

# Higher Daily Air Temperature Is Associated with Shorter Leukocyte Telomere Length: KORA F3 and KORA F4

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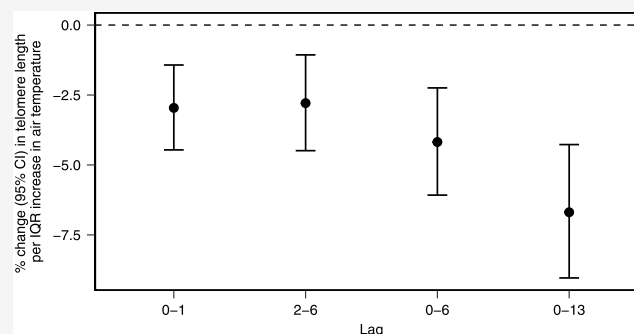
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**ABSTRACT:** Higher air temperature is associated with increased age-related morbidity and mortality. To date, short-term effects of air temperature on leukocyte telomere length have not been investigated in an adult population. We aimed to examine the short-term associations between air temperature and leukocyte telomere length in an adult population-based setting, including two independent cohorts. This population-based study involved 5864 participants from the KORA F3 (2004–2005) and F4 (2006–2008) cohort studies conducted in Augsburg, Germany. Leukocyte telomere length was assessed by a quantitative PCR-based method. We estimated air temperature at each participant's residential address through a highly resolved spatiotemporal model. We conducted cohort-specific generalized additive models to explore the short-term effects of air temperature on leukocyte telomere length at lags 0–1, 2–6, 0–6, and 0–13 days separately and pooled the estimates by fixed-effects meta-analysis. Our study found that between individuals, an interquartile range (IQR) increase in daily air temperature was associated with shorter leukocyte telomere length at lags 0–1, 2–6, 0–6, and 0–13 days (%change:  $-2.96$  [ $-4.46$ ;  $-1.43$ ],  $-2.79$  [ $-4.49$ ;  $-1.07$ ],  $-4.18$  [ $-6.08$ ;  $-2.25$ ], and  $-6.69$  [ $-9.04$ ;  $-4.27$ ], respectively). This meta-analysis of two cohort studies showed that between individuals, higher daily air temperature was associated with shorter leukocyte telomere length.



**KEYWORDS:** short-term effects, air temperature, telomere length

## 1. INTRODUCTION

Climate change is a major public health concern that is becoming increasingly important worldwide. The global surface temperature for July 2021 was the highest for July in the 142-year record of the National Centers for Environmental Information of National Oceanic and Atmospheric Administration (NOAA), which dates back to 1880.<sup>1</sup> The climate is warming quickly in the World Health Organization European Region, which is experiencing accelerated rates of temperature increase and increased frequency and intensity of heat waves.<sup>2</sup> Previous studies have shown that the frequency and severity of extreme weather events are increasing as a consequence of climate change.<sup>3</sup> Prominent examples are the heat waves in America and Canada and the floods in Germany and China in 2021. Importantly, accumulating evidence shows that increases in air temperature endanger human health and well-being in numerous ways and are associated with increased morbidity and mortality, especially in age-related vulnerable population subgroups, such as the elderly.<sup>4–10</sup> A recent worldwide study based on data from 750 locations in 43 countries showed that the global heat-related excess death ratio increased by 0.21% between 2000–2003 and 2016–2019.<sup>7</sup>

The global population is aging rapidly and the prevalence of age-related diseases is quickly increasing.<sup>11</sup> Telomeres are highly conserved tandem repetitive nucleotide sequences (TTAGGG), which provide a protective cap at the ends of chromosome to maintain genome stability.<sup>12,13</sup> Telomeres are fundamental for cell division and shorten after each round of cell division.<sup>14</sup> Consequently, leukocyte telomere length shortening is evaluated as a potential biomarker for biologic aging, and telomere shortening has been associated with increasing numbers of age-related diseases such as stroke, cardiovascular disease, or cancer.<sup>15–18</sup> A recent large cohort study from the United Kingdom Biobank found that shortened leukocyte telomere length was associated with increased overall cardiovascular, respiratory, digestive, musculoskeletal, and COVID-19 mortality.<sup>19</sup> A further review study showed that telomere attrition was influenced by genetic and environmental

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factors.<sup>12</sup> Evidence is rapidly growing that telomere shortening can be accelerated by exposure to nonoptimal environmental factors like air pollution,<sup>20,21</sup> and pesticides.<sup>22</sup>

Air temperature is an important environmental factor, especially in the context of climate change. A study in the three largest English cities (Greater London, Greater Manchester, and West Midlands) found that heat and cold exposure increased the risk of mortality and years of life lost.<sup>23</sup> In addition, high air temperature or heat stress has been associated with higher levels of oxidative stress and inflammatory biomarkers.<sup>24–27</sup> As oxidative stress and inflammation can speed up telomere attrition,<sup>28,29</sup> these findings suggest that air temperature might affect telomere length. However, only one birth study has reported that prenatal high and low air temperature exposures were associated with shorter cord blood telomere length.<sup>30</sup> So far, the effect of air temperature on leukocyte telomere length has not been investigated among an adult population.

Therefore, we aimed to examine the short-term associations between air temperature and leukocyte telomere length in the region of Augsburg, Germany, within two independent adult cohorts.

