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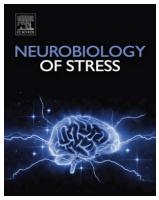

Greater stress and trauma mediate race-related differences in epigenetic age between Black and White young adults in a community sample

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ABSTRACT

Black Americans suffer lower life expectancy and show signs of accelerated aging compared to other Americans. While previous studies observe these differences in children and populations with chronic illness, whether these pathologic processes exist or how these pathologic processes progress has yet to be explored prior to the onset of significant chronic illness, within a young adult population. Therefore, we investigated race-related differences in epigenetic age in a cross-sectional sample of young putatively healthy adults and assessed whether lifetime stress and/or trauma mediate those differences. Biological and psychological data were collected from self-reported healthy adult volunteers within the local New Haven area (399 volunteers, 19.8% Black, mean age: 29.28). Stress and trauma data was collected using the Cumulative Adversity Inventory (CAI) interview, which assessed specific types of stressors, including major life events, traumatic events, work, financial, relationship and chronic stressors cumulatively over time. GrimAge Acceleration (GAA), determined from whole blood collected from participants, measured epigenetic age. In order to understand the impact of stress and trauma on GAA, exploratory mediation analyses were then used. We found cumulative stressors across all types of events (mean difference of 6.9 $p = 2.14e\text{-}4$) and GAA ($\beta = 2.29$ years [1.57–3.01, $p = 9.70e\text{-}10$] for race, partial $\eta^2 = 0.091$, model adjusted $R^2 = 0.242$) were significantly greater in Black compared to White participants. Critically, CAI total score (proportion mediated: 0.185 [0.073–0.34, $p = 6e\text{-}4$]) significantly mediated the relationship between race and GAA. Further analysis attributed this difference to more traumatic events, particularly assaultive traumas and death of loved ones. Our results suggest that, prior to development of significant chronic disease, Black individuals have increased epigenetic age compared to White participants and that increased cumulative stress and traumatic events may contribute significantly to this epigenetic aging difference.

1. Introduction

Life expectancy amongst Black Americans in the United States has consistently been less than the national average. Despite advances in modern medicine and governmental policies that have improved access to care for all Americans, National Vital Statistics Services in 2020 had reported life expectancy amongst Black Americans as 2–3 years less than the general population (National Vital Statistics Services, 2021), a gap that widened during the COVID-19 pandemic (Lundberg et al., 2023). Additionally, even controlling for income, gender, and socioeconomic status, Black Americans have greater prevalence, increased burden, and earlier onset age of chronic illness when compared to the general population (Williams et al., 2010). While these race-related health disparities and some of the potential causes that may underlie them are widely reported (Colen et al., 2018; Pascoe and Richman, 2009), our understanding of how race-related differences in the experience of psychosocial stress or trauma, the pathological means of how such experiences may be biologically embedded, and its impact on the observed race-related mortality gap remains obscured.

The GrimAge epigenetic clock has been identified as a reliable predictor of age-related morbidity and mortality (Horvath and Raj, 2018a; Lu et al., 2019; McCrory et al., 2020). Comparing epigenetic age to

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chronological age provides a biomarker for biological age, indicating whether aging is advanced or delayed (Horvath and Raj, 2018b). Chronic diseases such as type II diabetes mellitus, hypertension, cardiovascular disease, and obesity, have been associated with advanced aging and shorter life expectancies (Ayotte et al., 2012; Kho et al., 2021). Similarly, traumatic or adverse events correlate with various metabolic and inflammatory disorders (Mathur et al., 2016; Pantesco et al., 2018; Sullivan et al., 2018), and long-term stress increases aging markers in chronically ill individuals (Chae et al., 2016; Mathur et al., 2016; Simons et al., 2018; Xu et al., 2018). Both our research and other studies have found that cumulative stress and trauma significantly accelerate epigenetic aging (Harvanek et al., 2021; Sullivan et al., 2018; Wolf et al., 2016) in young non-ill community samples.

Though social factors such as differential healthcare access and systemic racial bias significantly drive life expectancy disparities following disease onset (Cerdeña et al., 2021; Fitzgerald and Hurst, 2017), differences in trauma and stressor frequency and/or intensity may influence epigenetic aging prior to evident disease, subsequently impacting health outcomes (Kho et al., 2021). How these stressors are biologically embedded is currently unclear, though is an area of active study (Geronimus et al., 2016). Longitudinal studies have indicated that race-related differences in childhood stress and trauma exposure can negatively impact epigenetic aging (Wolf et al., 2018) and neurological development (Dumornay et al., 2023). In contrast, protective factors like supportive family environments do not appear to affect epigenetic aging despite trauma exposure (Brody et al., 2016). Prior research has noted signs of accelerated aging in self-identified Black Americans (Kho et al., 2021), though these studies typically focus on individuals with chronic medical or psychiatric diseases (Chae et al., 2016; Geronimus et al., 2010; Simons et al., 2021). The presence of race-related disparities in epigenetic age before evident disease and the role of adverse stress experiences in these differences among a young, ostensibly healthy population remains uncertain.

