subpopulation that did not move throughout the study period and after excluding outliers. Thirdly, alternative outcome metrics (epigenetic age and epigenetic age acceleration: residuals) also showed similar effects. Additionally, the restriction to participants with repeated measurements of epigenetic age acceleration did not affect most of our results, expect for effects of the annual average temperature on GrimAA were decreased. Fifth, when we used the 25th and 75th percentile of the air temperature distribution as reference values, the effect estimates still showed significant associations, although the effect estimates values

Table 2
Descriptive statistics and Spearman correlation coefficients of epigenetic age acceleration across all observations.

	Mean	SD	25%	Median	75%	Correlation coefficients				
						HorvathAA	HannumAA	PhenoAA	GrimAA	SkinBloodAA
HorvathAA (years)	−2.3	5.1	−5.5	−2.1	1.1	–				
HannumAA (years)	0.6	10.1	−7.7	−0.9	8.9	0.34	–			
PhenoAA (years)	−9.7	6.8	−14.3	−10.1	−5.5	0.40	0.41	–		
GrimAA (years)	−0.2	5.2	−3.7	−0.7	2.6	0.41	0.43	0.37	–	
SkinBloodAA (years)	−2.7	5.2	−6.3	−2.9	1.1	0.44	0.81	0.43	0.36	–

Note: *HorvathAA*: Horvath's epigenetic age acceleration. *HannumAA*: Hannum's epigenetic age acceleration. *PhenoAA*: PhenoAge acceleration. *GrimAA*: GrimAge acceleration. *SkinBloodAA*: Epigenetic Skin and Blood Age acceleration. *SD*: standard deviation.

Table 3
Descriptive analysis of meteorological variables and air pollutants.

	Mean	SD	2.5%	25%	Median	75%	97.5%
Medium-term							
4-week moving average of temperature							
Tmean (°C)	9.4	5.6	1.5	4.1	9.7	14.5	18.5
RH (%)	74.8	7.4	59.3	69.2	75.5	80.7	85.9
$PM_{2.5}$ (μg/m^3)	12.7	4.7	6.2	8.9	12.2	16.2	21.5
O_3 (μg/m^3)	41.5	17.2	18	26.4	37	58.4	70.1
NO_2 (μg/m^3)	29.2	5.5	20.6	24.5	28.5	33.6	39.8
8-week moving average of temperature							
Tmean (°C)	9.5	5.3	1.4	4.2	9.7	14.3	18.3
RH (%)	74.8	6.6	63.2	69.1	76.1	80.7	84.3
$PM_{2.5}$ (μg/m^3)	12.9	3.8	7.7	9.5	12.7	15.9	20.1
O_3 (μg/m^3)	41.2	16.2	18.6	26.1	37	57.2	66.8
NO_2 (μg/m^3)	29.3	4.8	20.7	25	29.5	33.7	36.8
Long-term							
Annual average temperature							
Tmean (°C)	9.3	0.8	8	8.6	9.2	9.9	11
$PM_{2.5}$ (μg/m^3)	11.8	1	9.6	11.1	11.9	12.5	13.6
O_3 (μg/m^3)	39.1	2.4	34.6	37.4	39.2	40.9	43.4
NO_2 (μg/m^3)	14.1	4.4	7	10.6	13.7	17.4	23

Note: *Tmean:* mean temperature. *RH:* relative humidity. *$PM_{2.5}$:* particulate matter with an aerodynamic diameter of ≤ 2.5 μm. *O_3*: ozone; *NO_2*: nitrogen dioxide. *SD*: standard deviation.

decreased for the medium-term effects on HannumAA and SkinBloodAA. Sixth, when we incorporated season into the model as a four-factor category consisting of spring, summer, fall and winter, the results were consistent with the main analyses. Finally, there were also no significant medium-term effects of air temperature on PhenoAA when the 4- and 8-week moving averages of temperature were included as a linear term in the GEE model (Supplementary Table S3).