## 2. MATERIALS AND METHODS

**2.1. Study Design.** Data were from the Cooperative Health Research in the Region of Augsburg (KORA) F3 study (February 9, 2004–May 13, 2005) and F4 study (October 9, 2006–May 31, 2008), which were follow-up studies of the population-based KORA S3 and KORA S4 survey conducted in 1994–1995 and 1999–2001. The study area is located in the city of Augsburg and two surrounding counties in Southern Germany.<sup>31</sup> The study design, standardized sampling method, and data collection have been described in detail elsewhere.<sup>31–33</sup> Of 2974 and 3080 individuals who participated in KORA F3 and KORA F4, the current analysis included 2865 F3 and 2999 F4 participants, with no missing information on leukocyte telomere length, air temperature, or covariates of interest.

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

**2.2. Exposure Assessment.** Countrywide high-resolution (1 km × 1 km) minimum (T<sub>min</sub>), mean (T<sub>mean</sub>), and maximum (T<sub>max</sub>) daily air temperature data were estimated using hybrid spatiotemporal regression-based models, following the approach from Kloog et al.<sup>34,35</sup> Several data sets from multiple sources were incorporated in the modeling process, including air temperature measurements from weather stations as well as satellite-derived land surface temperature (LST), elevation, vegetation, urban fabric, arable land, pastures, forests, and inland waters, which were harmonized into 366,536 grid cells of 1 km × 1 km based on the European INSPIRE (Infrastructure for Spatial Information in the European Community) standard using the Lambert Azimuthal Equal-Area projection, EPSG: 3035 (GeoBasis-DE/BKG (2021)) before modeling. We trained three-stage models to achieve air temperature predictions with complete temporal and spatial coverage. In the first stage, a linear mixed effects model with daily random intercepts and slopes for LST and adjusted for the aforementioned spatial predictors was trained in the combinations of days and grid cells, where air temperature measurements and satellite LST were both

available. In the second stage, the first stage model was used to predict air temperature for grid cells without air temperature measurements but with available LST data. For the remaining days and grid cells with neither LST data nor air temperature measurements available, we regressed the second-stage air temperature predictions against thin plate spline interpolated air temperature values to obtain fully covered air temperature countrywide. We performed internal and external out-of-sample 10-fold cross-validation to quantify the prediction accuracy of our models. All models achieved excellent performance ( $0.91 \leq R^2 \leq 0.98$ ) and low errors ( $1 \text{ }^\circ\text{C} < \text{root-mean-square error} < 2 \text{ }^\circ\text{C}$ ). The individual subject-specific data have been linked to the environmental exposure data with daily resolution over the pseudonymized unique participant ID and over the grid ID of the exposure. The data-linkage processes have been performed using the geocoded participants' residential addresses. Care was taken to remove all spatial information from the data set. Pseudonymized data were provided to the research team. Finally, we matched phenotype data with exposure data by date, according to different lag days.

The daily concentrations of relative humidity (RH), ozone (O<sub>3</sub>), nitrogen dioxide (NO<sub>2</sub>), particulate matter with an aerodynamic diameter < 2.5 μm (PM<sub>2.5</sub>), and black carbon (BC) were assessed via fixed monitoring sites within Augsburg, Germany.<sup>36–38</sup> O<sub>3</sub> and RH were obtained from an official urban background monitoring site operated by the Bavarian Environment Agency (LfU, Bayerisches Landesamt für Umwelt), which was located about 5 km south of the city center. NO<sub>2</sub> was measured at an urban background measurement station located approximately 2 km north of the city center [also operated by the Bavarian Environment Agency (LfU, Bayerisches Landesamt für Umwelt)]. PM<sub>2.5</sub> and BC were measured at a single urban background site located 1 km south of the city center and assessed via a tapered element oscillating microbalance (TEOM model 1400A, Thermo Fisher Scientific) equipped with the filter dynamics measurement system (FDMS, model 8500b; Thermo Fisher Scientific) and an aethalometer (model series 8100; Thermo Fisher Scientific), respectively. Daily 24-h average relative humidity, daily maximum 8-h average O<sub>3</sub>, daily 24-h average NO<sub>2</sub>, daily 24-h average PM<sub>2.5</sub>, and daily 24-h average BC were calculated if at least 75% of the hourly measurements were available.

**2.3. Measurement of Leukocyte Telomere Length.** Standardized procedures for measuring leukocyte telomere length have been described previously in detail.<sup>39</sup> In brief, blood samples were collected on the same day the questionnaires were completed. Before the KORA study center visit, participants were asked to fast for at least 8 h and avoid exercising and smoking the day before and the morning before blood sampling. Blood samples were taken in a sitting position. Samples for measurement of leukocyte telomere length were stored at  $-80 \text{ }^\circ\text{C}$  until analysis.

Telomere length in samples of F3 and F4 was assayed at the same time and normalized together. Leukocytes from peripheral blood samples were used to extract genomic DNA, and the telomere length was assessed using a quantitative PCR-based method and expressed as the ratio between the telomere repeat copy number (T) and a single-copy gene: 36B4 (S) (T/S ratio).<sup>39,40</sup> We ran DNA samples in duplicate in 25 μL reactions on a Rotorgene-Q real-time thermal cycler and CAS-1200 liquid handling system (Qiagen, U.K.). A no-template control and a calibrator sample (genomic

DNA from the K562 cell line) in duplicate were included in each run to standardize the measurement across PCR plates. The PCR output was analyzed using comparative quantification (Qiagen Rotorgene analysis software, Qiagen, U.K.), and quantification was relative to calibrator DNA. For quality control, all samples were checked for concordance between duplicate values and to ensure that the experiment ran within the linear range of the assay established. Furthermore, to ensure the reproducibility of the assay, samples were regularly re-run at random on a different day and/or machine. All samples reproduced well, and the inter-run coefficient of variability (CV) for the T/S ratio was 2.63% in KORA F3 and 3.08% in KORA F4, and the intra-run CV for the T/S ratio was 2.84% in KORA F3 and 3.07% in KORA F4. Correlation coefficients ( $r^2$ ) of the measurements from different days were 0.85 for KORA F3 and 0.93 for KORA F4.