Drawing upon previous research (de Mendoza et al., 2018; Everage et al., 2012; Geronimus et al., 2010; Heard-Garris et al., 2018; Simons et al., 2018), we hypothesize that there will be significant race-related differences in the number of lifetime stress and traumatic events between Black and White participants. We propose that higher number of stress and traumatic events will be associated with greater epigenetic aging in Black compared to White participants. Using a cross-sectional study involving young to middle-aged volunteers in self-reported good health, we assessed the relationship between stress and trauma, race, and epigenetic aging via GrimAge. Our investigation initially sought to determine whether race is associated with cumulative stressful events and with GrimAge acceleration (GAA) in a healthy community sample. Through an exploratory mediation analysis, we then examined whether cumulative stress and trauma mediates the relationship between race and GAA and whether specific types of stressors, particularly traumatic events, primarily contribute to this effect. Finally, we incorporated socioeconomic and biobehavioral covariates differing between the populations to ascertain if stress and trauma continue to mediate the relationship between race and GAA, even after considering these factors.

2. Material and methods

2.1. Cohort recruitment

Participants for this research were 399 community adults between the ages of 18–50 who self-identified as Black (79 individuals) or White (320 individuals) from the greater New Haven, CT area who provided written and verbal informed consent to participate in this research at the Yale Stress Center (Table 1) (Xu et al., 2018). Those who identified in a racial group other than Black or White were excluded. Participants were recruited via advertisements to participate in a study on the effects of stress on their health via advertisements online, in local newspapers, and at a community center. Participants were excluded if they had an active mental health disorder or substance use disorder (not including nicotine) as assessed via the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders 4th Edition(American Psychiatric Association, 1994); were pregnant; had a chronic medical condition (e.g., hypertension, diabetes, hypothyroidism); were unable to read English at or above the 6th grade level; had a head injury; or were using any prescribed medications for any psychiatric or medical disorders. Urine toxicology and breathalyzer screens were conducted at each

Table 1
Demographics of community population.

Category		Black (n = 79)			White (n = 320)			P value (odds ratio[1]/location difference[2], 95% conf int)
		Frequency[1]/ mean[2]	5th% to 95th%	Stdev	Frequency[1]/ mean[2]	5th% to 95th%	Stdev	
Gender[1]	*Female*	41.8%			46.3%			0.529 (0.83, 0.49–1.41)
	Male	58.2%			53.8%			
Smoker[1]	*No*	78.5%			77.8%			1 (1.04; 0.56–2.02)
	Yes	21.5%			22.2%			
Age[2]		31	19–48	10.1	28.4	19–46	8.59	0.104 (2, 0–3)
BMI[2]		28.8	20.8–39.1	5.4	26.7	20.1–37.1	5.2	**3.96e-4 (2.3, 1.1–3.5)**
Days drinking past 4 weeks[2]		4.01	0–18	6.5	7.18	0–21	7	**8.19e-7 (-3, -4 - -1)**
CAI total score[2]		25.2	7–48.5	14.3	18.3	6–33	8.5	**2.14e-4 (5, 2–8)**
Stress Subscale[2]		11.4	1–25	7.7	9.1	2–17	4.9	0.068 (1, 0–3)
Major Life Event Subscale[2]		2.7	0–6	1.9	1.8	0–5	1.6	**1.63e-5 (1, 1–1)**
Recent Life Event Subscale[2]		3.1	0–8	2.7	2.4	0–7	2.1	0.082 (0, 0–1)
Trauma Subscale[2]		7.9	1–17	5.6	5	1–12	3.3	**6.39e-6 (2, 1–3)**
Years of Education[2]		14.1	12–18	1.9	15.6	12–20	2.4	**1.73e-8 (-2, -2 - -1)**
Total Income (monthly) [2]		$1,327.00	0–3897	$1,409	$1,117.00	0–3500	$1,455	0.0772 ($180, 0–400)
Cornell-total[2]		17.8	0–67	20.4	15.2	2–43	12.9	0.504 (−1, -3 - 2)
Cornell-bio Subscale[2]		12	0–40	13.1	10	2–30	8.2	0.791 (0, -2 - 1)
Cornell-psych Subscale[2]		5.8	0–28	8.5	5.2	0–19	6.2	0.279 (0, -1 - 0)

P values derived from either Fisher exact test (categorical variables) or Wilcoxon rank sum test (continuous variables, Wilcoxon test used due to non-normality in distributions). Abbreviations: BMI = Body Mass Index; CAI = Cumulative Adversity Inventory.

appointment to ensure drug abstinence. The research protocol was reviewed and approved by the Yale Institutional Review Board (IRB).

2.2. Psychological measures

Cumulative stress was assessed using the Cumulative Adversity Inventory (CAI(Turner et al., 1995)), which is a 140-item well-validated, retrospective structured interview that assesses the occurrence of specific types of stressful life events, including work, financial, relationship, traumatic, major life events, family and neighborhood and health related stressors across the lifetime, and in addition, the participants' perceived sense of being overwhelmed by specific events. Occurrence of the specific stressful life events listed above and frequency of occurrence of each were quantified and summed to make up the CAI life events total score. In addition, the events were categorized by three subscales: major life events, traumatic life events, and recent life events. For purposes of scoring, a "yes" to the specific stressful event occurring led to a "1" and a sum of all the "yes" endorsements comprised the subscale score. A fourth chronic stress subscale assessed the participant's sense of feeling overwhelmed by the specific life events (see our prior paper, (Harvanek et al., 2021). The chronic stress subscale was rated on a "not true", "somewhat true", or "very true" scale, with assigned scores of 0, 1, and 2, respectively. The final score is a sum of these values for the chronic stress subscale. The CAI total score was a sum of each of the subscale scores, with a higher score indicating a higher overall level of lifetime cumulative stress. To further understand traumatic stress, traumatic events were sub-categorized into four areas: assaultive violence, other injury or shocking event, learning of traumas of a closer friend or relative and the death of a loved one, based on previous work utilizing the Detroit Area Survey(Breslau et al., 1998). This method has been used to classify different types of trauma and their effects(Breslau et al., 2004). The alpha reliability of the CAI and trauma subscale are 0.87 and 0.77 respectively.

