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Climate-related disasters and biological aging based on DNA methylation: a twin and family study in Australian women

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Abstract

Background: Weather-related disasters are devastating and may exhibit greater intensity globally under a changing climate, leaving survivors with greater and sustained health risks. However, the potential epigenetic mechanisms underlying the persistent adverse health impacts remain unclear. We aimed to examine the association between tropical cyclones (TCs) or flood exposure and biological aging based on DNA methylation.

Methods: We analysed peripheral blood samples from 479 women in 130 families across Australia and derived six metrics of DNA methylation age acceleration (DNAmAgeAC) for each participant, including Horvath's, Hannum's, and Zhang's DNAmAge, PhenoAge, and GrimAge versions 1 (GrimAge1) and 2 (GrimAge2). Linear mixed-effect and distributed lag nonlinear models accounting for familial clustering and delayed effects were used to estimate the DNAmAgeAC associated with TCs or flood exposure.

Results: TCs or flood exposures were generally associated with higher DNAmAgeAC of various metrics, which persisted for ≤6 months after exposure. Overall, participants exposed to TCs or floods had higher DNAmAgeAC based on Horvath's age [2.66 years, 95% confidence interval (CI): –2.94 to 8.27; $P = .357$], Hannum's age (6.81 years, 95% CI: 1.75–11.88; $P = .008$), PhenoAge (8.96 years, 95% CI: 2.35–15.57; $P = .008$), Zhang's age (0.93 years, 95% CI: –0.56 to 2.42; $P = .224$), GrimAge1 (2.60 years, 95% CI: –0.64 to 5.83; $P = .115$), and GrimAge2 (4.31 years, 95% CI: 0.52–8.09; $P = .026$). Socioeconomic status, age, smoking, and drinking behaviors modified the associations, with generally stronger adverse associations observed among the participants living in lower socioeconomic areas, <60 years of age, with higher smoking indices, or being current/former drinkers. The adverse associations were partially mediated by a shift in leucocyte distributions, particularly the change in the proportions of naive $CD8^+$ T cells, exhausted cytotoxic $CD8^+$ T cells, and granulocytes.

Conclusion: TC or flood exposures were associated with accelerated biological aging measured by using DNA methylation in Australian women, especially for those living in lower socioeconomic areas, <60 years of age, who were more smokers or drinkers. The accelerated aging may be partially contributed by the potential infections and alterations in the immune status in human bodies after climate-related disasters.

Keywords: tropical cyclones; floods; biological aging; DNA methylation; leucocytes

Introduction

Accelerated biological aging, defined as a greater biologic than chronological age, is a major risk factor for the occurrence and aggravation of cardiometabolic diseases (e.g. stroke, diabetes), cognitive decline, dementia, as well as multimorbidity and increased mortality [1–3]. Accelerated biological aging acts as a key and shared pathogenic process underlying the development and progression of a wide variety of diseases,

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Key Messages

- Survivors of climate-related disasters may experience persistent accelerated aging for ≤6 months in the aftermath.
- Individuals residing in lower socioeconomic areas, those <60 years of age, and current or former smokers and drinkers may be particularly vulnerable to the impacts of climate-related disasters.
- Accelerated aging in the aftermath of climate-related disasters may be partially attributed to the occurrence of infections and subsequent alterations in immune function in affected individuals.

reflecting integrated molecular and cellular damage, as well as systemic dysregulation [2, 4, 5]. To effectively mitigate biological age acceleration, there is an urgent need to better understand the determinants of the biological aging process.

Except for genetics, ambient environmental factors are a major contributor to biological aging [6]. Exposure to climate-related disasters has been found to be associated with persistent elevated risks of morbidity [7] and mortality [8, 9] in the population. At the cellular and molecular levels, these long-term adverse health effects may be partially attributed to epigenetic aging acceleration after exposures, as severe hardship could induce acute and chronic stress responses such as chronic low-grade inflammation and immune-cell expression changes (e.g. the abundance and functional state of leucocyte subtypes), thereby advancing canonical hallmarks of aging [10–12]. However, to our knowledge, no population-based studies have yet been conducted to assess the association of extreme weather event exposures and biological aging acceleration. This would help elucidate the potential mechanisms by which climate-related disasters affect human health, which is particularly important given the aging population and the increasing severity of climate-related disasters in a changing climate [13].