**2.4. Assessment of Covariates.** Participants completed a computer-assisted personal interview and a self-administered questionnaire with information regarding demographic characteristics, including age (year), sex (male, female), education (years), and body mass index (BMI [ $\text{kg}/\text{m}^2$ ]); lifestyle characteristics, including smoking status, alcohol consumption (g/day), and physical activity; medical history of the participants, including hypertension (no/yes), angina pectoris (no/yes), myocardial infarction (no/yes), and stroke (no/yes); and current medications, including antihypertensive (no/yes), lipid-lowering (no/yes), and antidiabetic medication (no/yes). Body weight and height were obtained during physical examinations. BMI was calculated as weight in kilograms divided by height squared in meters.

Four categories of smokers were defined in the questionnaire: never smokers, former smokers, occasional smokers, and regular smokers. Participants were divided into three categories for the present analysis: never-smokers, former smokers, and current smokers (including occasional and regular smokers). Alcohol consumption was rated by asking participants how many alcoholic drinks (beer, wine, or spirits) they consumed during the previous weekday and the previous weekend. Physical activity levels were estimated by asking subjects how much time each week they spent engaging in physical activity during their leisure time in summer and winter (almost no or no physical activity, irregularly about 1 h per week, regularly about 1 h per week, and regularly more than 2 h per week). For this analysis, participants were categorized into three categories: low (almost no exercise), medium (regularly or irregularly approx. 1 h per week), and high (regularly more than 2 h per week). Seasons at blood draw were defined as spring (March–May), summer (June–August), autumn (September–November), and winter (December–February).

Participants with a history of hypertension were defined by measured blood pressure (over 140/90 mm Hg) or reported use of antihypertensive medications. Participant history of myocardial infarction or stroke was based on self-reported physician diagnoses treated in hospitals. The history of angina pectoris was based on self-reported physician diagnoses.

Data on the use of medications were collected using the standardized software IDOM (an instrument for database-supported online medication registration).<sup>41</sup> The following classes were considered as antihypertensive medication: antihypertensive medication, diuretics, calcium antagonists,  $\beta$ -blockers, ACE inhibitors, and angiotensin antagonists; lipid-lowering medication: lipid-lowering, including herbal sub-

stances, statins, and fibrates; and antidiabetic medication, including antidiabetics, insulin, and oral antidiabetics.

Serum total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides were measured using the CHOL Flex, AHDL Flex, ALDL Flex, and TGL Flex (Dade Behring, Germany), respectively.

**2.5. Statistical Analysis.** Characteristics of the study population were given as mean and standard deviation (SD) for continuous variables and frequency and percentage for categorical variables. We compared the demographic characteristics of two cohort study populations using chi-squared tests for categorical variables and *t*-tests for continuous variables. The levels of meteorological variables and air pollutants were presented as mean, SD, 5, 25%, median, 75, 95%, and interquartile range (IQR), and Spearman's correlation was used to evaluate their correlations.

We applied cohort-specific generalized additive models (GAMs) to explore the short-term effects of mean air temperature on leukocyte telomere length. To explore the potential cumulative effects of mean temperature, we investigated the moving averages of daily mean temperature at lags 0–1, 2–6, 0–6, and 0–13 days before blood draw. In preliminary analyses, we investigated the shape of the association by including the temperature term as a nonlinear function (spline with three degrees of freedom). Since none of the curves indicated significant deviations from linearity (Supporting Information, Figure S1), we included air temperature as a linear term for the main analyses. Leukocyte telomere length was natural log-transformed to increase normality of residuals. We controlled for age, sex, BMI, education, smoking status, alcohol consumption, physical activity, day of the week, season, time trend (cubic spline with ten degrees of freedom), and relative humidity with the same lag period as the air temperature. The time trend was calculated as the day of the year. We included the time trend in our model to adjust for unmeasured confounding, such as variables varying over time, even in this short period.

We conducted effect modification analysis by including an interaction term between air temperature and the potential effect modifier: sex (male vs female), age (<65 years vs  $\geq 65$  years), physical activity (low vs medium or high), obesity (BMI <30  $\text{kg}/\text{m}^2$  vs  $\geq 30 \text{ kg}/\text{m}^2$ ), smoking status (current vs former or never smoker), hypertension (yes vs no), cardiovascular disease (defined as a history of angina pectoris, myocardial infarction, or stroke [yes vs no]), season (warm: April–September vs cold: October–March), and  $\text{O}_3$  (low [ $< \text{median } \text{O}_3$ ] vs high [ $\geq \text{median } \text{O}_3$ ]).

