Title
Early life adversity, pubertal timing, and epigenetic age acceleration in adulthood

Journal
Developmental Psychobiology, 63(5)

ISSN
0012-1630

Authors
Hamlat, Elissa J
Prather, Aric A
Horvath, Steve
et al.

Publication Date
2021-07-01

DOI
10.1002/dev.22085

Peer reviewed

HHS Public Access

Author manuscript

Dev Psychobiol. Author manuscript; available in PMC 2022 July 01.

Published in final edited form as:

Dev Psychobiol. 2021 July ; 63(5): 890–902. doi:10.1002/dev.22085.

Early Life Adversity, Pubertal Timing, and Epigenetic Age Acceleration in Adulthood

Elissa J. Hamlat,
University of California, San Francisco

Aric A. Prather,
University of California, San Francisco

Steve Horvath,
University of California Los Angeles

Jay Belsky,
University of California, Davis

Elissa S. Epel
University of California, San Francisco

Abstract

Background: Given associations linking early-life adversity, pubertal timing and biological aging, we examined direct and indirect effects of early life trauma on adult biological aging (via age of menarche).

Methods: Participants were premenopausal women (N = 183). Path models evaluated whether early life trauma predicted early pubertal timing and thereby, adult epigenetic age acceleration (indexed via four epigenetic clocks: Horvath DNAm Age, Hannum DNAm Age, DNAm PhenoAge, DNAm GrimAge). Secondary analyses explored effects of type of trauma (abuse, neglect) and adult chronic stress status (caregiver of child with autism, non-caregiver).

Results: Early life trauma and earlier age at menarche independently predicted accelerated aging based on one of the four epigenetic clocks, DNAm GrimAge, though early life trauma was not associated with age of menarche. Childhood abuse, but not neglect predicted faster epigenetic aging; results did not differ by chronic stress status.

Conclusions: Early trauma and early menarche appear to exert independent effects on DNAm GrimAge which has been shown to be the strongest epigenetic predictor of mortality risk. This study identifies a potential correlate or determinant of accelerated epigenetic aging — menarcheal age. Future research should address the limitations of this study by using racially diverse samples.

Targeting the mechanisms by which childhood circumstances confer risk for disease in adulthood can lead to the earlier identification and treatment of those most at risk for

Correspondence regarding this article should be addressed to Elissa J. Hamlat, Department of Psychiatry, University of California, San Francisco, 3333 California St., Suite 4655, San Francisco, CA 94118. Elissa.Hamlat@ucsf.edu.

The authors report no conflicts of interest.

physical and mental illness. Early life adversity has been associated with physical and mental health problems later in life. Experiencing adversities in childhood has been associated with cardiovascular disease, obesity, diabetes, and depression in adulthood (Chapman et al., 2004; Danese et al., 2009; Gilbert et al., 2015; Su et al., 2015). Early pubertal timing (i.e., maturing earlier than same-sex peers) has also been associated with higher rates of mortality from all causes, particularly those related to cardiovascular disease and reproductive cancers (Charalampopoulos et al., 2014; Golub et al., 2008; Giles et al., 2010; Jacobsen et al., 2007, 2009; Lakshman et al., 2009, Tamakoshi et al., 2011). These pubertal timing effects could be due to its association with higher fasting insulin, higher diastolic blood pressure, and decreased HDL cholesterol (Prentice & Viner, 2013, Widen et al., 2012), as well as higher adult BMI (e.g., Laitinen et al., 2001; Pierce et al., 2010; Pierce & Leon, 2005; Prentice & Viner, 2013; Widen et al., 2012), higher insulin resistance (HOMA-IR), and fasting glucose (Frontini et al., 2003). Moreover, early pubertal timing increases risk for depression and other psychiatric disorders (Mendle et al., 2007).

Theoretical work based on evolutionary thinking (i.e., life history theory) suggests that living in an adverse/stressful childhood environment, individuals may begin pubertal maturation at younger ages in order to enhance reproductive fitness (Belsky, 2012; Belsky et al., 1991); such accelerated development may be achieved by means of the contextual calibration of the HPA-axis (Del Giudice et al., 2011). Conceivably, this process might account, at least in part, for how early-life adversity comes to predict increased morbidity and premature mortality later in life (Belsky, 2019; Belsky & Shalev, 2016). Events in early life may lead to poor health through earlier pubertal maturation; notably, this possibility has rarely been empirically examined. In one study, greater maternal depression in early life was associated with early adrenarche, which predicted lower self-reported health and behavior in female adolescents (Ellis & Essex, 2007). Another study found that early adversity predicted age of menarche (via BMI and general health), and early menarche resulted in riskier behavior in adolescents (Hartman et al., 2017). In adverse early life environments, individuals may accelerate pubertal maturation to increase the chances of reproducing before dying or becoming developmentally compromised, at the expense of later health and longevity (Belsky, 2019; Belsky & Shalev, 2016; Belsky et al., 2011).