To address this research gap, using blood data from participants across Australia, we calculated the DNA methylation age (DNAmAge)—a very robust biomarker of biological aging in predicting the physical and physiological functional capability of a person (e.g. musculoskeletal strength and mobility) compared with other biological aging indicators [14, 15]. Furthermore, DNA methylation is modifiable by environmental factors and interventions, making it a more sensitive indicator of environmental stresses and a validated tool for identifying healthy aging determinants [16]. Although there are stressor-specific patterns observed in chronic (e.g. socioeconomic stress) versus acute (e.g. trauma) exposures [17, 18], DNAmAge integrates these diverse impacts into a composite measure of biological aging. Tropical cyclones (TCs) and floods are the two most common and destructive climate-related disasters [19] and share similar pathways in affecting public health (e.g. interrupting health services, increasing psychosocial stress) [7]. Therefore, we aimed to investigate whether these exposures were associated with higher DNAmAge acceleration (DNAmAgeAC, i.e. the difference between DNAmAge and chronological age) in the population and to evaluate various leucocyte subtypes as potential mediators reflecting immune states or responses following these exposures.

Methods

Study settings, design, and participants

We leveraged the existing data and study design from the Australian Mammographic Density Twins and Sisters Study (AMDTSS), described in detail previously [20, 21]. This study employed a twin and family design, focusing on female twins aged 40–70 years who had no historical records of breast cancer and were not pregnant or nursing mothers. Eligible participants residing in three distinct Australian urban centers (Melbourne, Sydney, and Perth) were recruited through the Australian Twin Registry between 1995 and 1999. An extended recruitment was subsequently conducted between 2004 and 2009 to include additional eligible participants [20].

All AMDTSS participants with DNA methylation measurements were eligible for the present study, which comprised 479 women from 130 families. Written informed consent was obtained from all individuals prior to participation. Ethical approval for the AMDTSS was obtained from the Human Research Ethics Committee of the University of Melbourne. This specific analysis received approval from the Monash University Human Research Ethics Committee (reference number 17813).

DNA methylation data and DNAmAge

Between 2005 and 2008, the participants provided a 27-ml peripheral blood sample via a visit to a designated pathology laboratory. Trained phlebotomists conducted blood collection at their homes in cases in which participants were unable to access the designated laboratory. All blood samples were dispatched to the biobank for processing within 48 hours of collection. Blood processing included the preparation of a Guthrie card for each participant. DNA was extracted from the Guthrie cards for DNA methylation measurement. The methylation of blood-derived DNA samples was measured by using the Illumina Infinium HumanMethylation450 BeadChip arrays [22] and processed by utilizing the Bioconductor minfi package [23], with detailed methodology elucidated in our previous work [21, 24].

Based on the cleaned DNA methylation data and an online calculator (https://dnamage.clockfoundation.org/), we calculated six metrics of DNAmAge, including Horvath's age (derived from 353 cytosine-phosphate-guanine sites [CpGs]) [25], Hannum's age (71 CpGs) [26], PhenoAge (513 CpGs) [27], Zhang's age (514 CpGs) [28], and GrimAge versions 1 (GrimAge1) and 2 (GrimAge2) (both derived from 1030 CpGs) [29]. A summary of the relevancy of these markers is provided in Supplementary Table S1. This calculator, which uses well-established and widely validated DNA methylation-based epigenetic clock algorithms, has been widely applied in previous studies to estimate biological age [21, 30, 31].

TC and flood exposures

We obtained the global TC and flood events data for between 1993 and 2009 from the International Best Track Archive for Climate Stewardship [32] and Dartmouth Flood Observatory [33], respectively, to estimate the TC and flood exposure of

each individual based on their residential address. A participant was considered exposed to a flood or TC if their home was located within the affected areas. A detailed methodology of the exposure assessment is provided in Supplementary Text S1. Our primary exposure was defined for each subject based on whether they had been exposed to TCs or floods.

Covariates and candidate mediators

We collected demographic information and self-reported lifestyles from each participant through a telephone-administered questionnaire. Detailed questions were reported in our previous work [21].

We defined potential confounding variables as factors that could affect both the TC and flood exposures and DNAmAge, but were not on the pathways between them [34]. We used a directed acyclic graph, constructed by using DAGitty v3.1 software [35], to identify potential covariates to adjust for confounding and candidate mediators between the exposure and outcome based on the literature (Supplementary Fig. S1). The covariates included were chronological age, educational level, marital status, smoking and drinking status, area-level socioeconomic status (SES), and annual mean temperature and relative humidity (RH). We incorporated various types of leucocyte cells as candidate mediators, based on the assumptions that (i) TC and flood exposures could influence DNAmAge by changing their levels [36, 37] and (ii) these blood cell types were unlikely to affect the probability of TC and flood exposure (i.e. not a confounder) (Supplementary Fig. S1). A detailed definition of these covariates and mediators is given in Supplementary Text S2.