Self-reported current health was assessed by the Cornell Medical Index (CMI)(Brodman et al., 1949). Physical and psychological heath symptoms are captured by a 195-question interview, a validated reliable measure of current general health used by various studies(Abramson, 1966; Brodman et al., 1949; Perlmutter and Nyquist, 1990). CMI alpha reliability is 0.95. Self-report was also used to identify smoking status (current smoker or non-smoker), and alcohol use (here quantified by standard drinks per 28 days).

2.3. DNA methylation and epigenetic clock analysis

As previously described, DNA was extracted from whole blood(Xu et al., 2018). Methylation for DNA samples were profiled using Illumina Infinium HumanMethylation450 Beadchips, which covers 96% of CpG islands and 99% of RefSeq genes. Quality controls are as previously published(Xu et al., 2018), further information regarding DNA methylation is available in the supplementary methods.

The New Methylation Age Calculator at https://dnamage.genetics.ucla.edu/new(Lu et al., 2019), was used to estimate epigenetic age as outlined by Lu et al. As per their protocol, normalized data and advanced analysis option were used. We utilized GrimAge acceleration (GAA), which is defined as the residuals of a linear correlation of GrimAge to chronologic age.

In the analyses of GAA, we accounted for proportions of B Cells, $CD4^+$ T cells, $CD8^+$ T cells, Monocytes, and NK cells by incorporating them as covariates in a linear model. The Houseman method(Houseman et al., 2012) was used to calculate the proportions. Our conclusions were not significantly altered by exclusion of these cell proportions from our models.

2.4. Statistical analysis

Data organization and analysis were conducted using R 3.6.3(Bunn and Korpela, 2016) and RStudio. We utilized Wilcoxon rank-sum tests to address the non-normality of variables, except the variable of assaultive trauma. Due to the higher frequency of scores of 0, assaultive trauma was compared using a Poisson regression. For GAA analysis, all multivariable linear regressions adjusted for sex and cell proportions (dropping granulocytes to avoid overfitting).

All tests were two-tailed with alpha of 0.05, with Bonferroni corrections used when assessing multiple subscales at once as indicated in the text. Exploratory mediation analysis was performed to determine if race (independent variable) impacts GAA (dependent variable) via CAI or its subscales, including trauma (mediating variables). All mediation effects were calculated via the mediation package in R using 10,000 simulations with bootstrapping, including covariates of sex and cell proportions. Preliminary analyses showed similar effects using quasi-Bayesian monte carlo simulations, though only the bootstrapping models are presented for simplicity. Mediation was considered significant if the proportion mediated was greater than 0 with an alpha of 0.05, and with Bonferroni corrections applied when assessing the subscales (2) and types of trauma (4).

3. Results

3.1. Race-related differences in reported stress and specific traumatic events

A significantly higher number of total stressful life events were reported by Black participants compared to White participants (mean difference: 6.9, median difference: 5 [95% conf int: 2–8, p = 2.14e-4 by Wilcox test]) (Fig. 1A). This remained true when sub-grouped by sex (Males: median difference: 5 [1–9, p = 0.0148]; Females: median difference: 5 [2–9, p = 0.00485]), and there was no interaction between race and sex via two-way ANOVA ($\beta = -1.39$ [−6.33 – 3.55, p = 0.580]). Race continued to be associated with CAI when accounting for covariates of sex, age, income, smoking, BMI, alcohol use, marital status, and years of education ($\beta = 4.98$ [2.48–7.47, p = 1.06e-4], partial $\eta^2 = 0.038$, model adjusted $R^2 = 0.150$).

We next explored whether there were differences in CAI subscales between Black and White participants. After accounting for multiple comparisons (adjusting for 4 comparisons), Black participants reported significantly higher traumatic life events (TE subscale) (mean difference: 2.9, median difference: 2, adjusted CI/p [1–4, p = 2.55e-5], Fig. 1B): and major life events (mean difference: 0.9, median difference: 1, adjusted CI/p: [0–1, p = 6.52e-5], Supplementary Fig. 1A). However, we found no significant difference between Black and White participants on chronic stress (mean difference: 2.3, median difference: 1, adjusted CI/p [−1 – 3, p = 0.272], Supplementary Fig. 1B): or recent life events subscales (mean difference: 0.7, median difference: 0, adjusted CI/p: [0–1, p = 0.328], Supplementary Fig. 1C) (Table 1). Further assessment of specific traumatic event types revealed Black participants experiencing 87% more assaultive violence, 104% more personal injuries or shocking events, 38% more traumas of a close friend/relative, and 34% more deaths of a close friend or relative, as compared to White participants (Table 2).

