Biological Aging in Maltreated Children Followed up into Middle Adulthood

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Conflict of Interest

DWB is listed as an inventor on a Duke University and University of Otago invention that was licensed to a commercial entity.

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Abstract (344 of 350 words)

Importance: Childhood adversity has been linked to many indicators of shorter healthy lifespan, including earlier onset of disease and disability as well as early mortality. These observations suggest the hypothesis that childhood maltreatment may accelerate aging. We tested this hypothesis in a prospective cohort of individuals with documented childhood maltreatment and controls matched on demographic and socioeconomic factors.

Objective: To characterize the relationship between childhood maltreatment and accelerated biological aging in a prospective cohort of documented cases of childhood maltreatment and matched controls.

Design: Prospective cohort study

Setting: Cases were drawn from juvenile and adult court records from the years 1967 through 1971 in a large Midwest metropolitan geographic area. Controls were selected from the same schools and hospitals of birth and matched on age, sex, race, and approximate socioeconomic status.

Participants: 357 individuals with documented cases of childhood maltreatment and 250 matched controls

Exposure: Court-substantiated cases of childhood physical or sexual abuse, or neglect occurring at age 11 or younger

Outcome: Biological aging quantified using two blood-chemistry algorithms, the Klemera-Doubal method Biological Age (KDM BA) and the PhenoAge, developed and validated in data from the National Health and Nutrition Examination Surveys (NHANES) using published methods and publicly available software.

Results: Participants (55% women, 49% non-White) had mean age of 41 years (SD=4). Those with court substantiated childhood maltreatment history exhibited more advanced biological aging as compared with matched controls, although this difference was statistically different for only the KDM BA measure (KDM BA Cohen's D=0.20, 95% CI=[0.03,0.36], p=0.02; PhenoAge Cohen's D=0.09 95% CI=[-0.08,0.25], p=0.296). In subgroup analyses, maltreatment effect sizes were larger for women as compared to men and for White participants as compared to non-White participants, although these differences were not statistically significant at the α =0.05 level.

Conclusions and Relevance: As of midlife, effects of childhood maltreatment on biological aging are small in magnitude but discernible. Interventions to treat psychological and behavioral sequelae of exposure to childhood maltreatment, including in midlife adults, have potential to protect survivors from excess burden of disease, disability, and mortality in later life.

Introduction

Almost 3.5 million children were referred for suspected child abuse and neglect in fiscal year 2019 and 656,000 of these children were found to be victims of substantiated child maltreatment in the United States (U.S. Department of Health & Human Services, 2021). Childhood abuse and neglect have long-term consequences, with the potential to negatively affect physical health (Springer et al., 2007; Tracy et al., 2021; Widom et al., 2012), psychological and emotional well-being (Danese and Widom, 2020; Mills et al., 2013; Widom et al., 2007), and cognitive functioning (Nikulina and Widom, 2013) decades later. Children who grow up in higher adversity environments die younger than children who do not encounter those adversities (Brown et al., 2009; Hughes et al., 2017; Riem and Karreman, 2019). Despite the fact that not all maltreated children will manifest these problems, knowledge is needed about the mechanisms through which exposure to maltreatment drives poor health outcomes.

Little is known about the biology through which these pathways of life-course risk drive aging-related morbidity and mortality. One hypothesis to explain why people exposed to childhood adversity have poorer physical health outcomes as they grow older is that childhood adversities, including maltreatment, induce stress-related wear and tear on the body (Danese and McEwen, 2012). A further elaboration of this hypothesis proposes that stress-related wear and tear drives risk for aging-related disease through an acceleration of biological processes of aging (Colich et al., 2020; Shalev, 2012).