Statistical analysis

To account for the clustering within families in our data, we used a linear mixed-effect and distributed lag nonlinear model to assess the DNAmAgeAC associated with TC or flood exposures. A distributed lag term of ≤12 months after exposures was included in the model to account for the potential delayed effects [38]. Detailed model descriptions and specifications are provided in Supplementary Text S3. The results are presented as the change (i.e. the regression coefficient of β), with 95% confidence intervals (CIs), in DNAmAgeAC among the participants exposed to TC or flood compared with those unexposed. A series of sensitivity analyses (e.g. different model specifications) was conducted to test the robustness of our results, as detailed in Supplementary Text S4.

To identify potential effect modifiers and vulnerable populations, we further conducted a pre-specified subgroup analysis by using the same modeling strategy as in the main model analysis. Subgroup analyses were performed by using area-level SES (lowest 50% vs highest 50%), educational level (secondary or below vs higher than secondary), age group (<60 vs ≥60 years), smoking behavior (never smoked vs current/former smoker), DNA methylation-based smoking index (≤ median vs > median), alcohol use (never drank vs current/former drinker), marital status (married or living as married vs never married/widowed/separated/divorced), and suburban residence (rural vs urban). Between-subgroup statistical difference in effect estimates was tested by using a Wald-type test [39]. A causal and parallel mediation analysis was performed to assess the potential mediation effects of the candidate mediators [i.e. the seven types of leucocytes, including naive $CD8^+$ T cells, exhausted cytotoxic $CD8^+$ T cells, plasma blasts, $CD4^+$ T cells, granulocytes, monocytes, natural killer (NK) cells] [40], as detailed in Supplementary Text S5.

All analyses were performed via R software (version 4.1.3), using the R packages of 'mice' [five multiple imputations by chained equations to impute missing values for educational level (two participants) and area-level SES (one participant)], 'lme4' (linear mixed-effect model), 'splines' (nature cubic splines), and 'dlnm' (cross-basis function).

Results

A total of 479 participants from various regions across Australia were included in this study (Fig. 1). All participants were female, with an average chronological age of 56.4 years (SD: 7.9) (Tables 1 and 2). The distribution of participants across different area-level SESs and educational levels was similar. Approximately 28.4% (136/479) were exposed to TCs or floods during the 12 months before their blood draw and the remaining 71.6% (343/479) were not exposed during this period (Table 1). Among the six metrics of DNAmAgeAC, Zhang's age acceleration exhibited the smallest variation [SD: 1.34, interquartile range (IQR): 1.47], whereas PhenoAge acceleration showed the largest variation (SD: 5.78, IQR: 8.17) (Table 2). The distributions of these metrics by exposure status and subgroup variables are presented in Supplementary Tables S2–S6.

Figure 2 shows the temporal pattern of DNAmAgeAC related to TC or flood during the 0- to 12-month post-exposure period. The magnitude of the DNAmAgeAC associated with TCs or floods generally decreased over time after exposures (P for trend was consistently $< .001$ for the six DNAmAgeAC metrics). The effects of a TC or flood on DNAmAgeAC tended to be minimal 6 months after exposure. We thus focused on the effect estimates of DNAmAgeAC in the first 6 months after exposure. The cumulative effects of a TC or flood on DNAmAgeAC over the 6 months after exposures are shown in Fig. 3. Overall, participants exposed to TCs or floods had higher DNAmAgeAC based on Horvath's age (2.66 years, 95% CI: –2.94 to 8.27; $P = .357$), Hannum's age (6.81 years, 95% CI: 1.75–11.88; $P = .008$), PhenoAge (8.96 years, 95% CI: 2.35–15.57; $P = .008$), Zhang's age (0.93 years, 95% CI: –0.56 to 2.42; $P = .224$), GrimAge1 (2.60 years, 95% CI: –0.64 to 5.83; $P = .115$), and GrimAge2 (4.31 years, 95% CI: 0.52–8.09; $P = .026$), and compared with those unexposed. Similar results were observed in the sensitivity analyses (Supplementary Figs S2–S6).

When the effects across population subgroups were assessed (Fig. 3), the age acceleration of GrimAge2 related to TC or flood exposures was higher among the participants whose area-level SES was below the median of Australia compared with those with a higher area-level SES (8.99 years, 95% CI: 1.07–16.90, $P = .026$ vs 0.98 years, 95% CI: –3.85 to 5.80; $P = .704$). The effect estimates also varied between age groups, with greater TC- or flood-associated age acceleration in PhenoAge and Hannum's age for participants <60 years old compared with their counterparts. However, there was not sufficient evidence to detect the between-group difference for other DNAmAgeAC metrics.