To assess the robustness of the results, we performed several sensitivity analyses. First, we applied four different confounder models. Model 1 only adjusted for age, sex, BMI, day of the week, time trend, and relative humidity. Model 2 included all covariates of the main model and additionally adjusted for total cholesterol, triglyceride, LDL, and HDL. Model 3 extended Model 2 by additionally adjusting for medication intake (antihypertensive, lipid-lowering, or antidiabetic medication). In Model 4, we further included air pollutants ( $\text{O}_3$ ,  $\text{PM}_{2.5}$ ,  $\text{NO}_2$ , and BC) with the same lag period as the air temperature. These four pollutants were additionally included in the model separately to avoid collinearity. Further, we only additionally adjusted for BC only in KORA F4 because there was no BC data available in KORA F3. Second, instead of Tmean, we used Tmin and Tmax as alternative exposure metrics. Third, we excluded outliers in leukocyte telomere length values less than

the first quartile of the data (Q1)  $- 1.5 \times$  IQR or more than the third quartile of the data (Q3)  $+ 1.5 \times$  IQR to avoid overestimating the effects induced by extreme values. Fourth, to avoid the effects of extreme air temperature and the influence of elevated environmental temperature on the quality of blood samples, we excluded subjects exposed to air temperature greater than 95% of temperature. Finally, we extended the lag days and investigated the effect of 4-week moving air temperature averages (lags 0–27 days) on leukocyte telomere length.

All models were first fitted separately for each cohort, and the results from the individual cohorts were then pooled using fixed-effect meta-analysis. Heterogeneity was examined using the  $I^2$ -squared ( $I^2$ ) statistic. A  $P$ -value  $> 0.05$  and/or  $I^2 < 50\%$  was considered homogeneous.

To compare the effect estimates across different exposure windows, effect estimates were presented as percent changes of the geometric outcome mean with 95% confidence intervals (CIs) per IQR increase in air temperature.  $P < 0.05$  was considered to be statistically significant for all statistical tests. All statistical analyses were performed using R (Version 4.1.2) with “mgcv” and “metafor” packages.

### 3. RESULT

**3.1. Study Population and Exposure Data.** The characteristics of the study population and level of leukocyte telomere length are described in Table 1. The overall geometric mean level of leukocyte telomere length was lower in KORA F3 with 1.7 T/S compared to 1.8 T/S in KORA F4. The KORA F3 population was older, had a lower level of education, higher proportions of current smokers and hypertension, and higher levels of triglycerides, HDL, and total cholesterol than the KORA F4 population. The KORA F4 population had a higher level of LDL and a higher proportion of antihypertensive medication intake than the KORA F3 population.

Mean daily mean temperature was 7.2 °C in KORA F3 and 7.8 °C in KORA F4 (Table 2). Spearman’s correlation coefficients ( $r$ ) between meteorological variables and air pollutants ( $O_3$ ,  $PM_{2.5}$ ,  $NO_2$ , and BC) were similar for both studies (Supporting Information, Figure S2). The correlations between the different temperature variables and  $PM_{2.5}$ ,  $NO_2$ , and BC were generally high ( $r \geq 0.72$ ), whereas the correlations between temperature variables, RH, and air pollutants were only weak to moderate.

**3.2. Short-Term Effects of Air Temperature on Leukocyte Telomere Length.** Our meta-analyses showed that between individuals, higher air temperature was associated with shorter leukocyte telomere length for all investigated lags (Figure 1). We found that between individuals, an IQR increase in daily mean air temperature (10.77, 10.11, 10.15, and 9.54 °C, respectively) was significantly associated with shorter leukocyte telomere length at lags 0–1, 2–6, 0–6, and 0–13 days (%change:  $-2.96 [-4.46; -1.43]$ ,  $-2.79 [-4.49; -1.07]$ ,  $-4.18 [-6.08; -2.25]$ , and  $-6.69 [-9.04; -4.27]$ , respectively). The cohort-specific associations (KORA F3 and KORA F4) showed similar results with slightly more pronounced estimates for F4 and lags 2–6 days for F3 being the only weaker association (Figure 2). Effect estimates expressed as absolute changes between individuals with 95% CIs per IQR increase in air temperature are shown in Figure S3 (Supporting Information).

**Table 1. Descriptive Statistics of Participant Characteristics and Leukocyte Telomere Length in KORA F3 (2004–05) and KORA F4 (2006–08)**

	mean $\pm$ SD or N (%)		$P$ -value
	KORA F3 ( $n = 2865$ )	KORA F4 ( $n = 2999$ )	
leukocyte telomere length (T/S) <sup>a</sup>	1.7 $\pm$ 0.3/1.7	1.9 $\pm$ 0.3/1.8	<0.001
age (years)	57.1 $\pm$ 12.8	56.1 $\pm$ 13.2	0.004
sex (male)	1391 (48.6)	1447 (48.2)	0.837
body mass index (kg/m <sup>2</sup> )	27.7 $\pm$ 4.6	27.6 $\pm$ 4.8	0.727
education (years)	11.4 $\pm$ 2.6	11.7 $\pm$ 2.7	<0.001
Smoking Status			
never smoker	1276 (44.5)	1248 (41.6)	0.016
former smoker	1055 (36.8)	1213 (40.4)	
current smoker	534 (18.6)	538 (17.9)	
Physical Activity			
low (none or <1 h per week)	941 (32.8)	967 (32.2)	0.240
medium (~1 h per week)	1279 (44.6)	1301 (43.4)	
high (~2 h per week or more)	645 (22.5)	731 (24.4)	
alcohol consumption (g/day)	15.3 $\pm$ 19.6	14.4 $\pm$ 19.6	0.063
triglycerides (mmol/L)	1.9 $\pm$ 1.5	1.4 $\pm$ 1.0	<0.001
HDL (mmol/L)	1.5 $\pm$ 0.4	1.4 $\pm$ 0.4	<0.001
LDL (mmol/L)	3.3 $\pm$ 0.8	3.5 $\pm$ 0.9	<0.001
total cholesterol (mmol/L)	5.64 $\pm$ 1.0	5.58 $\pm$ 1.0	0.011
History of Diseases			
hypertension (yes)	1432 (50.0)	1153 (38.4)	<0.001
cardiovascular disease (yes)	319 (11.1)	308 (10.3)	0.297
Medication Intake			
antihypertensive medication (yes)	746 (26.0)	954 (31.8)	<0.001
lipid-lowering medication (yes)	312 (10.9)	377 (12.6)	0.05
antidiabetic medication (yes)	181 (6.3)	173 (5.8)	0.41
Season			
spring	939 (32.8)	864 (28.8)	<0.001
summer	479 (16.7)	407 (13.6)	
autumn	776 (27.1)	804 (26.8)	
winter	671 (23.4)	924 (30.8)	