3.2. Race is associated with increased GrimAge Acceleration in the absence of differences in symptomatology

Black and White participants demonstrated strong correlations between GrimAge (not GAA) and chronologic age (Fig. 1C). Assessing GAA, we found that GAA was nearly 1.7 years higher in Black compared to White participants before accounting for covariates. This difference persisted after accounting for sex and cell proportions (Fig. 1D, $\beta = 2.29$ years [1.57–3.01, p = 9.70e-10], partial $\eta^2 = 0.091$, model adjusted $R^2 = 0.242$). This remained significant in both males ($\beta = 2.45$ years [1.34–3.56, p = 2.28e-5]) and females ($\beta = 2.14$ years [1.17–3.12, p = 2.22e-5]), with no significant interaction via two-way ANOVA ($\beta =$

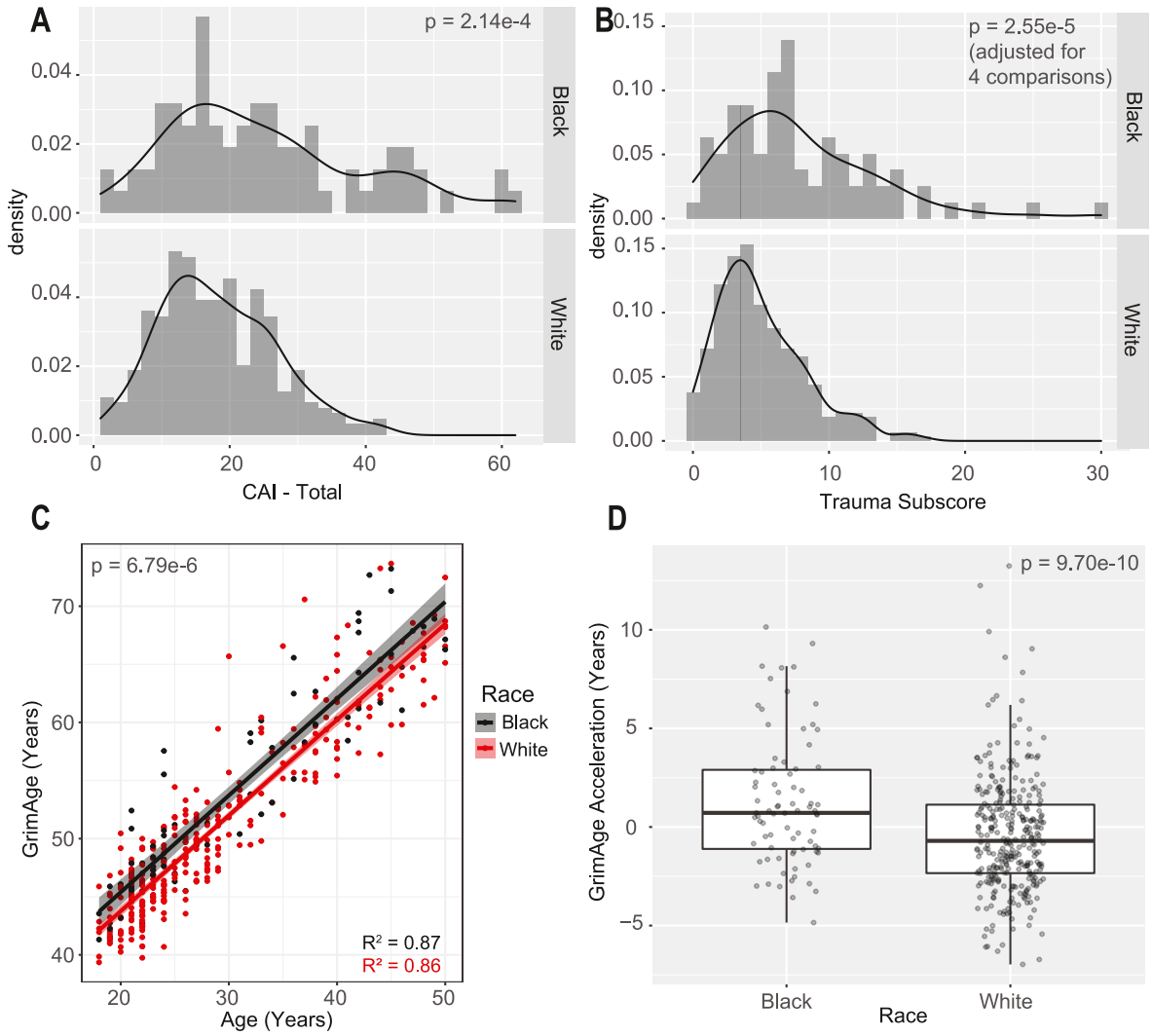

Fig. 1. Racial differences in reported stress and GrimAge Acceleration (GAA) (A) Black participants report a significantly higher level of cumulative stress as measured by the total Cumulative Adversity Inventory (CAI) when compared to White Americans (p = 2.14e-4 by Wilcoxon rank sum test). (B) Black versus White participants report a significantly higher level of traumatic events as measured by the CAI trauma subscale (adjusted p for 4 comparisons = 2.55e-5). (C) Both Black and White study participants demonstrate a strong correlation between chronologic age and GrimAge (R^2 presented on graph represents univariate correlation between age and chronologic age). When considering a linear model with GrimAge dependent on both chronologic age and race, race accounts for a 1.73-year difference between Black and White participants. (D) Black participants, on average, have a higher GAA when compared to White study participants.

−0.30 years [−1.64 – 1.03, p = 0.654]).

Assessing self-reported health symptoms between Black and White participants utilizing the Cornell Medical Index (CMI), we found overall low self-reported health symptoms in the sample, indicative of their good health status. Despite the difference in GAA, there was no difference between Black and White individuals in reported health symptoms (Table 1 and Supplementary Fig. 2, mean difference = 2.6, median difference: −1 [−3 – 2, p = 0.504]).