For participants in different smoking categories, no difference in the DNAmAgeAC level was found between current/former smokers and never smokers after TC or flood exposures (Fig. 3). However, when a DNA methylation-based continuous smoking index was used to indicate the smoking

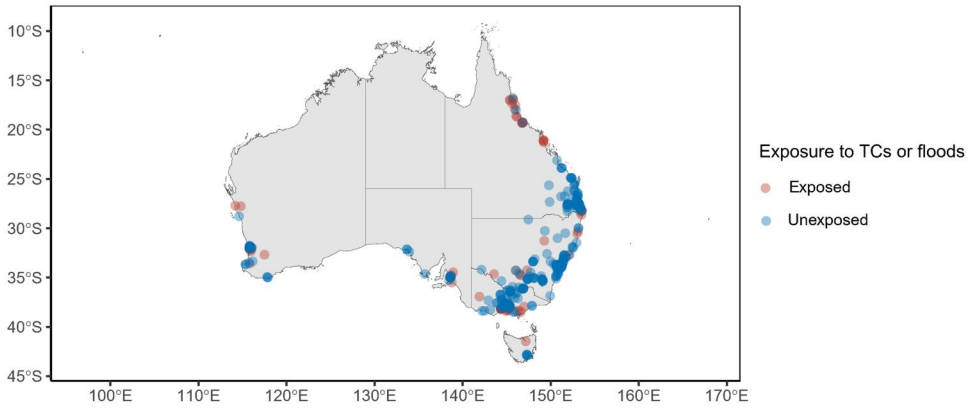

Figure 1. Spatial distribution and exposure to TCs or floods for the 479 study participants in Australia during 2004–2009. Exposure was defined for each subject based on whether they had been exposed to TCs or floods during the 12 months before their blood draw.

Table 1. Basic characteristics of the 479 study participants in Australia during 2004–2009 by exposure status.[a]

Characteristics	*n* (%)		
	Total	Unexposed	Exposed
Women	479 (100)	343 (100)	136 (100)
Age group (years)			
<60	323 (67.4)	233 (67.9)	90 (66.2)
≥60	156 (32.6)	110 (32.1)	46 (33.8)
Education level			
Secondary or below	198 (41.3)	139 (40.5)	59 (43.4)
Vocational training	135 (28.2)	100 (29.2)	35 (25.7)
University	144 (30.1)	102 (29.7)	42 (30.9)
Missing	2 (0.4)	2 (0.5)	0 (0.0)
Area-level SES percentile			
(0, 25)	88 (18.4)	67 (19.5)	21 (15.4)
(25, 50)	103 (21.5)	77 (22.4)	26 (19.1)
(50, 75)	136 (28.4)	92 (26.8)	44 (32.4)
(75, 100)	151 (31.5)	106 (30.9)	45 (33.1)
Missing	1 (0.2)	1 (0.3)	0 (0.0)
Marital status			
Married or living as married	369 (77.0)	263 (76.7)	106 (77.9)
Never married	28 (5.9)	20 (5.8)	8 (5.9)
Widowed/separated/divorced	82 (17.1)	60 (17.5)	22 (16.2)
Smoking status			
Current	41 (8.6)	33 (9.6)	8 (5.9)
Former	147 (30.7)	109 (31.8)	38 (27.9)
Never	291 (60.8)	201 (58.6)	90 (66.2)
Drinking status			
Current	235 (49.1)	165 (48.1)	70 (51.5)
Former	52 (10.9)	36 (10.5)	16 (11.8)
Never	192 (40.1)	142 (41.4)	50 (36.8)

[a] Exposure was defined for each subject based on whether they had been exposed to TCs or floods during the 12 months before their blood draw.

Table 2. Descriptive statistics of continuous variables in the 479 participants in Australia during 2004–2009.

Variables	Mean ± SD	Q1	Median	Q3	IQR
Chronological age (years)[a]	56.4 ± 7.9	50.2	55.7	61.9	11.8
DNAmAge (years)					
Horvath's age	55.5 ± 6.5	50.9	55.2	60.0	9.1
Hannum's age	57.3 ± 6.4	52.9	57.1	61.5	8.6
Zhang's age	64.7 ± 2.1	63.2	64.8	66.3	3.1
PhenoAge	53.0 ± 7.4	48.0	52.8	57.7	9.8
GrimAge1	54.2 ± 6.5	49.5	53.9	58.5	9.0
GrimAge2	57.6 ± 6.3	53.0	57.1	61.7	8.8
DNAmAgeAC (years)[b]					
Horvath's age acceleration	0.0 ± 4.9	–3.2	–0.2	3.0	6.3
Hannum's age acceleration	0.0 ± 4.4	–2.8	0.2	2.7	5.4
Zhang's age acceleration	0.0 ± 1.3	–0.7	0.1	0.7	1.5
PhenoAge acceleration	0.0 ± 5.8	–4.2	0.3	4.0	8.2
GrimAge1 acceleration	0.0 ± 3.1	–2.2	–0.4	1.7	3.9
GrimAge2 acceleration	0.0 ± 3.6	–2.4	–0.4	2.0	4.4
Annual mean temperature (°C)	17.7 ± 2.8	15.3	17.8	20.3	5.0
Annual mean RH (%)	69.8 ± 3.8	67.9	70.1	72.1	4.2