Breakthroughs in aging biology have revealed a set of molecular changes that accumulate as individuals grow older, undermining resilience and driving vulnerability to multiple different chronic diseases, disability, and mortality (Campisi et al., 2019). These molecular changes, sometimes referred to as “hallmarks of aging”, comprise cellular senescence, epigenetic alterations, mitochondrial dysfunction, dysregulated proteostasis, among others (López-Otín et al., 2013). In part because aging hallmarks are difficult to measure in humans, there is currently no gold standard measure of biological aging (Ferrucci et al., 2020). However, several methods have been proposed and some show evidence of accelerated aging in people with histories of childhood adversities. For example, telomere length (TL), a proposed biomarker of cellular aging (Blackburn et al., 2015; Chakravarti et al., 2021), tends to be shorter in children and adults with histories of childhood adversities (Epel and Prather, 2018; Hanssen et al., 2017; Lang et al., 2020); however, there is debate about the extent to which telomere length is a biomarker of aging (Nettle et al., 2021; Sanders and Newman, 2013). Current state-of-the-art methods for measuring biological aging are multivariate algorithms that combine information from clinical or genomic measurements to track changes that occur in peoples’ bodies as they age (Jylhävä et al., 2017). These algorithm-based measurements are proposed to summarize the effects of accumulating aging hallmarks by integrating information across multiple biological systems in the body (Belsky et al., 2018). These measurements also show evidence of accelerated aging in children and adults with histories of exposure to childhood adversities, including maltreatment (Belsky et al., 2020; Belsky et al., 2017; Colich et al., 2020; Dunn et al., 2019). To the extent that biological aging is modifiable, effective interventions to address the impacts of childhood adversity may interrupt processes that accelerate aging and associated health risks.

To evaluate whether childhood maltreatment exposure accelerates aging, two challenges must be overcome. A first challenge is bias arising from methods of ascertainment of maltreatment exposure. There is no “gold standard” to ascertain whether child abuse or neglect has occurred. Rather, each of the traditional methods used to assess child maltreatment (official records, self-reports, and observations) has limitations as well as strengths. The strongest evidence that actual maltreatment took place is the legal standard, namely a case substantiated (adjudicated) by the court after a judge makes a decision based on evidence provided by child protection services, law enforcement officers, witnesses, and experts. Because childhood maltreatment is often retrospectively reported, differential recall and reporting bias may result in over- or under-estimates of the true effect of childhood maltreatment on accelerated aging (Danese and Widom, 2020; Reuben et al., 2016). A second challenge is confounding of maltreatment with other risks for accelerated aging. Childhood socioeconomic risk is associated with many aging-related diseases and may also contribute to an acceleration of biological aging (Belsky et al., 2020; Belsky et al., 2017; Raffington et al., 2021; Snyder-Mackler et al., 2016), making it difficult to isolate the impacts of maltreatment. It is theoretically plausible that any relationship between child abuse and neglect and subsequent outcomes is confounded with or explained by social class differences (Adler et al., 1994; Bradley and Corwyn, 2002; Conroy et al., 2010; MacMillan et al., 2001; Widom, 1989). To overcome these challenges, prospective studies using objective measures of childhood maltreatment status to compare maltreated children with non-maltreated children of similar demographic and socioeconomic background are needed.

We tested the relationship between childhood maltreatment and accelerated aging using a prospective cohort of 357 individuals with documented childhood maltreatment (including physical or sexual abuse or neglect) from the years 1967 through 1971 and 250 participants matched on age, race, sex, and socioeconomic background drawn from the same Midwest geographic area. This sample addresses the challenges related to ascertainment of maltreatment status by using court-adjudicated instances of maltreatment, rather than relying on retrospective recall of individuals or reports by caregivers. Court cases of child abuse and neglect are more likely to represent severe cases of childhood maltreatment (Hampton and Newberger, 1985; O'Toole et al., 1999; Webster et al., 2005). This sample also addresses the challenge of confounding maltreatment with socioeconomic factors, because county hospital and school records were used to include children from families in the same area, and of the same age, sex, race, and approximate family social class in the study, along with participants who experienced abuse or neglect. Because of the matching procedure, the participants are assumed to differ only in the risk factor, that is, having experienced childhood maltreatment. Because it is not possible to assign participants randomly to groups, the assumption of equivalency for the groups is an approximation. The control group may also differ from the abused and neglected individuals on other variables nested with abuse or neglect. For complete details of the study design and participant selection criteria, see Widom (1989).

We quantified biological aging from blood chemistries assayed when participants were ages 32-49 years using two published algorithms, the Klemera-Doubal method Biological Age (Klemera and Doubal, 2006) and the PhenoAge (Levine, 2013), validated to predict morbidity and mortality. We tested if adults with documented cases of childhood maltreatment showed more advanced biological aging as compared to matched controls.