4. Discussion

To our knowledge, this study, for the first time, explores the impact of temporal-spatial variation of 4-week and 8-week -averages of air temperature and the spatial variation of annual average air temperature on epigenetic age acceleration. In this study, we found significant associations between medium-term exposures to high temperature and increased HorvathAA, HannumAA, GrimAA, and SkinBloodAA. Furthermore, higher annual average temperature exposure was significantly associated with an increase in HorvathAA, HannumAA, PhenoAA, GrimAA, and SkinBloodAA.

Aging involves the accumulation of biological changes in an individual over time that increase the risk for disease and death. Epigenetic clocks provide an opportunity to assess the biological age and general health of individuals (Noroozi et al., 2021; Oblak et al., 2021). Importantly, there has been increasing recognition of the association of epigenetic age acceleration with multiple clinical traits, morbidity, and mortality (Noroozi et al., 2021; Simpson and Chandra, 2021; Oblak et al., 2021; Roberts et al., 2021). We firstly found medium- and long-term effects of higher air temperature on increased epigenetic age accelerations. Our study provides new insights that fill an important

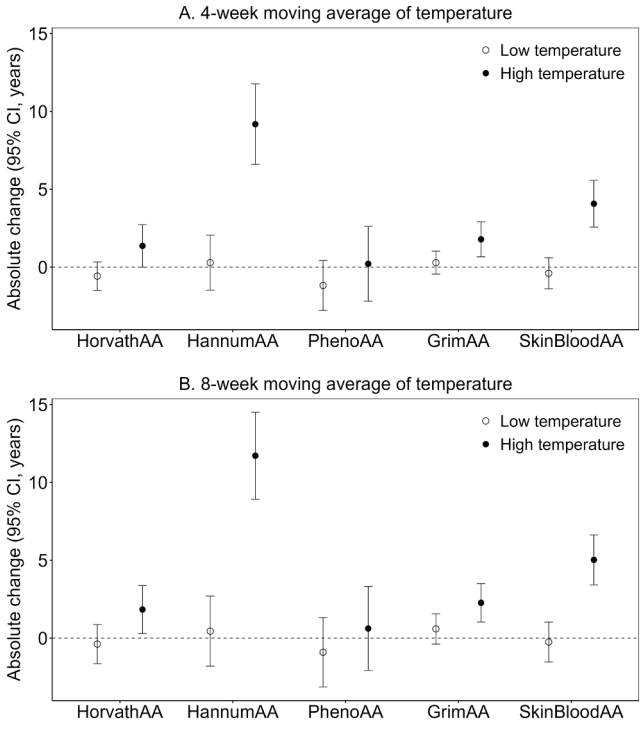

Fig. 1. Medium-term effects of 4- and 8-weeks moving average of air temperature on epigenetic age acceleration.
Note: *Low temperature*: effects of low temperature exposure, 2.5th percentile of temperature compared to median temperature. *High temperature*: effects of high temperature exposure, 97.5th percentile of temperature compared to median temperature. The median temperature was 9.7 °C; 2.5th percentile of temperature was 1.5 °C and 1.4 °C for 4-week and 8-week moving averages of temperature, respectively; 97.5th percentile of temperature was 18.5 °C and 18.3 °C for 4-week and 8-week moving averages of temperature, respectively. *HorvathAA*: Horvath's epigenetic age acceleration. *HannumAA*: Hannum's epigenetic age acceleration. *PhenoAA*: PhenoAge acceleration. *GrimAA*: GrimAge acceleration. *SkinBloodAA*: Epigenetic Skin and Blood Age acceleration.

knowledge gap in the context of a changing climate and, simultaneously, a worldwide aging population (Peters et al., 2021). Furthermore, our findings suggest that implementing policies to slow the rate of climate change may contribute in part to prolonging lifespans and decreasing or delaying health risks associated with aging.