[a] Chronological age was calculated as the difference between the birth date and the date of the blood draw.
[b] DNAmAgeAC was calculated as the residuals of regressing each DNAmAge metric on chronological age.
IQR, interquartile range.

levels, participants with a higher smoking index (> median) had greater age acceleration in PhenoAge and Zhang's age compared with those with a lower smoking index (≤ median). By comparison, current/former drinkers exhibited higher age acceleration in more DNAmAgeAC metrics, including PhenoAge, Horvath's age, Hannum's age, and Zhang's age, compared with the nondrinkers. There was insufficient evidence to detect the differences in DNAmAgeAC metrics between subgroups based on educational level, suburban residence, or marital status.

In the mediation analyses (Table 3), we found that the seven subsets of leucocytes mediated a major part of the effects TC or flood exposures on DNAmAgeAC based on PhenoAge (48.3%, 95% CI: 28.0%–76.9%), GrimAge2 (74.3%, 95% CI: 46.3%–124.9%), and Hannum's age (58.4%, 95% CI: 36.9%–92.4%). In general, naive $CD8^+$ T cells, exhausted cytotoxic $CD8^+$ T cells, and granulocytes were the leading types of cells that contributed most to the mediation effects. The mediated proportions of naive $CD8^+$ T cells, exhausted cytotoxic $CD8^+$ T cells, and granulocytes ranged from 23.0%–29.4%, 9.1%–28.3%, and 10.3%–20.5%, respectively, across various DNAmAgeAC metrics. In contrast, consistently weaker and nonsignificant mediation effects were observed for plasma blasts and $CD4^+$ T cells.

Discussion

To our knowledge, few population-based studies have evaluated the association and potential pathways between biological aging and exposure to climate-related disasters. We found that exposures to TCs or floods were associated with persistent biological aging acceleration, especially among

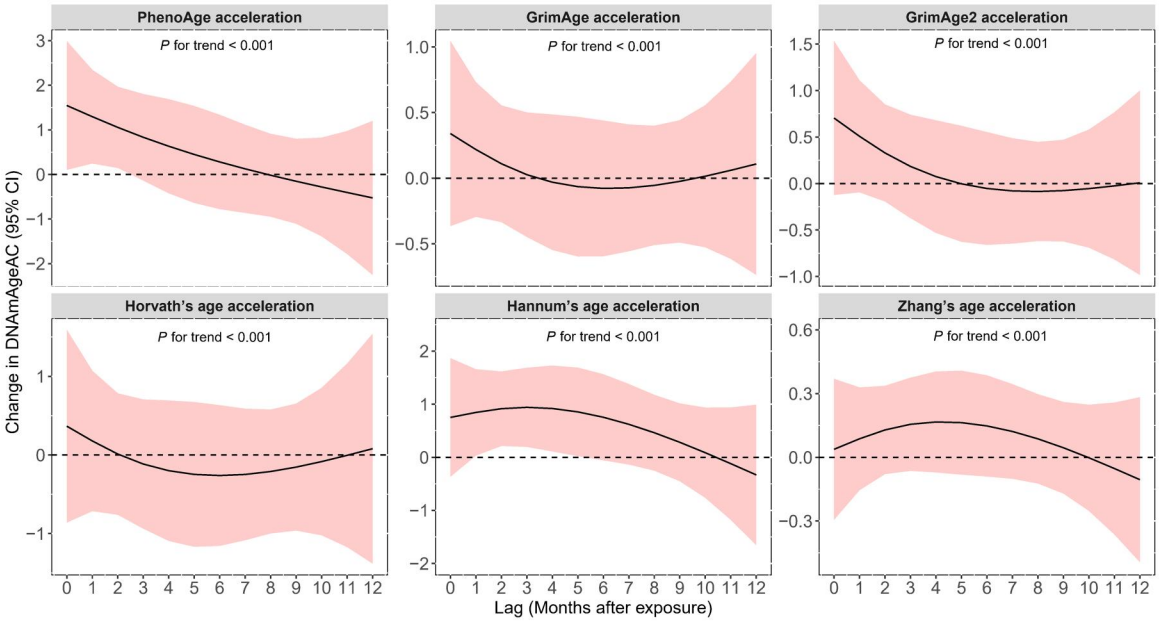

Figure 2. Changes in DNAmAgeAC among the participants exposed to TCs or floods compared with those unexposed during the 0- to 12-month post-exposure period. The shaded areas indicate the 95% CIs. The effect estimates were derived from within-sibship analyses fitted by a distributed lag and linear mixed model adjusting for the individual's chronological age, educational level, marital status, area-level SES, smoking behavior, alcohol use, annual mean temperature, and annual mean RH.