Is pubertal timing a mechanism by which early adversity influences adult biological aging?

It is widely appreciated that two individuals of the same chronological age can vary greatly in their risk of disease and dysfunction, and accumulating research suggests that variations in biological aging may account for these differences in risk. Indeed, an emerging view is that it is biological rather than chronological age that primarily informs and contributes to such risk (Field et al., 2018). Consistent with this claim, accelerated biological aging robustly predicts higher morbidity and mortality (Fransquet et al., 2019; Horvath, 2013, 2015; Levine et al., 2018, Liu et al., 2018). As early reproductive opportunities are also associated with later disease and death, consistent with life history theory (Belsky & Shalev, 2016; Shalev & Belsky, 2016), early pubertal maturation and accelerated biological aging may represent the same evolutionary-developmental process (Belsky, 2019). In general,

studies of pubertal timing and biological aging have been carried out as independent lines of research and the relationship between the two constructs has rarely been examined—with the exception of one recent report indicating that accelerated epigenetic aging (using Horvath's original pan tissue epigenetic clock; Horvath, 2013, 2015) predicts earlier pubertal development in females (Binder et al., 2018).

Epigenetic "clocks" are a new composite measure of biological age based on the methylation of specific sites in the genome, CpGs (where a cytosine nucleotide is followed by a guanine nucleotide). They are one of the most promising biomarkers available to predict disease outcomes (Horvath & Raj, 2018). Horvath's original epigenetic clock (Horvath, 2013, 2015) was developed by selecting CpGs across different cell and tissue types whose methylation sites as a composite correlate highly ($r > .90$) with chronological age by design. The clock's deviation from actual chronological age reflects aging faster or slower than expected. Another epigenetic index, the Hannum clock, was similarly developed by using CpGs that minimize error in the estimation of chronological age, using solely blood methylation data (Hannum et al., 2013). Both Horvath DNA methylation (DNAm) Age and Hannum DNAm Age have been widely used and correlate highly with risk for age-associated diseases (Horvath et al., 2018; Horvath & Raj, 2018). Unlike Horvath DNAm Age and Hannum DNAm Age, a newer generation of biological clocks (DNAm PhenoAge, DNAm GrimAge) selected CpGs associated with risk factors for age-related disease and dysfunction instead of chronological age. For example, a measure of phenotypic age (calculated with ten clinical biomarkers of health and aging) was regressed on blood methylation data to identify CpGs used for DNAm PhenoAge (Levine et al., 2018). Subsequently, DNAm PhenoAge predicts 10-year and 20-year mortality risk more accurately than Horvath DNAm Age and Hannum DNAm Age (Levine et al., 2018). Lastly, DNAm GrimAge, the newest clock, was developed by predicting time to death using DNAm surrogates of seven plasma proteins as well as smoking pack years (Lu et al., 2019). So far, DNAm GrimAge appears to outperform other epigenetic clocks in the prediction of time-to-death, time-to-coronary heart disease, and time-to-cancer (Lu et al., 2019). DNAm GrimAge also out performs other epigenetic clocks when it comes to estimating age at menopause in postmenopausal women (Lu et al., 2019).

The current study

The primary aim of the current study was to investigate relationships between early life trauma, age at menarche, and epigenetic indices of biological aging. Guided by Belsky and Shalev's life history model of human development (Belsky, 2012, 2019; Belsky & Shalev; 2016; Belsky et al., 1991), we examined using the four different epigenetic clocks (Horvath DNAm Age, Hannum DNAm Age, DNAm PhenoAge, and DNAm GrimAge), the direct and indirect effects (through age at menarche) of early life trauma on accelerated biological aging in adulthood. For all epigenetic clocks, epigenetic age was regressed on chronological age and the residual was used as the index of *age acceleration*, which reflects to what extent an individual's biological age is older or younger than their chronological age.