We observed that HannumAA and SkinBloodAA appeared to be the most sensitive biomarkers to high temperature exposures. However, high temperatures also affected three other epigenetic age acceleration metrics: HorvathAA, PhenoAA, and GrimAA. These five clocks seem to capture different aspects of aging based on how they are constructed (Simpson and Chandra, 2021). HannumAA is a first-generation blood-specific age predictor designed to improve the accuracy of blood age estimation (Simpson and Chandra, 2021). Previous studies have shown

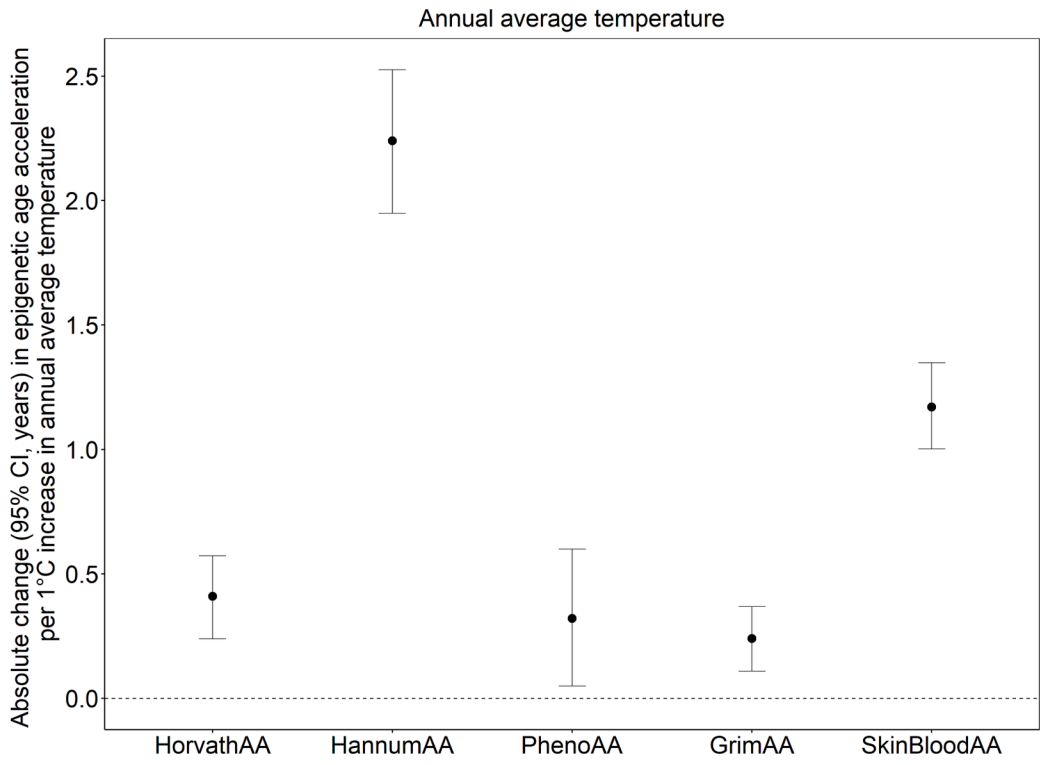

Fig. 2. Long-term effects of annual average temperature per 1 °C increase on epigenetic age acceleration.
Note: *HorvathAA*: Horvath's epigenetic age acceleration. *HannumAA*: Hannum's epigenetic age acceleration. *PhenoAA*: PhenoAge acceleration. *GrimAA*: GrimAge acceleration. *SkinBloodAA*: Epigenetic Skin and Blood Age acceleration.

that Hannum's clock indicates immune system aging (Stevenson et al., 2018; Gibson et al., 2019; Jonkman et al., 2022; Dhingra et al., 2018). For example, a *meta*-analysis of genome-wide association studies of epigenetic age acceleration showed that genes associated with Hannum's clock, which several involved in innate immune system pathways (such as *TRIM46* and MUC1) or with metabolic and immune system functions (*MANBA*, *UBE2D3*) (Gibson et al., 2019). Therefore, this suggests that HannumAA may be particularly associated with environmental exposures, e.g., higher air temperature. SkinBloodAA and HorvathAA are both multi-tissue age predictors, and the novel SkinBloodAA is considered to be a more accurate age estimator of blood methylation data (Horvath, 2013; Horvath et al., 2018). To date, few studies are available about the effect of environmental exposures on SkinBloodAA. A previous study showed that SkinBloodAA was the most sensitive to occupational benzene and trichloroethylene exposure (van der Laan et al., 2022). Given these findings and the higher accuracy of SkinBloodAA, it is suggested that SkinBloodAA, which is not yet widely used, maybe a suitable biomarker to explore the association between environmental exposures and biological aging. PhenoAA is optimized to predict physiological dysregulation across multiple systems and predict physical functioning more accurately than previous epigenetic clocks (Levine et al., 2018). GrimAA is a powerful mortality predictor, and strongly predicts lifespan and healthspan (Lu et al., 2019; McCrory et al., 2021). Our results suggest that epigenetic age acceleration may reflect processes that contribute to the often observed associations between high air temperature and mortality and risk of age-related diseases (Chen et al., 2018; Khraishah et al., 2022; Gasparrini et al., 2022); opening up a potentially new pathophysiological pathway in the field of weather, climate, and health research.