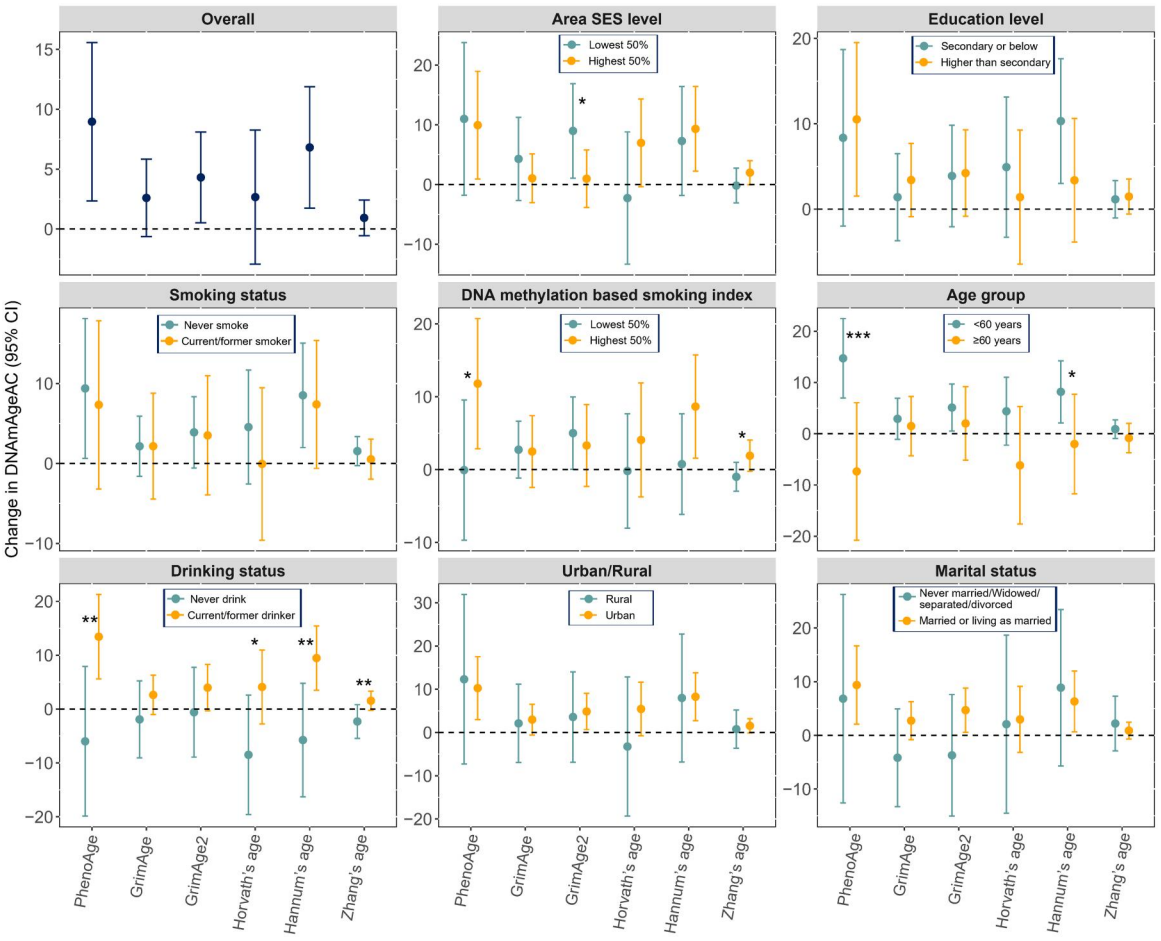

Figure 3. Changes in DNAmAgeAC among the participants exposed to TCs or floods compared with those unexposed in the overall and subgroup populations. Subgroup analyses were conducted by area-level SES, education level, smoking status, DNA methylation-based smoking index, chronological age, drinking status, location types (urban/rural), and marital status. The error bars indicate the 95% CIs. The effect estimates were derived from within-sibship analyses fitted by a distributed lag and linear mixed model adjusting for the individual's chronological age, educational level, marital status, area-level SES, smoking behavior, alcohol use, annual mean temperature, and annual mean RH. *P for difference $< .10$, **P for difference $< .05$, ***P for difference $< .01$.

Table 3. Estimated proportion mediated (with 95% CI) through the change in different types of blood cells for the acceleration in DNAmAge after exposures to TCs or floods.