3.3. *Cumulative stressful and traumatic events are associated with GrimAge Acceleration in both black and white populations*

We found that CAI total scores were associated with GAA in both Black (β = 0.079 [0.032–0.125, p = 0.00112], partial η^2 = 0.140, model adjusted R^2 = 0.251) and White (β = 0.053 [0.019–0.086, p = 0.00205], partial η^2 = 0.030, model adjusted R^2 = 0.244) participants (Fig. 2A). When Black and White participants are analyzed together, CAI (β = 0.063 [0.036–0.089, p = 3.56e-6], partial η^2 = 0.054) and race (β = 1.87 [1.14–2.59, p = 5.62e-7], partial η^2 = 0.062, model adjusted R^2 = 0.280) each demonstrated significant main effects on GAA. When we assess for a moderating effect between race and CAI on GAA, we see no significant interaction effect (race × CAI interaction term β: 0.026; [−0.027 – 0.079, p = 0.336], partial η^2 = 0.002, model adjusted R^2 = 0.280).

As Black participants reported significantly higher traumatic life events and major life events, we next asked whether these subscale scores also are associated with GAA in Black and White participants. After accounting for sex and cell proportions as well as multiple comparisons (adjusting for 2 comparisons), traumatic life events are associated with higher GAA in both Black (β = 0.20 adjusted CI/p: [0.06–0.34, p = 0.00258], partial η^2 = 0.137, model adjusted R^2 = 0.248) and White (β = 0.11 adjusted CI/p: [0.01–0.20, p = 0.0328], partial η^2 = 0.018, model adjusted R^2 = 0.235) participants (Fig. 2B). Major life events showed an association with GAA in White participants (β = 0.26 adjusted CI/p: [0.05–0.46, p = 0.0117], partial η^2 = 0.024, model adjusted R^2 = 0.240), but not in Black participants (β = 0.31 adjusted CI/p: [−0.12 – 0.73, p = 0.210], partial η^2 = 0.037, model adjusted R^2 = 0.161) (Supplementary Fig. 3).

Table 2
Subtypes of traumatic events by race.

Type of trauma	proportion experiencing the event		Difference in summed proportions; [95% conf int, P value]
	Black	White	
Assaultive violence simple sum of proportions across items:	**1.013**	**0.543**	**mean difference: 0.62 [0.35 - 0.88, P = 4.16e-6]**
In military service: shot with a gun or badly injured with another weapon	0	0.003	
physically assaulted or mugged	0.165	0.188	
tortured	0.038	0.006	
participate in combat as a member of the military or organized non-military group	0.063	0.009	
shot with a gun or badly injured with another weapon	0.089	0.031	
regularly physically abused by one of your parents, stepparents, grandparents, or guardians	0.101	0.047	
forced to touch someone in a sexual way	0.114	0.075	
forced to have sexual intercourse when didn't want to	0.139	0.056	
physically abused or injured by a spouse/boyfriend/girlfriend	0.152	0.081	
physically abused or injured by someone else you knew	0.152	0.047	
Other injury or shocking event simple sum of proportions across items:	**2.785**	**1.358**	**median difference: 1 [1–2, P = 2.68e-7]**
Were you ever a refugee - (fled from your home to another or place to escape danger)	0	0.009	
unarmed civilian in a place where there was a war, revolution, military coup or invasion	0.025	0.047	
In military service: shot at with a gun or threatened with another weapon but not injured	0.025	0.006	
kidnapped or held captive	0.038	0.009	
Lost home because of a natural disaster	0.051	0.025	
been in a car crash in which someone was killed or badly injured	0.089	0.041	
had a serious accident, injury or illness that was life threatening or caused long-term disability	0.114	0.091	
chased but not caught when you thought you could really get hurt	0.228	0.094	
witnessed mother or close female relative being regularly physically or emotionally abused	0.266	0.141	
shot at with a gun or threatened with another weapon but not injured	0.266	0.163	
witnessed a serious accident or disaster where someone was hurt very badly or killed	0.329	0.216	
seen someone get shot at or attacked with another weapon	0.342	0.103	
seen someone seriously injured by gunshot or some other weapon?	0.367	0.109	
seen someone chased but not caught or threatened with serious harm?	0.392	0.144	
regularly emotionally abused by one of your caretakers	0.152	0.138	
seen someone get killed by being shot, stabbed, or beaten	0.101	0.022	
Learning of traumas of a friend/relative simple sum of proportions across items:	**1.975**	**1.432**	**median difference: 1 [0–1, P = 0.00179]**
told that someone you knew had been raped	0.291	0.391	
told that someone you knew had been shot, but not killed	0.519	0.119	
told that someone you knew had been killed with a gun or other weapon	0.532	0.125	
knew someone who died suddenly or been seriously hurt	0.405	0.409	
told that someone you knew killed themselves	0.228	0.388	
death of a friend/relative simple sum of proportions across items:	**2.025**	**1.516**	**median difference: 0 [0–1, P = 0.00461]**
grandparent died	0.544	0.697	
child died	0.013	0	
spouse/sig other died	0.038	0.009	
sibling died	0.139	0.031	
mother died	0.203	0.078	
father died	0.278	0.113	
close friend died	0.266	0.238	
another loved one died	0.544	0.35	
Other Unclassified Traumatic events	**0.164**	**0.175**	

Black participants were more likely to have experienced assault, the death of a friend/relative, learning of traumas of a friend or relative, or other injuries/shocking events than White participants. For individual events, data presented represents proportion of Black or White participants who reported having experienced that event.
For groupings, values represent the simple sum of proportions of all specific traumatic events within that category for the number of individuals in the sample. This allows for a quantitative assessment of trauma exposure for each individual. Poisson regression was used to compare summed proportions for assaultive trauma subgroup, given higher frequency of 0s. Statistics for other comparisons of summed proportions derived via Wilcox test.