We used two exposure window definitions (4- and 8-week moving averages) to assess the medium-term effects of air temperature modeled in space and time on epigenetic age acceleration. We found heat effects for both exposure windows on epigenetic age acceleration. The results of the two time periods were almost identical, indicating our findings' robustness. The medium-term effects of high air temperature on epigenetic age acceleration may be thought to be short lived, as 4- and 8-week high air temperature exposure may not be expected to permanently accelerate epigenetic aging. However, epigenetic age acceleration may be a potential mechanism between air temperature and cardiovascular disease and cerebrovascular disease, as a previous study has revealed that medium-term high air temperature exposures are associated with increased cardiovascular disease and cerebrovascular disease mortality (Wang et al., 2015). Importantly, by using 4- and 8-week moving average temperatures, we can capture the broader temporal context and identify potential cumulative effects that may be missed when focusing solely on long-term exposures. Furthermore, medium-term temperatures encompass both temporal and spatial variability, diverging from capturing to such an extent day-to-day changes of temperature (short-term effects) as well as the climate-related patterns observed in annual assessments. Instead, it captures the variability resulting from distinct weather classes that bring specific weather types to a region and typically dominate the weather for durations longer than days but shorter than a full year. Additionally, as climate change progresses, individuals and communities implement various adaptation strategies to cope with shifting temperature patterns. Investigating medium-term effects helps us understand the delayed responses and adaptation mechanisms of individuals to changing temperature conditions, which often operate on timescales of weeks to months.

In addition to the medium-term effects, we also found significant long-term effects of air temperature on all five epigenetic age acceleration metrics. This implies that spatial variability in annual average temperature strongly affects epigenetic age acceleration and shows a high stability of our results across the different biomarkers. In other research contexts, it is often observed that results are rather inconsistent between the different epigenetic age acceleration metrics (Xu et al., 2021; van der Laan et al., 2021). Hence our study is affirming to see consistent effects of air temperature across the different biomarkers. More importantly, long-term air temperature exposure may have a more