Leucocyte subtypes	Mediation proportion (%, 95% CI)[a]					
	Horvath's age acceleration	Hannum's age acceleration	Zhang's age acceleration	PhenoAge acceleration	GrimAge1 acceleration	GrimAge2 acceleration
Naive $CD8^+$ T cells	18.7 (–14.1, 34.8)	29.4 (16.8, 50.7)	38.6 (–17.4, 78.8)	27.2 (15.4, 46.4)	24.3 (5.0, 51.6)	23.0 (11.2, 44.4)
Exhausted cytotoxic $CD8^+$ T cells[b]	44.6 (–38.7, 71.7)	9.1 (2.8, 18.8)	18.8 (–4.5, 42.1)	12.1 (4.7, 22.4)	47.5 (10.9, 94.6)	28.3 (12.2, 55.8)
Plasma blasts	–3.8 (–10.1, 7.2)	–1.4 (–5.2, 0.9)	–5.7 (–16.0, 8.9)	1.1 (–1.2, 4.2)	–2.8 (–9.8, 3.4)	–0.3 (–3.2, 2.7)
$CD4^+$ T cells	14.6 (–22.2, 47.3)	–9.1 (–27.6, 1.8)	–34.8 (–79.2, 29.8)	–7.0 (–22.6, 3.3)	–12.1 (–38.7, 13.8)	–9.9 (–29.2, 1.9)
Granulocytes	–12.0 (–25.8, 17.1)	13.0 (2.1, 25.9)	4.4 (–9.8, 17.9)	10.3 (0.5, 21.6)	23.2 (–1.9, 50.3)	20.5 (3.6, 40.0)
Monocytes	–3.3 (–20.6, 23.8)	5.8 (–0.7, 14.3)	1.3 (–16.6, 24.4)	4.4 (–2.5, 12.4)	9.2 (–5.1, 24.9)	11.3 (3.1, 25.9)
NK cells	4.4 (–10.2, 17.6)	11.5 (2.9, 23.9)	5.9 (–7.6, 17.5)	0.2 (–3.5, 5.0)	–0.9 (–10.8, 8.0)	1.3 (–3.9, 6.9)
Total[c]	63.4 (–40.3, 108.3)	58.4 (36.4, 91.2)	28.4 (–23.1, 83.6)	48.3 (29.2, 75.6)	88.3 (31.9, 159.6)	74.3 (44.9, 124.1)

[a] Mediation proportion was calculated as the indirect effect divided by the total effect (%).
[b] Exhausted cytotoxic $CD8^+$ T cells were defined as those exhibiting a phenotype marked by positivity for CD8 and negativity for both CD28 and CD45R.
[c] Total proportions mediated through the change in these seven types of blood cells.

participants who were aged <60 years, resided in areas with lower SES, had higher smoking indices, or were current/former drinkers. The adverse associations were partially contributed by leucocyte distribution shifts.

We found that participants exposed to TCs or floods generally exhibited higher DNAmAgeAC compared with those unexposed. However, there is limited evidence available regarding the effects of climate-related disasters on human biological aging. To our knowledge, only one animal study has been conducted to investigate these effects, examining the effects of Hurricane Maria on a group of rhesus macaques, with samples taken 4 years before ($n = 435$) and 1 year after ($n = 108$) the hurricane [37]. Our results aligned with these findings, which suggested that the macaques exposed to the hurricane exhibited greater biological aging when measured based on human transcriptional age predictors [41, 42] compared with those unexposed. Specifically, the exposed macaques exhibited greater biological aging by an average of 2 years compared with the unexposed individuals, equivalent to ∼7–8 years of a human lifespan. These consistent findings across human and animal studies underscore the potentially substantial and enduring adverse impacts of climate-related disasters (see Supplementary Text S6 for more discussions). However, the strength of the associations varied for different metrics of DNAmAgeAC, as these metrics relied on distinct sets of CpG sites tailored to capture various aspects of biological aging [21, 43]. More discussions on this point are provided in Supplementary Text S7.

To provide evidence on the potential cellular mechanisms and vulnerable populations underlying the health impacts of climate-related disasters, we performed mediation and subgroup analyses. In the mediation analysis, we found that the variations in naive $CD8^+$ T cells, exhausted cytotoxic $CD8^+$ T cells, and granulocytes mediated a large number (9.1%–29.4%) of the adverse associations between TC or flood exposures and biological aging. Currently, evidence on the biological mechanisms underlying the health impacts of climate-related disasters is scarce, particularly within the context of human physiology [44]. The leading contributions of naive $CD8^+$ T cells, exhausted cytotoxic $CD8^+$ T cells, and granulocytes to the mediation effects suggest that these cell types might play a significant role in the biological response to flood exposure, possibly through immune system activation or stress response pathways. $CD8^+$ T cells, both naive and exhausted cytotoxic, along with granulocytes, are key players involved in inflammation and the immune response against infections [45, 46]. For example, T-cell exhaustion is a common feature of many chronic infections in both mice and humans [47]. The aftermath of TC or flood exposure (e.g. infections due to contaminated water, mental and physical stress due to property loss or displacement) might trigger acute and chronic immune activation, systemic inflammation, and stress, thereby prompting alterations in the distribution and functionality of specific cell subsets [7]. More discussions on the potential physiological and pathophysiological mechanisms are provided in the Supplementary Text S8. Understanding the drivers of health stress in the aftermath of climate-related disasters is essential for safeguarding human health via appropriate resilience and recovery strategies and interventions, especially given the increasing frequency and intensity of such events in a changing climate [44]. More discussions on potentially vulnerable populations are provided in Supplementary Text S9.