While accelerated aging in childhood has been related to earlier age of menarche (Binder et al., 2018), age at menarche has yet to be assessed as a predictor of *adult* epigenetic age

acceleration. The research reported herein is thus the first to examine associations between age at menarche and adult epigenetic aging. We hypothesized that early life trauma would be associated with earlier pubertal maturation and with faster age acceleration, and that there would be an indirect effect of trauma on epigenetic age acceleration through age at menarche. As clocks have shown differential associations with other constructs (Horvath & Raj, 2018; Wolf et al., 2018), we did not make a priori hypotheses about any of the four specific clocks.

Secondly, we examined specificity of effects due to type of trauma. Associations between early life experiences, pubertal timing, and epigenetic aging may be dependent upon the specific type of childhood maltreatment. Recent evidence suggests that early life threat (e.g., physical abuse) but not deprivation (e.g., neglect), is associated with advanced pubertal development and epigenetic age acceleration in children (Sumner et al., 2019). Thus, in the current study, after analyzing a composite index based on both types of trauma, we evaluated whether abuse and/or neglect are related to age at menarche or epigenetic age acceleration, and if there is an indirect effect of abuse and/or neglect on epigenetic age acceleration through age at menarche. Based on Sumner et al.'s (2019) findings, we predicted that it would be abuse and not neglect that is most strongly associated with age at menarche and epigenetic age acceleration.

Method

Participants and procedure

The current study was part of a larger project focused on chronic caregiving stress and aging. Participants were premenopausal mothers (N = 183, M_{age} = 42.43, SD = 5.09, range = 25 to 51) of children between 2 and 16 years of age recruited through local schools, parenting-related media, the University of California, San Francisco Autism Program and other relevant clinics and community sites. Participants were either (1) mothers of a child with a diagnosis of autism spectrum disorder (n = 92; herein referred to as the "caregiver" group), or (2) mothers of typically developing children (n = 91; herein referred to as the "control" group). See Aschbacher et al. (2017) for additional participant detail. Mothers in the two groups were matched on age, ethnicity, BMI, and education. Before beginning analyses, we evaluated whether the parameters of each model differed by chronic stress status (caregiver vs. control). For all models, fit indices when model parameters were free to vary across groups (caregivers and controls) did not fit significantly better than the fit statistics when parameters did not vary for the two groups; consequently, caregivers and controls were treated as one integrated sample.

All participants were non-smokers, had a body mass index (BMI) <40 kg/m2, and were English-speaking. Exclusion criteria included major chronic diseases (e.g., diabetes, cardiovascular, autoimmune, history of stroke, brain injury, cancer, endocrine disorders), current PTSD, bipolar disorder, or eating disorder, and regular use of steroid prescription medications. Participants provided retrospective reports of age at menarche and early life trauma. They also completed two fasting blood draws six months apart. Whole blood DNA was used for DNA methylation analyses. Epigenetic clock values were averaged across the two measurement time points. As 22 participants did not have complete early trauma reports

(total scores are calculated only when all items are present), the final sample size for the current study was 161 (78 caregivers, 83 controls). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. This research was approved by the Committee for Human Research at the University of California, San Francisco, and all participants gave written consent.

Measures

Menarche.—Participants provided self-reports of menstrual history including age at menarche (M_{age} = 12.86, SD = 1.37, range = 9 to 16).

Early life trauma.—The brief screening version of the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998, Bernstein et al., 2003) is a 28-item assessment of maltreatment in early life. Items are rated on a 5-point scale from *Never True* to *Very Often True* (Bernstein et al., 1994). Scores on emotional abuse, physical abuse, and sexual abuse subscales were summed to create a composite abuse variable, as has been done in previous studies to capture threat-related maltreatment (Lambert et al., 2017). The physical neglect items were summed to create the neglect variable in the current study. We did not include items pertaining to emotional neglect due to low validity of the latter (Bernstein et al., 1997) and because the emotional neglect sub-scale diverges from accepted methods for assessing neglect (Straus & Kantor, 2005). The abuse and neglect variables were combined for a total measure of trauma.