<sup>a</sup>Geometric mean, additionally shown for telomere length. Data are mean (SD)/geometric mean. LDL, low-density lipoproteins; HDL, high-density lipoproteins.

Our study also showed that between individuals, a 1 °C increase in daily mean air temperature was significantly associated with shorter leukocyte telomere length at lags 0–1, 2–6, 0–6, and 0–13 days (%change:  $-0.28 [-0.42; -0.13]$ ,  $-0.28 [-0.45; -0.11]$ ,  $-0.42 [-0.62; -0.22]$ , and  $-0.72 [-0.99; -0.46]$ , respectively) (Supporting Information, Figure S4).

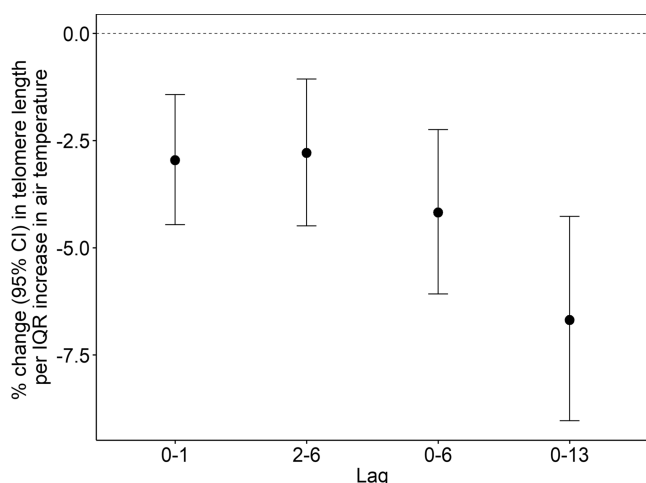
**3.3. Effect Modification.** Our analysis mainly indicated no significant effect modification by the investigated potential effect modifiers (Figure 3). Only participants examined in the cold season showed significantly shorter leukocyte telomere length for air temperature at lags 0–1 days. In contrast, no association was observed for participants examined in the warm season.

Effect estimates were presented as percent changes of the geometric outcome mean with 95% CIs per IQR increase in air

Table 2. Descriptive Statistics of Meteorological Variables and Air Pollutants<sup>a</sup>

	mean	SD	5%	25%	median	75%	95%	IQR
KORA F3 (09th February, 2004–13th May, 2005)								
Tmean (°C)	7.2	7.6	-4.8	0.8	8.1	13.3	18.5	12.5
Tmin (°C)	2.9	7	-9.9	-1.8	3.7	8.6	12.5	10.4
Tmax (°C)	11.9	9	-1.5	3.4	12	19.3	26.1	15.9
RH (%)	72.6	13	51.2	61.5	73.4	83.7	92.1	22.2
O <sub>3</sub> (μg/m <sup>3</sup> )	45.5	23.1	5.6	27.2	48.3	63	82	35.8
PM <sub>2.5</sub> (μg/m <sup>3</sup> )	22.2	12.3	7.6	13.6	19.7	27.8	46.3	14.2
NO <sub>2</sub> (μg/m <sup>3</sup> )	38.6	15.9	18.3	27	36.7	45.5	69.5	18.5
KORA F4 (09th October, 2006–31st May, 2008)								
Tmean (°C)	7.8	6.1	-0.9	3	7.1	11.9	19.1	8.9
Tmin (°C)	3.7	5.3	-4	0	2.8	7.1	13.2	7.1
Tmax (°C)	12.5	7.5	2.3	7.1	11.6	17.7	26.3	10.6
RH (%)	76.5	9.9	58.6	70	77.7	84	91.1	14
O <sub>3</sub> (μg/m <sup>3</sup> )	39.8	22.6	6.5	20.1	38.5	57	78.1	36.9
PM <sub>2.5</sub> (μg/m <sup>3</sup> )	15.1	11.1	2.6	6.9	12.8	19.6	36.1	12.7
NO <sub>2</sub> (μg/m <sup>3</sup> )	32.8	11.7	16.4	23.3	31.8	41.1	53.3	17.8
BC (μg/m <sup>3</sup> )	1.8	1.1	0.7	1	1.5	2.1	4.3	1.1