Our study has three main strengths. First, we implemented a twin and family design, which compared each participant with her siblings, to reduce potential confounding by genetic background and shared familial factors (e.g. childhood living environment, familial dietary behavior) [21, 48]. This allowed us to more accurately reveal the true relationships between environmental exposures and DNAmAgeAC given that genetic and familial factors explain a substantial proportion of the variation in DNAmAge [16, 21, 49]. Additionally, compared with prior relevant studies that solely focused on a group of macaques after a single TC event (i.e. Hurricane Maria) [37], we included population-based data, along with all TC and flood events during the study period, to more comprehensively capture the human health impacts of climate-related disasters. Finally, we employed a mediation analysis approach to quantify the extent to which leucocyte subsets mediated the effects observed, which offered insights into the potential mechanisms underlying the relationship between climate-related disasters and human biological aging.

However, it is important to acknowledge some limitations of our work to inform future studies. For each participant, we took one blood sample and only one biological age measurement during the study period. Further longitudinal studies

with follow-up assessments are warranted to verify our findings. Moreover, the relatively small size of our sample increased the uncertainty of our results, as indicated by the wide CIs of the effect estimates. This limitation increased the likelihood of Type II errors and rendered our findings more conservative, particularly in subgroup analyses. Finally, this study included only women. Prior studies have indicated that women appeared to be more likely to suffer psychological distress (e.g. anxiety, posttraumatic stress disorder, gender-based violence) than men in the aftermath of cyclones [50]. Therefore, the adverse associations between TC or flood exposures and DNAmAgeAC might be weaker in men.

Conclusions

In summary, TC or flood exposure was associated with accelerated biological aging measured by using DNA methylation in Australian women. In particular, the impacts appeared to be more evident among those who were living in lower socioeconomic areas, were <60 years of age, had higher smoking indices, or were current/former drinkers. Leucocyte subsets, especially $CD8^+$ T cells, including both naive and exhausted cytotoxic subtypes, along with granulocytes, could be important mediators of the observed adverse associations. Our findings highlight the substantial health implications of climate-related disasters extending beyond direct injuries, emphasizing the importance of and urgency for understanding their physiological effects on human health under a changing climate.

Ethics approval

The AMDTSS was approved by the Human Research Ethics Committee of the University of Melbourne. Written informed consent was obtained from all participants. The present study was approved by the Monash University Human Research Ethics Committee (reference number 17813).

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Author contributions

W.H.: conceptualization, data curation, methodology, formal analysis, visualization, software, writing—original draft; R. X.: conceptualization, data curation, methodology, writing—review and editing; Y.W.: data curation, writing—review and editing; Z.Y.: data curation, writing—review and editing; E. M.W.: data curation, writing—review and editing; M.C.S.: data curation, writing—review and editing; J.L.H.: data curation, resources, writing—review and editing; M.J.A.: supervision, writing—review and editing; E.A.R.: methodology, supervision, writing—review and editing; Sha.L.: supervision, writing—review and editing; Shu.L.: supervision, data curation, methodology, software, writing—review and editing; Y. G.: conceptualization, supervision, resources, methodology, funding acquisition, writing—review and editing.

Supplementary data

Supplementary data is available at *IJE* online.

Conflict of interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: M.J.A. holds investigator-initiated grants from Pfizer, Boehringer-Ingelheim, GlaxoSmithKline, and Sanofi for unrelated research. He has undertaken an unrelated consultancy for Sanofi. He also received a speaker's fee from GSK. The other authors declare no competing interests.

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Data availability

The raw and processed DNA methylation dataset is open for access or free from the Gene Expression Omnibus (accession number GSE100227). As required according to the ethics approval conditions, the other data (e.g. covariates) are not allowed to be open for access. However, these data could be accessed on reasonable request to J.L.H. (j.hopper@unimelb.edu.au).

Use of artificial intelligence (AI) tools

AI tools were not used in this study or for writing the paper.

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