Methods

Sample. The sample used for this analysis has been characterized elsewhere (Widom, 1989; Widom et al., 2012). Briefly, the cohort was identified in 1986 as part of a large group of documented cases of childhood physical and sexual abuse and neglect (N = 908), and a matched comparison group of children (N=667). Of the original group of 1,575 identified through official records, 1,307 participants (83%) were located and 1,196 (76%) interviewed for the first time from 1989 to 1995 (first follow-up). Of these 1,196 individuals interviewed, 896 (75%) were interviewed again during 2000–2002 (second follow-up) and 807 were interviewed during 2003-2005 (third follow-up). Although there has been attrition from the sample due to death, refusals, and our inability to locate participants, the demographic characteristics of the sample have remained essentially the same over time (**Table 1**). The findings reported here include data from the first and third follow-ups. In the present paper, we use data from all participants who agreed to provide blood samples during the 2003-2005 wave of data collection (n=607). The current sample is (45% male, 61% White, non-Hispanic, mean age=41, SD=4). **Table 1** provides a comparison of the analysis sample used here and the full sample at interview 3. As can be seen, there are no significant differences in age, sex, or race between the analytic sample and the interview 3 sample.

Interviewers and participants were blind to the purpose of the study. Participants were told that they had been selected as part of a large group of individuals who grew up in the Midwest during the late 1960s and early 1970s. Institutional Review Board approval was obtained for the procedures involved in this study, and participants signed a consent form acknowledging that they were participating voluntarily.

Maltreatment Status. Cases of maltreatment were identified based on juvenile court records and adult criminal court records from 1967-1971. Only cases of child abuse and neglect that had been validated and substantiated by the court were included in the sample. Cases was restricted to those in which children were 11 years of age or less at the time of the incident. The maltreatment group in this sample includes court substantiated cases of childhood physical and sexual abuse and neglect. Physical abuse cases included injuries such as bruises, welts, burns, abrasions, lacerations, wounds, cuts, and bone and skull fractures. Sexual abuse cases included felony sexual assault, fondling or touching, sodomy, incest, and rape. Neglect cases reflected a judgment that the parents' deficiencies in child care were beyond those found acceptable by community and professional standards at the time and represented extreme failure to provide adequate food, clothing, shelter, and medical attention to children. Participants in the control groups were drawn from schools in the area and county birth record information and were matched to the maltreated children on the basis of age, sex, race, and approximate social class of the family during the period under study.

Biomarkers and Biological Aging. Biomarkers were assessed during the third follow-up (2003-2005). A licensed registered nurse performed a medical status exam in the participant's home or other quiet location of the person's choosing, including drawing of blood that was sent to a hospital laboratory for testing and measured health outcomes (see Widom et al., 2012 for details). The results from the blood tests provided data for the biomarkers, including albumin, creatinine, C-reactive protein (CRP), white blood cell count, lymphocyte %, mean cell volume, red cell distribution width, alkaline phosphatase, and glycated hemoglobin (HbA1c).

Biological aging is the gradual and progressive decline in system integrity that occurs with advancing chronological age, mediating aging-related disease and disability (Kirkwood, 2005). While there is no gold standard measure of biological aging, several proposed methods have accumulated substantial evidence as valid indicators of risk for aging-related disease, disability, and death, including in young to midlife adults (Ferrucci et al., 2020; Jylhävä et al., 2017). Among these, algorithms that combine information from clinical parameters that measure organ system integrity are among the most predictive of morbidity and mortality, have validation evidence in young and midlife as well as older adults, and indicate more advanced aging in adults with a history of childhood adversity (Belsky et al., 2017; Belsky et al., 2018; Li et al., 2020; Liu et al., 2018; Murabito et al., 2018). We measured biological aging using two such algorithms, the Klemera-Doubal method (KDM) Biological Age and the PhenoAge method (Klemera and Doubal, 2006; Levine et al., 2018).

The KDM Biological Age is derived from modeling associations of biomarkers with chronological age in a reference sample and then applying parameters derived from these models in the target dataset to compute participants' biological age values. The predicted biological age value represents the age at which a participant's physiology would be approximately normal in the reference sample.

The PhenoAge is derived from modeling associations of biomarkers and chronological age with mortality in a reference sample and then applying parameters derived from these models in the target dataset to compute participants' biological age values. The predicted biological age value represents the age at which a participant's physiology-predicted mortality risk would be approximately normal in the reference sample.