3.4. Cumulative stress and traumatic life events mediate race-related effects on GrimAge Acceleration

While these data are cross-sectional, we next pursued exploratory mediation analyses to determine if higher levels of stress and trauma would be a possible mechanism of these race-related differences in epigenetic aging. Accounting for sex and cell proportions, we found that CAI total score significantly mediated the relationship between race and GAA (proportion mediated: 0.185, [0.073–0.34, p = 6e-4], Fig. 2C). Next, we assessed whether the subscales of Traumatic Events and Major Life Events might be possible mediators. After accounting for sex, cell proportions, and multiple comparisons (adjusting for 2 comparisons), the traumatic life events subscale also mediated the relationship between race and GAA (Proportion mediated: 0.190; adjusted CI/p: [0.06–0.37, p = 0.0008], Fig. 2D), as did the major life events subscale (Proportion mediated: 0.112, adjusted CI/p: [0.026–0.25, p = 0.0052]). In all mediation models, race maintained a significant direct effect on GAA after accounting for the mediating effects of total CAI or the specified life trauma or major life events subscale (see Fig. 2C and D).

Notably, even after considering all behavioral and demographic covariates that differ between Black and White participants in Table 1 (years of education, BMI, and alcohol use) as well as sex and cell proportions, total CAI scores (proportion mediated: 0.136 [0.031–0.30, p = 0.0042]) showed significant mediating effects. When performing a similar analysis on the traumatic and major life event subscales and accounting for multiple comparisons (adjusting for 2 comparisons), the trauma subscale (proportion mediated: 0.147, adjusted CI/p: [0.020–0.37, p = 0.0152]) showed significant mediating effects, though the major life events subscale no longer had a significant mediating effect (proportion mediated: 0.062, adjusted CI/p: [−0.0061 – 0.19, p = 0.102]).