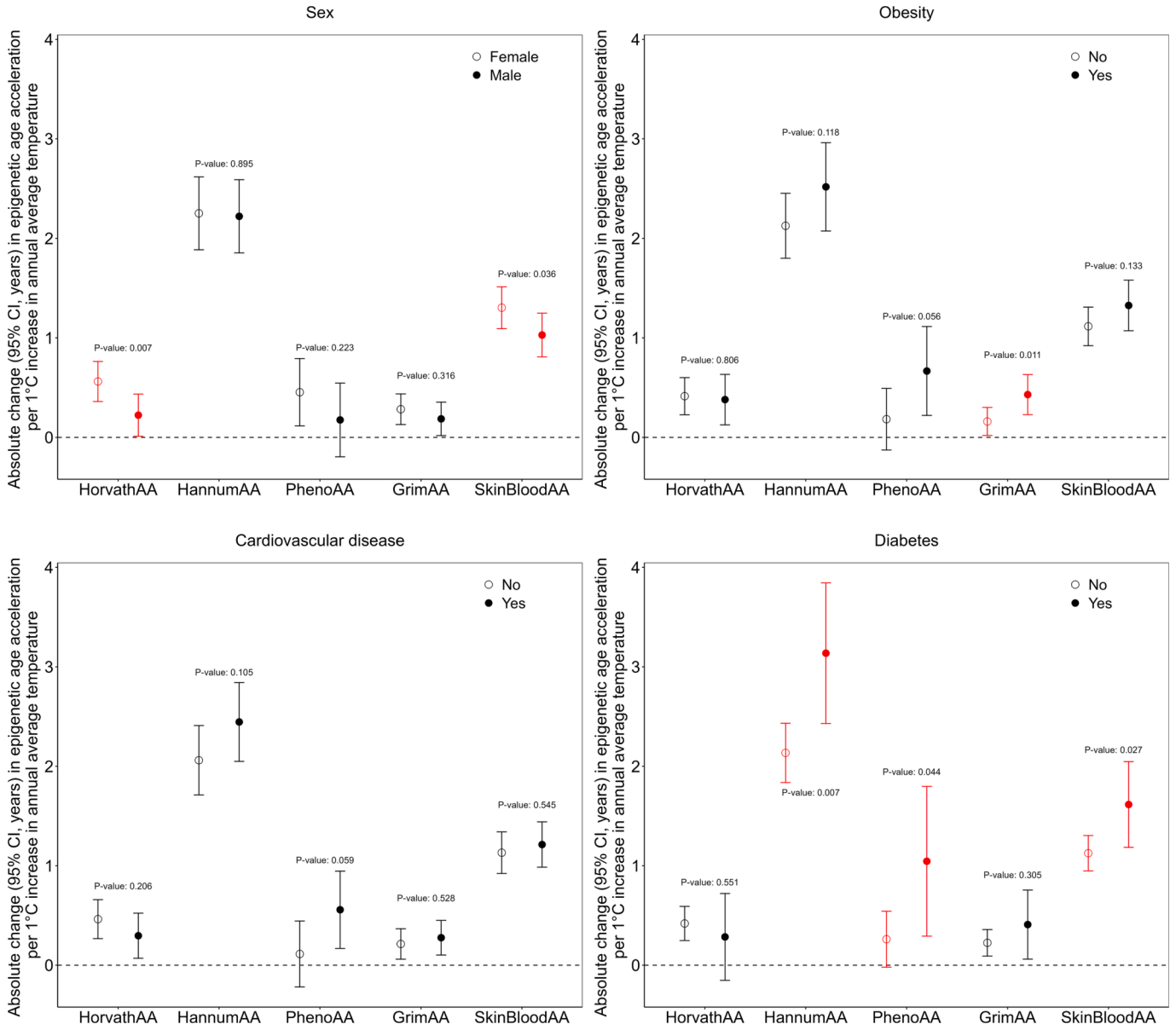

Fig. 3. Long-term effects of annual average temperature per 1 °C increase on epigenetic age acceleration modified by sex, obesity, cardiovascular disease, and diabetes.

Note: Red error bars show significantly different effect estimates between subgroups (*P*-value for the interaction term < 0.05). *HorvathAA*: Horvath's epigenetic age acceleration. *HannumAA*: Hannum's epigenetic age acceleration. *PhenoAA*: PhenoAge acceleration. *GrimAA*: GrimAge acceleration. *SkinBloodAA*: Epigenetic Skin and Blood Age acceleration.

pertinent and clinically relevant health effect, given that individuals are exposed to non-optimal temperatures over longer periods at their residential addresses. And the long-term effects may reflect more long-term stable alterations in accelerated aging as well as physiologic dysfunction that may affect health over an extended period of time. Furthermore, long-term effects help elucidate the relationship between climate-related temperature changes and epigenetic age acceleration. As climate change involves long-term shifts in temperature patterns, studying the long-term effects provides valuable insights into the potential consequences of ongoing climate change on human health and aging.