We computed KMD Biological Age and PhenoAge values using the set of biomarkers identified by Levine and colleagues in their original analysis to develop the PhenoAge method (Levine, 2013), with two modifications: we included eight of the original nine biomarkers, albumin, creatinine, CRP, white blood cell count, lymphocyte %, mean cell volume, red cell distribution width, and alkaline phosphatase; the ninth, fasting glucose, was substituted with HbA1c. In addition, because CRP values in the maltreatment cohort were not generated with a high-sensitivity method, we dichotomized values at a threshold of 3 mg/dL. Outliers out of 5 SDs are removed from the analyses. To define parameters for the algorithms, we conducted analysis using data from the National Health Nutrition Examination Surveys (NHANES) III (https://wwwn.cdc.gov/nchs/nhanes/nhanes3/default.aspx), the same data used by Levine to develop the original PhenoAge. We then compared our new algorithms to the versions originally published by Levine (Levine, 2013; Levine et al., 2018) using data from NHANES IV (https://wwwn.cdc.gov/nchs/nhanes/). Analysis to develop versions of the KDM Biological Age and PhenoAge algorithms for implementation in the maltreatment cohort dataset and to compare these new versions to published versions were conducted using the BioAge R package (https://rdrr.io/github/dayoonkwon/BioAge/). Details of this analysis are reported in **Supplemental Section 1.**

Analysis. For analysis, values of KDM Biological Age and PhenoAge were converted to biological-age advancement values by calculating the difference between algorithm-predicted values and true chronological age. (Residuals of the bivariate regression of biological age and chronological age were used in the regressions as outcome variables.) Positive values of biological age advancement indicate more advanced aging and increased risk of morbidity and mortality; negative values indicate the opposite.

We tested associations of maltreatment exposure with biological aging using linear regression with the following specification:

$BA = \alpha + \beta * Maltreatment + \gamma * X + \varepsilon$

where BA is the measure of biological aging, Maltreatment is an indicator of maltreatment (vs. control) status, and X is a matrix of covariates. All models included covariate adjustment for chronological age, sex, and self-identified race/ethnicity (non-Hispanic White and non-White). ε represents the error term. The coefficient β tests the association of maltreatment status with biological aging.

We tested consistency of the observed associations of maltreatment with biological aging between men and women, and between White and non-White participants. We conducted stratified analyses of the same relationship by age and race using the same model specification outlined above. We then added a cross-product interaction terms to our models to test the significance of differences by race/sex strata as follows:

$$BA = \alpha + \beta(Maltreatment) + \delta(Maltreatment * Z) + \gamma(X) + \mu + \varepsilon$$

where BA, maltreatment, and X terms are the same as in the previous model, and Z denotes the stratification variable (race or sex). The coefficient δ tests the hypothesis that the association of maltreatment with biological aging varies across level/strata of Z.

Results

We first conducted analysis to establish criterion validity of biological aging measures using data from the US National Health Nutrition Examination Surveys. The versions of the KDM Biological Age and PhenoAge algorithms we analyzed differed slightly from published versions. We therefore compared values for our measures to values computed using the original published versions of the algorithms. Correlations were high (KDM r=0.52; PhenoAge r=0.89). Next, we compared associations of our measures with mortality and morbidity to associations for the original published versions of the measures. Effect sizes were similar (e.g., for mortality, a standard deviation increase in our KDM Biological Age was associated a 42% increase in the hazard of mortality, 95% CI [38-45%] whereas for the original version of the measure, the increase was 43% per standard deviation, 95% CI [30-57%]; for PhenoAge, effect-sizes were HR=1.57 [53-61%] for our version and HR 1.50 [46-53%] for the original version). Complete results from comparative analysis are included in **Supplemental Section 1**.

We next applied the new algorithms to biomarker data in the maltreatment cohort. Participants' biological ages were similar to their chronological ages, but tended to be somewhat younger (KDM BA-advancement mean=-1.3, SD=7.9, chronological-age r=0.426; PhenoAge mean=-3.5, SD=4.6, chronological-age r=0.629). Those who had experienced childhood maltreatment exhibited more advanced biological aging as compared with matched controls, although this difference was statistically significant at the alpha=0.05 level only for KDM Biological Age. For KDM BA, the average biological-age advancement in maltreated participant was -0.6 years (SD=8.2) as compared to -2.2 (SD=7.4) in control participants (Cohen's D=0.20 95% CI=[0.03,0.36], p=0.02). For PhenoAge, the average biological-age advancement in maltreated participant was -3.3 years (SD=4.7) as compared to -3.7 (SD=4.6) in control participants (Cohen's D=0.09 95% CI=[-0.08,0.25], p=0.296) Comparison of biological aging in maltreated and control participants is reported in **Table 2.**