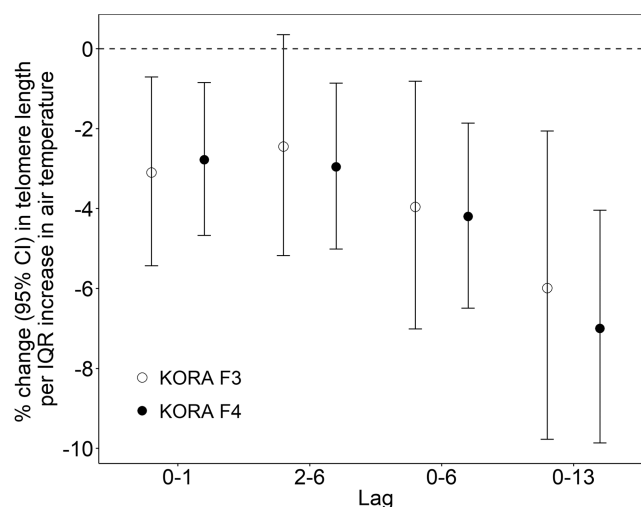
<sup>a</sup>Tmean: daily mean temperature; Tmin: daily minimum temperature; Tmax: daily maximum temperature; RH: relative humidity; O<sub>3</sub>: ozone; PM<sub>2.5</sub>: particulate matter with an aerodynamic diameter of  $\leq 2.5$  μm; NO<sub>2</sub>: nitrogen dioxide; and BC: black carbon. IQR: interquartile range.



**Figure 1.** Estimated effects (percent change [95% CI]) of geometric mean of air temperature on leukocyte telomere length between individuals at lags 0–1, 2–6, 0–6, and 0–13 days per IQR increase in air temperature. Generalized additive models were first fitted separately for KORA F3 and KORA F4 cohorts. The results from the individual cohorts were then pooled using fixed-effect meta-analysis. Heterogeneity testing across KORA F3 and KORA F4: lag 0–1,  $I^2 = 0$ ,  $P = 0.71$ ; lag 2–6,  $I^2 = 0$ ,  $P = 0.44$ ; lag 0–6,  $I^2 = 0$ ,  $P = 0.42$ ; lag 0–13,  $I^2 = 13.46$ ,  $P = 0.28$ . All models were adjusted for age, sex, BMI, education, smoking status, alcohol consumption, physical activity, day of the week, season, time trend (cubic spline with ten degrees of freedom), and relative humidity with the same lag period as the air temperature. Effect estimates were presented as percent changes of the geometric outcome mean with 95% CIs per IQR increase in air temperature. The respective IQR increases were 10.77 °C for lags 0–1 days, 10.11 °C for lags 2–6 days, 10.15 °C for lags 0–6 days, and 9.54 °C for lags 0–13 days.

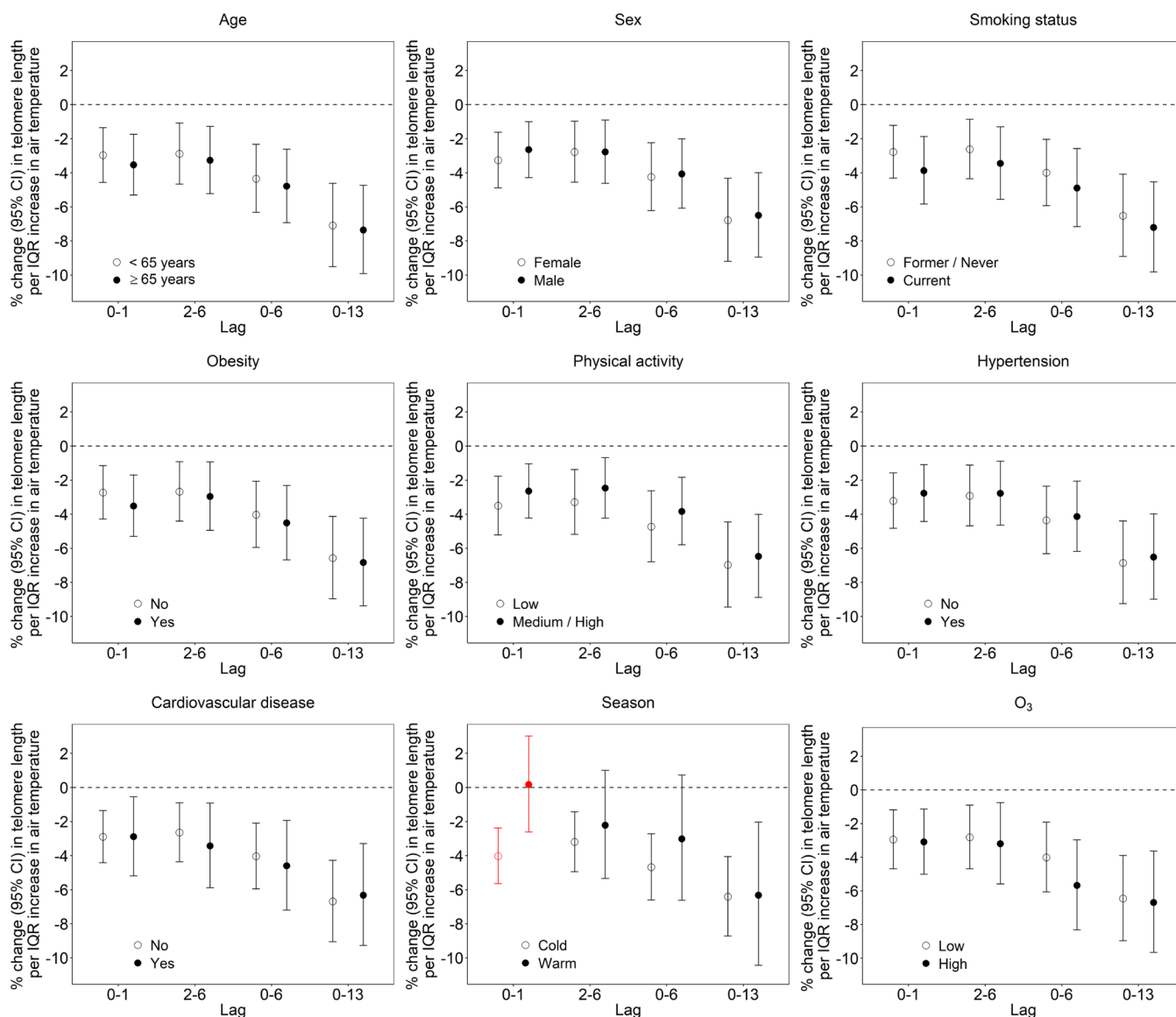
temperature. Error bars in red indicate significant differences in effect estimates between subgroups ( $P$ -value for the interaction term  $< 0.05$ ). The respective IQR increases were 10.77 °C for lags 0–1 days, 10.11 °C for lags 2–6 days, 10.15 °C for lags 0–6 days, and 9.54 °C for lags 0–13 days.