Epigenetic aging.—"DNA methylation analyses with whole blood samples were performed at the Semel Institute UCLA Neurosciences Genomics Core (UNGC, Los Angeles, CA) using the Illumina Infinium HumanMethylation450 BeadChip (Illumina, Inc., San Diego, CA). Genomic DNA was isolated using temperature denaturation and subjected to bisulfite conversion, PCR amplification, and DNA sequencing (EZ DNA Methylation-Gold Kit, ZymoResearch, Irvine, CA). To obtain outcome measures, methylation profiles were input to Horvath's online calculator https://dnamage.genetics.ucla.edu/, which automatically imputes any missing CpGs. After selection of the advanced analysis option and normalization based on the BMIQ method (Teschendorff, 2013), the calculator output files containing DNAm age of each participant estimated according to the four epigenetic age estimation methods (i.e., Horvath DNAm Age, Hannum DNAm Age, DNAm PhenoAge, DNAm GrimAge), blood cell counts, and measures of predictive accuracy and data quality (e.g., for identifying array outliers, corSampleVSgoldstandard). No participants were excluded due to quality control issues.

For our primary outcome for each of the clocks, we used AgeAccelerationResidual, the studentized residual resulting from a linear regression model where DNAm age is regressed on chronological age. Positive residual values reflected an individual being older biologically than chronological age and negative residual values reflected the reverse. Of the 161 participants, 39 completed one blood draw and 122 completed the two blood draws (6 months apart). In the latter case, epigenetic clock values were averaged across the two

blood draws. To account for confounding due to blood cell composition, we included counts of naïve CD8+ T and exhausted cytotoxic CD8+ T cells (defined as CD8 positive CD28 negative CD45R negative) as covariates in all analyses (Horvath & Levine, 2015).

Horvath DNAm Age (Horvath, 2013, 2015).: Horvath's original clock was developed by identifying 353 specific CpGs in the genome whose methylation states correlate highly with chronological age across different cell and tissue types. This first multi-tissue epigenetic clock has been validated with individuals across a wide age range, including children (Horvath & Raj, 2018). The correlation between Horvath DNAm Age at the two blood draws was $r(122) = .71$, $p < .001$).

Hannum DNAm Age (Hannum et al., 2013).: Relying solely on methylation found in whole blood DNA, the Hannum clock was developed by selecting for 71 CpGs that minimize error in estimating chronological age. The correlation between Hannum DNAm Age at the two blood draws was $r(122) = .81$, $p < .001$).

DNAm PhenoAge (Levine et al., 2018).: First, phenotypic age was estimated using ten clinical biomarkers that accurately predict morbidity and mortality (i.e., chronological age, albumin, creatinine, glucose and C-reactive protein levels, lymphocyte percentage, mean cell volume, red blood cell distribution width, alkaline phosphatase, and white blood cell count). To create DNAm PhenoAge, phenotypic age was regressed on blood DNA methylation data to identify 513 relevant CpGs. DNAm PhenoAge strongly correlates with aging-related outcomes and is highly accurate in the prediction of mortality (Levine et al., 2018, Liu et al., 2018). The correlation between DNAm PhenoAge at the two blood draws was $r(122) = .74$, $p < .001$).

DNAm GrimAge (Lu et al., 2019).: DNAm GrimAge is based on 1,030 unique CpGs that predict time to death, which are DNAm surrogates of seven plasma proteins and smoking pack years (i.e., the number of packs of cigarettes smoked per day multiplied by the number of years an individual smoked). DNAm GrimAge may outperform older epigenetic clocks in the prediction of time to disease and time to death and have a stronger association with other outcomes such as age at menopause (Lu et al., 2019). The correlation between DNAm GrimAge at the two blood draws was $r(122) = .88$, $p < .001$).

Data availability—Research data are not shared.

Analytic plan—Path models were implemented in the "lavaan" library (Rosseel, 2012) within R (Team, 2017) using full information maximum likelihood (FIML) to account for missing data. Multiple-group comparisons were used to determine if model parameters varied by caregiver status (caregiver or control). For all models, fit statistics when model parameters were free to vary across groups were not significantly better than fit statistics when parameters did not vary for the two groups, ($p < .05$). For parsimony, model parameters were constrained to be equal across groups.

Using separate analyses for each epigenetic clock, age acceleration (i.e., epigenetic age accounting for chronological age) was regressed upon early life trauma and age at menarche,

and age at menarche was regressed upon early life trauma. Path analyses calculated both direct and indirect effects (through age at menarche) of early life trauma on epigenetic age acceleration. Secondary analyses examined whether relationships varied by type of early life trauma (i.e., abuse or neglect).

To correct for the testing of four variables of epigenetic age acceleration, we applied a Bonferroni correction, divided the original alpha level ($p < 0.05$) by four, and obtained a new significance level of $p < .01$.