We conducted subgroup analyses by race and sex. KDM Biological Age and PhenoAge values tend to indicate more advanced biological aging in men as compared to women and in Black as compared to White Americans (Graf et al., 2021; Hastings et al., 2019; Levine, 2013; Levine and Crimmins, 2014; Liu et al., 2018). We therefore repeated our analysis within groups of men and women and White and non-White participants. Characteristics of subgroups are reported in **Supplemental Table 3**.

In subgroup analyses, maltreatment effect sizes were larger for women as compared to men (PhenoAge β=0.12 for women vs. β=0.04 for men; KDM β=0.3 for women vs. β=0.05 for men), although differences were not statistically different from zero at the α=0.05 level. In parallel, maltreatment effect sizes were larger for White participants as compared to non-White participants (PhenoAge β=0.13 for White participants vs. β=0.00 for non-White participants;

KDM β=0.31 for White participants vs. β=-0.01 for non-White participants), although these differences were again not statistically different from zero at the α=0.05. Results from sex- and race-stratified analysis and tests of race and sex differences in associations are reported in **Table 3**.

Discussion

Biological aging is the gradual and progressive decline in system integrity that occurs with advancing age, driving disease, disability, and mortality. The physical and psychological stresses of childhood maltreatment and their sequelae, including up-regulation of chronic, systemic inflammation and metabolic dysregulation, have potential to accelerate the aging process. New methods proposed to measure biological aging show that young and older adults with histories of childhood adversity appear biologically older and experience more rapid pace of decline in system integrity (Belsky et al., 2020; Belsky et al., 2017). However, it remains unclear if these differences in aging are the product of maltreatment experiences or the many correlated risk factors that often co-occur in the lives of maltreated children. For example, children growing up in low socioeconomic status families and neighborhoods also evidence more advanced and faster biological aging (Raffington et al., 2021) and this risk persists into adult life (Castagné et al., 2018). We used data collected from a unique cohort ascertained from court records of childhood maltreatment and matched controls to disentangle the specific sequelae of childhood maltreatment from effects of correlated social adversities. Our analysis applied two published algorithms to blood chemistry data collected from cohort members when they were followed-up in their 30s and 40s. Our primary finding was that adults with a history of maltreatment showed mixed evidence of advanced biological aging relative to adults without a maltreatment history. Analysis with the KDM Biological Age measure indicated advanced biological aging in the maltreatment-exposed group, especially among women and White participants. In contrast, in analysis with the PhenoAge group, differences between maltreatment exposure groups were not statistically different from zero at the α=0.05 threshold.

Effect sizes of maltreatment were small (Cohen's d<0.2), similar to what has been reported for other forms of childhood adversity such as low educational attainment and material and social resource deficits (Belsky et al., 2017; Graf et al., 2021; Liu et al., 2019). One interpretation of the small effect-size is that the impact of childhood maltreatment on biological aging is minor. An alternative interpretation is that the persistence of biological signs of childhood adversity over three decades points to enduring impacts of maltreatment. Differences in biological aging may become more pronounced as the cohort ages into later life, when advanced biological age gives rise to chronic disease and disability.

Differences in biological aging between maltreated and control participants were most pronounced for White participants and for women, although tests of difference in effect magnitudes by race and sex were not statistically significant at α=0.05. Biological aging measures, which were developed in mostly White samples, may yield less precise measurements in non-White as compared with White participants (Parker et al., 2019). We and others have reported similar, if slightly smaller, magnitudes of associations of KDM and PhenoAge biological aging measures with morbidity and mortality in Black and White participants in a national US sample (Graf et al., 2021; Kwon and Belsky, 2021; Liu et al., 2019). In our analysis of NHANES data (**Supplemental Section 1**), we find effect-sizes for association with morbidity and mortality are somewhat smaller in Black as compared to White participants. However, other explanations are possible. For example, non-White populations may experience higher burdens of risk factors for advanced biological aging (Raffington and Belsky, 2021), which could reduce the contrast between maltreated and non-maltreated groups within the non-White sample. Further investigation of differences in the long-term effects of childhood maltreatment on trajectories of biological aging across population subgroups in the US is needed.