**3.4. Sensitivity Analysis.** In general, the associations between air temperature and leukocyte telomere length



**Figure 2.** Estimated effects (percent change [95% CI]) of geometric mean of air temperature on leukocyte telomere length between individuals at lags 0–1, 2–6, 0–6, and 0–13 days per IQR increase in air temperature in KORA F3 and KORA F4. All models were adjusted for age, sex, BMI, education, smoking status, alcohol consumption, physical activity, day of the week, season, time trend (cubic spline with ten degrees of freedom), and relative humidity with the same lag period as the air temperature. Effect estimates were presented as percent changes of the geometric outcome mean with 95% CIs per IQR increase in air temperature. KORA F3: the respective IQR increases were 12.42 °C for lags 0–1 days, 11.62 °C for lags 2–6 days, 11.80 °C for lags 0–6 days, and 10.74 °C for lags 0–13 days; KORA F4: the respective IQR increases were 9.12 °C for lags 0–1 days, 8.60 °C for lags 2–6 days, 8.50 °C for lags 0–6 days, and 8.35 °C for lags 0–13 days.

between individuals remained robust in the sensitivity analyses (Supporting Information, Figure S5). We observed similar associations when using different sets of confounder adjustment. Also, alternative exposure metrics Tmin and Tmax showed comparable effects as Tmean. Moreover, the exclusion of outliers and the exclusion of subjects exposed to air temperatures greater than 95% of temperature did not affect the results. Finally, we still found a significant effect of daily air



**Figure 3.** Estimated effects (percent change [95% CI] of geometric mean) of air temperature on leukocyte telomere length between individuals at lags 0–1, 2–6, 0–6, and 0–13 days per IQR increase in air temperature modified by age, sex, smoking status, obesity, physical activity, hypertension, cardiovascular disease, season, and O<sub>3</sub>.

temperature on leukocyte telomere length at lags 0–27 days (−11.77%, 95% CI: −14.91; −8.51%).

#### 4. DISCUSSION

To our knowledge, this is the first study to explore the short-term effects of air temperature on leukocyte telomere length within an adult population using data from two cohort studies. Pooling the results of the two cohort studies showed that between individuals, higher daily air temperature was significantly associated with shorter leukocyte telomere length.

Leukocyte telomere length measurement is increasingly recognized as a clinical indicator of the risk of age-related disease.<sup>42</sup> Our study is the first to show significant short-term associations between higher air temperature and shorter leukocyte telomere length between individuals in an adult population. To date, only one birth study on prenatal temperature exposure was able to demonstrate an association, finding that the strongest effect of a 1 °C increase in air temperature above the heat threshold (19.5 °C) took place at

week 36 of gestation, resulting in a significantly associated 3.29% (95% CI: 1.88, 4.67%) T/S shorter cord blood telomere length. However, the association with a 1 °C decrease in air temperature below the cold threshold (5.0 °C) was strongest at week 10 of gestation, with a 0.72% (95% CI: 0.46, 0.97%) T/S longer cord blood telomere length.<sup>30</sup> Another study explored the association between a normal body temperature range (35.0–37.5 °C) and leukocyte telomere length in middle-aged and older adults, reporting a significant negative correlation between baseline body temperature and telomere length. However, there was no association between body temperature and the follow-up leukocyte telomere length and the 6-year longitudinal differences in telomere length.<sup>43</sup>

We found both significant immediate and lagged effects of air temperature on leukocyte telomere length at lags 0–1, 2–6, 0–6, and 0–13 days. The results indicate that high air temperatures over the preceding 2 weeks are associated with shorter telomere length. A recent epidemiological study based on 1792 participants with overweight/obesity reported a

decreasing trend in leukocyte telomere length in association with increasing PM<sub>10</sub>-levels, which was observed with a lag of up to 2 weeks.<sup>44</sup> These findings suggest that short-term effects of environmental factors on leukocyte telomere length should also be considered as adverse effects with potential health implications. Moreover, this study indicates that the more delayed effects (lags 0–13 days:  $-6.69\%$  [ $-9.04\%$ ;  $-4.27\%$ ]) are larger than the immediate effects (lags 0–1 days:  $-2.96\%$  [ $-4.46\%$ ;  $-1.43\%$ ]). It is conceivable that the immediate effects on telomere length on a day-to-day basis are at least partly compensated. However, the findings of this study suggest that repeated exposure to high temperatures may have compounding effects on telomere length. The reversibility of these effects still needs to be explored, in particular, to determine if there is an exposure level or frequency at which effects become partially or totally irreversible.