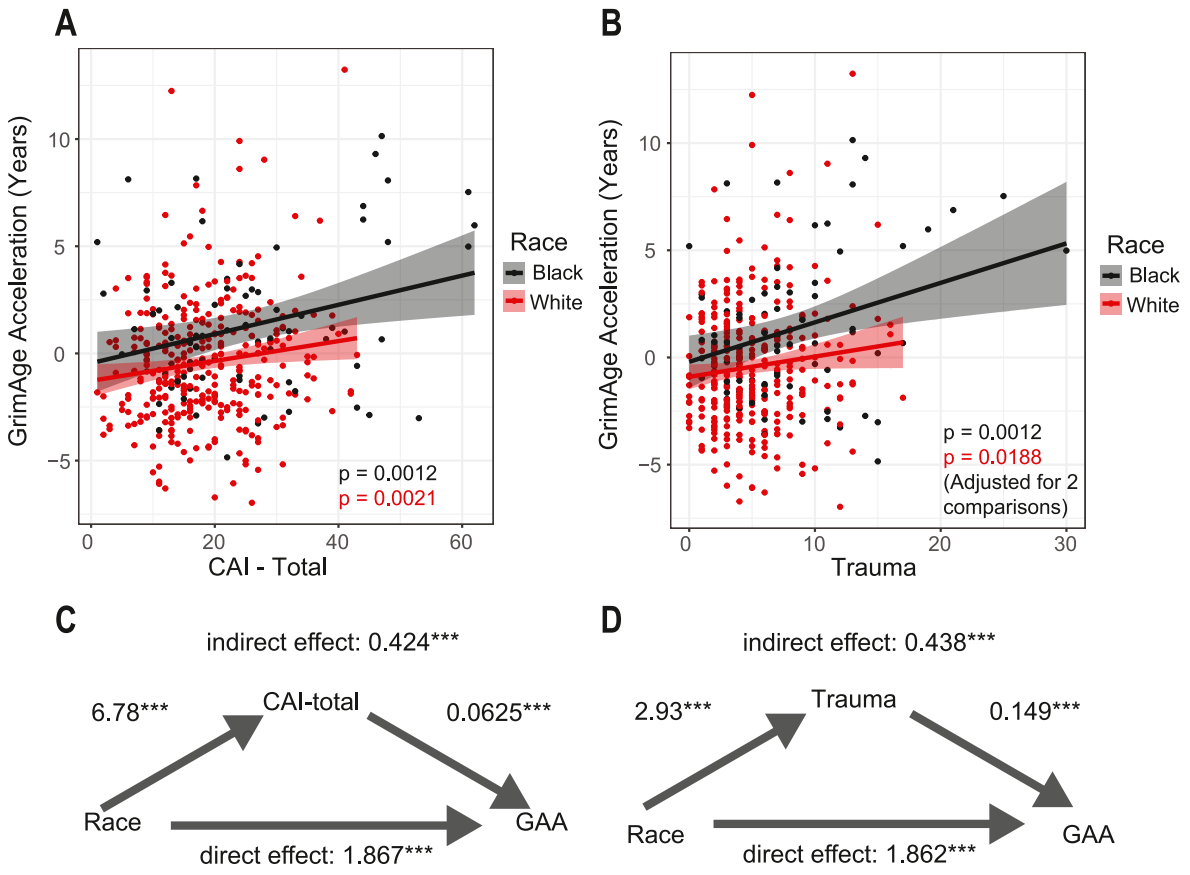

Fig. 2. Cumulative Stress, and particularly trauma, mediate the relationship between Race and GrimAge Acceleration (GAA) (A) Using a linear model, we identify a significant effect of CAI on GAA in both Black and White participants. (B) The trauma subscale of the CAI demonstrates a significant association to GAA in both Black and White participants (P values adjusted for 2 comparisons). (C) Stress shows a significant mediating effect (proportion mediated: 0.185, [0.071–0.34, p = 6e-4]) on the relationship between race and GAA, while there also remains a significant direct effect of race on GAA (direct effect: 1.87 years [1.15–2.60, p < 2e-16]). (D) We observe a significant mediating effect of the Trauma subscale of the CAI on the relationship between race and GAA (Proportion mediated: 0.190; adjusted CI/p: [0.06–0.37, p = 0.0008]). Again, we continue to see a significant direct effect of race on GAA (direct effect: 1.86 years [1.04–2.68, p < 2e-16]).

3.5. The sub-categories of assaultive trauma and death of loved ones demonstrate significant mediating effects

We next assessed whether specific sub-categories of trauma were related to GAA. After correcting for multiple comparisons (adjusted for 4 comparisons) as well as sex and cell count proportions, assaultive trauma ($\beta = 0.90$, adjusted CI/p: [0.58–1.21, p = 1.46e-11], partial $\eta^2 = 0.116$, model adjusted $R^2 = 0.262$), death of loved ones ($\beta = 0.55$, adjusted CI/p: [0.24–0.87, p = 5.88e-5], partial $\eta^2 = 0.047$, model adjusted $R^2 = 0.205$), trauma to loved ones ($\beta = 0.36$, adjusted CI/p: [0.067–0.65, p = 0.00876], partial $\eta^2 = 0.024$, model adjusted $R^2 = 0.185$), and other injuries or shocking events ($\beta = 0.24$, adjusted CI/p: [0.064–0.42, p = 0.00288], partial $\eta^2 = 0.029$, model adjusted $R^2 = 0.189$) all showed significant positive correlations with GAA.

We next assessed for mediation effects within the sub-categories of trauma. Accounting for multiple comparisons (adjusted for 4 comparisons), sex, and cell count proportions, we found assaultive trauma (proportion mediated: 0.161, adjusted CI/p: [0.012–0.37, p = 0.0216]) significantly mediated the relationship between race and GAA. Deaths of loved ones (proportion mediated: 0.098, adjusted CI/p: [0.007–0.25 p = 0.0176]) also demonstrated a significant mediating effect. Trauma of loved ones (proportion mediated: 0.062, adjusted CI/p: [−0.006 – 0.18, p = 0.10]) did not demonstrate a significant mediating effect after accounting for multiple comparisons, and other injuries or shocking events (proportion mediated: 0.0848, adjusted CI/p: [−0.044 – 0.25, p = 0.40]) revealed no significant mediating effect.

4. Discussion

These findings show significant race-related differences in the epigenetic age marker GrimAge in a young putatively healthy community population. As expected, Black compared to White sample showed both higher epigenetic aging and greater number of stressful and traumatic life events. Notably, exploratory mediation analyses suggested that the significantly higher number of traumatic stress events (particularly assaultive trauma and death of loved ones) in Black relative to White participants significantly mediated these differences. Even after accounting for significant behavioral and demographic differences (BMI, alcohol use, and education), this higher relationship in Black compared to White samples remained. These results suggest that young Black Americans exhibit significantly increased epigenetic age as a result of more adverse stressful life events, suggesting a possible “dose effect” of cumulative stressful and traumatic life events. Remarkably, despite the differences in epigenetic age, stressful life events and traumatic life events, there was no difference in reported health symptoms via the CMI. This suggests the biological embedding of stress and trauma in the epigenome may occur while individuals are healthy as per self-report, and before the development of differences in negative health symptoms. While these findings come from a cross sectional analysis of race, stress and epigenetic age and need replication in longitudinal samples, they suggest that interventions to mitigate assaultive and other traumatic stressors are paramount to improving provisional life expectancy of Black Americans.

In contrast to prior studies(Kho et al., 2021; Simons et al., 2016,

2018) which often included older or less healthy individuals, our study utilizes GrimAge Acceleration as a biomarker of disparities in aging between putatively healthy Black and White young adults (Kho et al., 2021; Philibert et al., 2020; Simons et al., 2021) with no significant difference in current health symptoms. Identifying accelerated aging prior to the onset of illnesses suggests possible intervention points to detect changes in epigenetic aging prior to the emergence of medical/-chronic illnesses. The impact of traumatic events on epigenetic age is consistent with an emerging literature implicating the number of psychosocial stressors and traumas as one factor contributing to health differences in Black and White adolescents and children (Harnett et al., 2019; Lavner et al., 2022).