Larger effect-sizes of maltreatment for women as compared with men also warrant further investigation. Biological-aging measures tend to perform similarly in men and women (Graf et al., 2021) (see also **Supplemental Section 1**), although men tend to exhibit more advanced biological age than women of the same chronological age (Levine, 2013; Liu et al., 2018). Gender differences in effect size could reflect differences in baseline experiences of maltreatment (e.g., type, frequency, or intensity) among men and women in our study, differences in the psychosocial sequelae of maltreatment exposure among men and women, and/or differences in manifestations of stress between men and women.

The average biological age in our sample was slightly younger than expectation by 1-4 years across measures and groups defined by maltreatment exposure. This difference could reflect overall healthier aging in this sample as compared with the NHANES III sample in which the algorithms were developed, consistent with the trend toward longer life expectancy in the general population across the 1990s and early 2000s. In support of this explanation, the difference in biological age between our sample and the expectation formed from NHANES III is similar to the differences reported for comparison of NHANES III to early 2000s NHANES waves by Levine and Crimmins (Levine and Crimmins, 2014). However, we cannot rule out technical artifacts of laboratory differences as an explanation.

We acknowledge limitations. There is no gold standard measure of biological aging (Ferrucci et al., 2020). Our results may be sensitive to the biological level of analysis and algorithms used to calculating biological aging. Our analysis included two blood-chemistry-based measures. Other proposed levels of analysis for quantification of biological aging include DNA methylation, proteomics, metabolomics. These molecular levels of analysis precede observable decrements in physiology and function and may therefore be more sensitive to effects at a life stage in which participants are near peak health status. Ultimately, integrating information across additional biological levels of analysis may yield more precise measurements of biological aging (Kothari and Belsky, 2021; Raffington and Belsky, 2021). Our sample was restricted to one geographic location and relatively narrow age range; replication in samples observed at later stages of the life course and in other geographic locations are needed. Court-adjudicated maltreatment cases may represent more severe cases and not all cases of maltreatment are reported. To the extent that controls experienced less severe forms of maltreatment or experienced childhood maltreatment that was not reported, this misclassification could result in an underestimate of the effects of maltreatment on biological aging.

The observation that childhood maltreatment is associated with more advanced biological aging builds on a body of evidence linking early adversity with poor health in later life. However, effect sizes were small and somewhat inconsistent across measures. Replication of findings across multiple biological levels of analysis and multiple measures of biological aging will increase confidence in our findings. Further study of mechanisms through which maltreatment leads to biological aging is needed and may help to explain observed heterogeneity of effects by race and sex. In addition to physiological wear-and-tear/weathering, maltreatment may lead to impaired neurodevelopment, increased engagement in health-risk behaviors, and later psychopathology. Psychopathology has recently been linked to accelerated aging in midlife, and may represent an important pathway through which to disrupt the linkage between childhood maltreatment and aging-related physiological decline (Moffitt and Caspi, 2019; Wertz et al., 2021). Finally, in order to identify leverage points for intervention, it is important to assess whether the observed effects of childhood maltreatment on biological-age advancement reflect biological embedding of childhood exposures, or whether childhood maltreatment leads to accumulation of damage over time consistent with a “chain-of-risk” model (Ben-Shlomo and Kuh, 2002; Moffitt and Caspi, 2019).

In sum, our results contribute support for the hypothesis that childhood maltreatment disrupts healthy aging processes. Observational studies reporting associations between childhood maltreatment and poor health outcomes are limited by concerns of confounding and reporting bias. Use of matched controls and court-adjudicated maltreatment cases, as in our sample, helps to mitigate these sources of bias. Further research is needed to assess consistency of findings at different stages of the life course, in different geographic locations, and different biological levels of analysis, and to identify pathways through which maltreatment leads to more-advanced biological aging.