Spatial variability of annual averages temperature had stronger effects on epigenetic age acceleration in women, participants with obesity or diabetes, compared to men, participants without obesity or diabetes. This suggests that certain subpopulations may be more susceptible to high temperature and need more protection than others. Some studies also found higher mortality risks associated with exposure to higher temperatures among women (Chen et al., 2018; Achebak et al., 2019; Petkova et al., 2021). This may be related to the fact that females have a lower thermosensitivity in their response to temperature stimuli and a lower sweating capacity, which causes a greater increase in body temperature (Gagnon et al., 2013; Gagnon and Kenny, 2011; Gagnon and Kenny, 2012). Further, it has been observed that women have a higher threshold for activating their sweating mechanisms at high temperatures (Bittel et al., 1975). Participants with certain pre-existing health conditions, including obesity or diabetes, may also be more susceptible to high temperature. People with diabetes often have impaired endothelial function or poor blood flow to the skin, which can compromise their thermoregulation and affect the mechanisms of heat dissipation at high temperatures (Petrofsky, 2011). In addition, the increased insulation in obese adults increases thermal resistance between the core and the skin, thereby reducing heat dissipation from the core to the skin (Zhang et al.,

2016).

There are several strengths of the present study. Firstly, this is the first study to explore the association between air temperature and epigenetic age acceleration with a relatively large sample size of 3,602 observations. Secondly, we used satellite, meteorological, and terrestrial data to estimate the temperature at each participant's residence for each calendar day by a novel hybrid spatiotemporal regression-based model. Thereby, we were able to capture the temporal-spatial variability in monthly averages of temperatures. In contrast, temperature data obtained through one or two fixed monitoring sites would only assess the temporal variation and ignore differences within a region. The novel model gave us sufficient spatial and temporal variability of the analyzed air temperature and reduced exposure misclassification. Thirdly, we used multiple biomarkers of epigenetic clocks to define epigenetic age acceleration. The robust associations across all used biomarkers make us confident that our associations were not observed by chance only.

However, our study also has several limitations. First, this study was performed in a single study center in Augsburg, Germany, which limits the generalizability of our findings and may not reflect individuals from other regions due to potential ethnic, climatic, and geographic differences. Secondly, as an observational study, the possibility of residual confounding and/or unmeasured confounders could not be excluded, although we already adjusted for a large set of covariates. Thirdly, the genome-wide DNA methylation in KORA FF4 was analyzed using the Infinium MethylationEPIC BeadChip, which lacked 19 CpG and 6 CpG sites used to calculate the Horvath' and Hannum' epigenetic age. This may lead to inaccurate estimates of these two epigenetic ages, so results from these should be interpreted with caution. Fourth, we used ambient area-level air temperatures rather than personal exposures to air temperature (including, e.g., also indoor temperatures), which may result in exposure misclassification. Finally, a limitation is that different DNA methylation profiling platforms were used for the two cohorts, which could introduce some technical discrepancy despite adjustments. Residual biases likely remain due to the challenges of fully correcting for different array types.

5. Conclusion

In conclusion, our results provide the first evidence that medium- and long-term exposures to high air temperature affect increases in epigenetic age acceleration. Providing this new pathophysiological pathway could be an important step in preventing the health effects of heat, especially for susceptible population subgroups - particularly when considering the predicted future increases in the number of hot days and more intense heat waves in times of climate change.

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CRediT authorship contribution statement

Wenli Ni: Conceptualization, Methodology, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Nikolaos Nikolaou:** Writing – review & editing. **Cavin K. Ward-Caviness:** Methodology, Writing – review & editing. **Susanne Breitner:** Methodology, Writing – review & editing. **Kathrin Wolf:** Methodology, Writing – review & editing. **Siqi Zhang:** Methodology, Writing – review & editing. **Rory Wilson:** Writing – review & editing. **Melanie Waldenberger:** Writing – review & editing. **Annette Peters:** Conceptualization, Supervision, Funding acquisition, Resources, Writing - review & editing. **Alexandra Schneider:** Conceptualization, Resources, Methodology, Writing – review & editing, Supervision.

Declaration of Competing Interest

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.

Data availability

The authors do not have permission to share data.

Acknowledgment

Methylation analysis in KORA FF4 was performed at the Core Facility Genotyping (Genome Analysis Center [GAC], Helmholtz Zentrum München) under the supervision of Dr. Sonja Kunze, Dr. Jennifer Kriebel and Dr. Eva Reischl.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108109.

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