Except for season with lags 0–1 days, no significantly different effects were found across investigated population subgroups concerning age, sex, smoking status, obesity, physical activity, hypertension, cardiovascular disease, or different O<sub>3</sub>-levels. Furthermore, it is noteworthy that we found between individuals significant short-term effects of higher air temperature on shorter leukocyte telomere length in all of these subgroups. This means that the significant effects of air temperature on leukocyte telomere length are robust across all population subgroups. Moreover, we found similar results for different temperature metrics (Tmean, Tmin, and Tmax), again suggesting the stability of our results.

Global warming is an increasingly critical global challenge. The Intergovernmental Panel on Climate Change (IPCC) Working Group II Sixth Assessment Report 2022 reported that there is at least a greater than 50% probability that global warming will reach or exceed 1.5 °C in the near term, even for the very low greenhouse gas emissions scenario.<sup>45</sup> Furthermore, leukocyte telomere length shortening is a clinical gauge for biological aging and age-related disease risk.<sup>15–18</sup> Our results showed that between individuals, an IQR/1 °C increased daily air temperature was associated with shorter leukocyte telomere length. The findings of our study support the growing evidence that climate change and subsequent temperature increases can lead to adverse human health effects. In light of these findings, public policies should be implemented to decrease the rate of global warming and prevent heat-induced health risks, which, to a certain extent, may help increase lifespan as well as delay or reduce age-related diseases.

The exact underlying mechanisms by which air temperature impacts leukocyte telomere length are still far from being understood. Telomere lengths tend to shorten with increasing age, and telomere attrition can be accelerated by oxidative stress and inflammation.<sup>28,29</sup> Because of rich guanine content in the 5-TTAGGG-3 repeat sequence, telomeres are highly sensitive to oxidative stress, which causes telomere DNA to be deficient in the repair of single-strand breaks.<sup>46</sup> A recent study among bakery workers found that heat stress can increase the level of malondialdehyde (oxidative stress biomarker).<sup>24</sup> Heat stress also has been shown to induce the production of reactive oxygen species and the increased expression of the interleukin (IL)-8 and IL-8 receptor genes in human dental pulp cells.<sup>25</sup> Increasing short-term air temperature was significantly associated with hypomethylation *TLR-2*, which may activate the expression of *TLR-2* gene and lead to biological responses activating the C-reactive protein expression.<sup>26,27</sup> Another

previous study showed that short-term apparent temperature increase was associated with an increase in the acute inflammation factor high-sensitivity C-reactive protein.<sup>47</sup> A significant decrease in leukocyte telomere length was found as high-sensitivity C-reactive protein levels increased.<sup>48,49</sup> Thus, oxidative stress and inflammation may be among the mechanisms by which exposure to increasing temperature could lead to telomere shortening. Furthermore, telomerase, an enzymatic activity that plays a pivotal role in stabilizing telomeres by which telomeric repeats are added to the ends of chromosomes,<sup>50</sup> has been shown to be temperature-dependent, peaking at 37 °C under experimental conditions, followed by a decrease in the human telomerase's processivity with increasing temperature, primer concentration, and potassium ion (K<sup>+</sup>).<sup>51</sup>

This study has several strengths. We estimated the air temperature at each participant's residential address for each calendar day by a sophisticated statistical modeling method using satellite, meteorological, and land-use data, which introduced sufficient spatial and temporal air temperature variability and reduced exposure misclassifications compared to a fixed monitoring site. However, no personal temperature exposure measurements have been considered. Second, this study combined two independent cohort studies with a large sample size (total  $N = 5,864$ ), which should be considered more representative and generalizable than a single cohort study. Third, the KORA cohort (F3 and F4) provided extensive information regarding subject characteristics, which allowed us to adjust for a large number of confounders and explore several potential effect-modifying factors. Fourth, this study gives insight into the short-term effect of air temperature on shorter leukocyte telomere length among an adult population, something that has not been previously studied. However, our study also has some limitations. First, since this is an observational study, we cannot ignore the influence of potential residual confounding. However, we applied several different confounders to our model, and the results stayed robust. Second, our results are based on single-center cohort studies in Augsburg, Germany, and may not be generalizable to other populations with different ethnic, climatic, or demographic conditions. Furthermore, we only used ambient area level air temperature, but we do not know the extent to which individuals were exposed to outdoor temperatures, which increases the likelihood of misclassification of exposures. Finally, due to the lack of data in the present study, the association between air temperature and leukocyte telomere length was not investigated for different leukocyte subtypes, which may be characterized by different telomere lengths.

In conclusion, we found that between individuals, higher daily air temperature was associated with shorter leukocyte telomere length. Our findings add to the burgeoning evidence regarding how increased air temperature can adversely impact human health.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.est.2c04486>.

Exposure–response functions of air temperature and leukocyte telomere length at lags 0–1, 2–6, 0–6, and 0–13 days (Figure S1); Spearman's correlation coefficients ( $r$ ) between meteorological variables and air

pollutants (Figure S2); estimated effects (absolute change [95% CI]) of air temperature on leukocyte telomere length between individuals at lags 0–1, 2–6, 0–6, and 0–13 days per IQR increase in air temperature (Figure S3); estimated effects (percent change [95% CI] of geometric mean) of air temperature on leukocyte telomere length between individuals at lags 0–1, 2–6, 0–6, and 0–13 days per 1 °C increase in air temperature (Figure S4); sensitivity analysis: estimated effects (percent change [95% CI] of geometric mean) of air temperature on leukocyte telomere length between individuals at lags 0–1, 2–6, 0–6, and 0–13 days per IQR increase in air temperature (Figure S5) (PDF)

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### Notes

The authors declare no competing financial 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.

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