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Supplemental material

Women in the sample were an average of 0.7 years older than the men (Women mean age=41.4 (SD=3.5), Men 40.7 (3.5); p=0.034). White and non-White participants were of similar ages (White participants 41.0 (3.5), Non-White participants 41.1 (3.5), p=0.744). On average, participants' biological ages were slightly younger than their chronological ages, indicating that this sample experienced less biological-age advancement compared to the NHANES III reference sample on which the biological-age samples were trained (PhenoAge: mean=37.6 (SD=6.0), PhenoAge-advancement mean=-3.5 (4.6); KDM: mean=39.8 (SD=8.7), KDM-advancement mean=-1.3 (SD=7.9)). In our sample, women exhibited more-advanced biological aging compared to men, although the difference was only statistically significant for KDM Biological Age (mean PhenoAge advancement -3.8 (4.4) for men, -3.2 (4.9) for women, p=0.104; mean KDM advancement -2.7 (7.6) for men, -0.1 (8.0) for women, p<0.001). Non-White participants exhibited more-advanced biological aging compared to white participants based on Klemera-Doubal Biological Age (mean KDM BA-advancement -0.3 (7.7) for non-White participants, -1.9 (8.0) for white participants, p=0.012). Results were in the same direction but not statistically significant for Levine PhenoAge (mean Levine PhenoAge-advancement -3.7 (4.8) for non-White participants, -3.4 (4.6) for White participants, p=0.454).

Tables and Figures

Table 1. Comparison of demographic characteristics for participants in the 3rd wave of the data collection and the subset of participants included in this analysis.

	Interview 3 sample			Analysis sample		
	Control	Maltreated	*p*	Control	Maltreated	*p*
	n = 349	n = 457		n = 250	n = 357	
Male	171 (49%)	209 (45.7%)	0.396	118 (47.2%)	157 (44%)	0.483
Age	41.1 (3.6)	41.3 (3.5)	0.505	40.9 (3.7)	41.2 (3.4)	0.418
Other race/ ethnicity	210 (60.2%)	267 (58.4%)	0.669	149 (59.6%)	219 (61.3%)	0.727

Table 2. Comparison of Biological Aging by Maltreatment Status

	Total n= 607	Control n = 250	Maltreatment n = 357		
		M (SD)		Cohen's D (95% CI)	P-value
Chronological Age	41.1 (3.5)	40.9 (3.7)	41.2 (3.5)		0.467
PhenoAge Advance	-3.5 (4.6)	-3.7 (4.6)	-3.3 (4.7)	0.09 (-0.08, 0.25)	0.296
KDM BA Advance	-1.3 (7.9)	-2.2 (7.4)	-0.6 (8.2)	0.20 (0.03, 0.36)	0.018

Table 3. Associations of biological aging measures with childhood maltreatment.

	KDM Biological Age Advancement (KDM BA – CA)	**Levine Phenotypic Age Advancement (Levine BA – CA)**
	b (95% CI)	**b (95% CI)**
	Full Sample	
Maltreatment	0.19 (0.03, 0.35)	0.08 (-0.08, 0.24)
	Stratified by Gender	
Maltreatment (Men)	0.05 (-0.18, 0.27)	0.04 (-0.19, 0.27)
Maltreatment (Women)	0.30 (0.08, 0.52)	0.12 (-0.12, 0.35)
	Stratified by Race/Ethnicity	
Maltreatment (White, non-Hispanic)	0.31 (0.10, 0.51)	0.13 (-0.08, 0.33)
Maltreatment (Non-white)	-0.01 (-0.26, 0.25)	0 (-0.27, 0.27)
	Full Sample Model with Maltreatment * Gender Interaction	
Maltreatment	-0.21 (-0.73, 0.30)	-0.05 (-0.58, 0.48)
Women	-0.1 (-0.63, 0.43)	-0.01 (-0.56, 0.53)
Interaction	0.26 (-0.06, 0.58)	0.09 (-0.24, 0.42)
	Full Sample Model with Maltreatment * Race/Ethnicity Interaction	
Childhood Maltreatment	0.31 (0.11,0.52)	0.13 (-0.08,0.34)
Non-White	0.38 (0.13,0.63)	0.01 (-0.25,0.26)
Interaction	-0.32 (-0. 64,0.01)	-0.13 (-0.46,0.21)

Note: Coefficients (b) and 95% confidence intervals (CI) are from linear regressions of biological aging measures on childhood maltreatment group with covariate adjustment for age, sex and race/ethnicity. KDM Biological Age and Levine Phenotypic Age measures were differenced from chronological age for analysis (i.e., values = BA-CA). These differenced values were then standardized to have Mean = 0, SD = 1 so that effect-sizes are comparable. Coefficients are reported only for focal variables in analysis and variables included in interaction terms.