While our exploratory mediation analysis is limited by the cross-sectional nature of our data, within that correlative framework we explored the relationship between race and epigenetic aging with stress and trauma significantly mediating that relationship. We identified specific stressful and traumatic events that may mediate the relationship between race and increased epigenetic age. While the CAI life events subscales measures the occurrence of specific significant events (including traumatic events, Table 2), the chronic stress subscale, measures perceived subjective response to those stressors. In contrast to CAI and trauma life event scores, which were associated with significant differences in epigenetic age, the relationship between race and chronic stress was not significant. This stood out as particularly salient as it suggests that the stress influence on epigenetic age may not be a result of the subjective perceived responses to stressful life events(Mathur et al., 2016), but rather via the biological embedding of the experience of specific stress and trauma events themselves. It is also notable that education, alcohol use, and BMI differed between Black and White participants in our study. While stress and trauma continued to show mediating effects after accounting for these covariates, prior studies have demonstrated relationships between epigenetic aging, education, alcohol, and BMI which could also contribute to differences in race-related aging (Crimmins et al., 2021; Lundgren et al., 2022; Quach et al., 2017). Future longitudinal studies could assess not only stress and trauma, but also behavioral and socioeconomic contributors to race-related differences in epigenetic aging.

When subcategorized by trauma type, Black participants had higher prevalence in each trauma subcategory. Assaultive trauma demonstrated both a significant relationship with increased epigenetic age and significantly mediated the relationship between race and GAA. This is particularly relevant and consistent with previous research showing that Black Americans are 22% more likely to experience a violent crime (Morgan and Oudekerk, 2019) and are more than twice as likely to have a violent or lethal encounter with law enforcement(Fagan and Campbell, 2020). Consistent with this trend, Black participants in the current sample reported such events (being assaulted, shot/threatened with a gun, or chased while fearing being hurt) more frequently (Table 2). These findings underscore the urgent need for early social and policy interventions, as our understanding of the biological effects of structural racism have become more prominent in the national consciousness (Lund, 2020). These changes in epigenetic age associated with trauma also suggest that targeting factors that decrease the higher rates of occurrence of trauma and adversity in Black Americans may mitigate their impact on epigenetic aging. The significant mediating effect of death of loved ones is also of interest. As work in both humans and model systems has suggested exposure to death may increase morbidity or even mortality (Gendron et al., 2023; Keyes et al., n.d.). This could represent a mechanism through which early mortality spreads within communities, suggesting that health effects of trauma may spread beyond the individual.

This study has several important limitations, and its findings should be understood in the context of limited sample size, a cross-sectional dataset, and geographic distribution. First, this study's overall sample size is small and limited to individuals from the greater New Haven Area that has an approximate population of 600,000. This study is also limited by only comparing Black and White participants and we were unable to assess other racial and ethnic groups or account for the diversity within the Black and White groups (i.e., ethnicity). Second, while the CAI is a broad and powerful tool covering numerous stressful life events for identifying many different types of traumas and adversity, it does not specifically measure perceived discrimination, and thus we cannot draw conclusions regarding how epigenetic aging is affected by a unique and asymmetric stressor such as perceived discrimination. Third, due to the cross-sectional nature of this study, we were also limited in our ability to draw causative inference nor comment on the various different theoretical life course models such as weathering/cumulative stress, predictive adaptive response, or stress generation models as outlined by Simons et al. (2018). The cross-sectional nature of our study also makes it possible that other, unmeasured variables such as inherited or intergenerational trauma could be correlated with potential trauma response of the participant and its effect on the rate of epigenetic aging. Future studies utilizing longitudinal data could provide more insight on the timeline of stress and trauma effects on epigenetic alterations and their consequent impact on health. Finally, some have suggested that epigenetic clocks such as GrimAge may be biased due to their method of construction(Levine, 2020), although more recent work has supported its use to compare Black and White populations (Graf et al., 2022).

While our observed direct effect of race on GAA could represent such racial bias in epigenetic clocks(Levine, 2020), this could also represent areas for future study. Over the past 5 years, a growing body of literature correlating unique stressors such as racial trauma, perceived/experienced discrimination, institutional barriers to care/access, housing instability, and citizenship status, have been shown to alter biomarkers of accelerated aging(Bastos et al., 2010; Chapman et al., 2018; Hicken et al., 2018; Williams et al., 2018; Williams et al., 2018). Understanding the intersectionality of these unique/nuanced stressors and increased epigenetic age is necessary to understanding their impact on health in these under-represented populations. Future studies could use longitudinal assessments that include measures of discrimination, incorporate a broader swath of the population, and utilize new epigenetic clocks trained on more diverse populations to elaborate on these findings. While GrimAge has the advantage of correlating with morbidity and mortality, as the field of epigenetic clocks advance future studies also may be able to provide more mechanistic details on specific aspects of aging and how they differ by race, stress, or discrimination.

5. Conclusions

Despite the above limitations, to our knowledge this is one of the first studies to investigate whether specific types of trauma may mediate differences in GrimAge between racial groups in a putatively healthy, young-to-middle-aged population. Increased epigenetic aging in Black participants is significantly mediated by cumulative stress, and particularly trauma, which may inform the biological underpinnings of the life expectancy gap in the United States. Health disparities observed later in life may begin during early adulthood, even in the absence of negative health symptoms or diagnosed medical illnesses or conditions, and may be detectable via epigenetic markers, particularly amongst Black Americans. Our findings underscore the need for better understanding the impact of these differences in social stress experiences and their effect on biological aging. Overall, these findings highlight an urgent public health need for societal reforms and policy interventions aimed at reducing the occurrence of such stressors and traumatic events. Such interventions may contribute to decreasing the morbidity and mortality gap between Black and White Americans.

Declaration of competing interest

Dr Rajita Sinha has research collaborations with Aelis Farma, Aptinyx Inc, CT Pharma and she is on the Scientific Advisory Board of Embera Neurotherapeutics. The current submission is unrelated to these

collaborations. Drs. Holloway, Harvanek, Gordon and Xu have no competing interests to declare.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2023.100557.

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