Results

Descriptive statistics are reported in Table 1. There were no significant differences between caregivers and controls in race (% who are White), educational background (% with at least a college degree), age at menarche, or epigenetic age acceleration using any of the four epigenetic clocks. Compared to controls, caregivers had lower annual income (% with an income at least $100,000, and higher levels of early life abuse, neglect, and trauma.

Correlations among study variables are reported in Table 2. There were no significant relationships between any of the four clocks and education (% college degree). There was a negative correlation between annual income and DNAm PhenoAge (but not Horvath DNAm Age, Hannum DNAm Age, or DNAm GrimAge), in that having an annual income above $100, 000 was associated with less DNAm PhenoAge acceleration. There was also a negative association between race and DNAm GrimAge (but not Horvath DNAm Age, Hannum DNAm Age, or DNAm PhenoAge), in that being White was associated with less DNAm GrimAge acceleration. Sensitivity analyses co-varied income in the model for DNAm PhenoAge acceleration and co-varied race in the model for DNAm GrimAge acceleration (Table S2).

Scores on the four epigenetic clocks were positively correlated with one another (range = .13 – .51), with only the association between Horvath DNAm Age and DNAm GrimAge not meeting conventional standards of significance. Increased DNAm GrimAge (i.e., faster age acceleration) was associated with higher levels of early life abuse and trauma and with younger age at menarche. The other three clocks (Horvath DNAm Age, Hannum DNAm Age, and DNAm PhenoAge) were not associated with abuse, trauma, or age at menarche. None of the four epigenetic clocks were significantly associated with early life neglect.

Horvath DNAm Age, Hannum DNAm Age, and DNAm PhenoAge[1]

In three of the four epigenetic clocks, Horvath DNAm Age, Hannum DNAm Age, and DNAm PhenoAge, childhood trauma failed to predict early trauma was not associated with age at menarche or epigenetic age acceleration, and no significant association linked pubertal timing with biological aging. Relationships between variables did not differ by category of trauma. Model results for Horvath DNAm Age, Hannum DNAm Age, and DNAm PhenoAge are listed in Table 3, Table 4, and Table 5 respectively.

[1]Sensitivity analyses found similar model results for DNAm PhenoAge when income was co-varied (Table S1).

DNAm GrimAge[2]

For DNAm GrimAge (Table 6), early trauma did not significantly predict age at menarche, $b = -0.02$, $p = .28$, ß =- .10; however, early trauma was significantly associated with faster age acceleration, $b = 0.07$, $p = .007$, ß = .24, and earlier menarche was significantly associated with faster age acceleration, $b = -0.42$, $p = .005$, ß =- .23. The indirect effect of early trauma on age acceleration through age at menarche was non-significant, $b = 0.01$, $p = .31$, 95% CI [−0.01, 0.02].

Secondary analyses (Table 6).—Consistent with findings using the composite trauma index, neither early abuse, $b = -0.02$, $p = .18$, or early neglect, $b = 0.01$, $p = .91$, predicted age at menarche. Notably, while early abuse was significantly associated with faster age acceleration using DNAm GrimAge, $b = 0.09$, $p = .007$, ß = .24, this was not the case for early neglect, $b = 0.18$, $p = .10$. Neither abuse nor neglect predicted pubertal timing and the hypothesized indirect effect of trauma on accelerated aging via pubertal timing proved insignificant (abuse: $b = 0.01$, $p = .23$, 95% CI [−0.01, 0.03]: neglect: $b = -0.003$, $p = .91$, 95% CI [−0.05, 0.05]).

Discussion

The present study examined the relationships between childhood adversity, pubertal timing, and four epigenetic measures of biological age acceleration. We did not find the expected indirect effect of early trauma on epigenetic aging through age at menarche (early trauma was not associated with early menarche); however, both early trauma and menarche were both associated with faster age acceleration, using one of the epigenetic clocks (DNAm GrimAge). Our results indicate that a woman with more early life trauma or who achieved menarche earlier than peers presents as biologically older in adulthood than women of the same chronological age. When trauma was partitioned into the domains of abuse and neglect, early abuse was associated with faster epigenetic age acceleration, but early neglect was not.

Study findings are largely congruent with previous work on early life adversity and biological aging. Childhood trauma has been associated with adult age acceleration using Hannum DNAm Age (associations were not found with childhood trauma and Horvath DNAm acceleration; Wolf et al., 2018; Zannas et al., 2015). To our knowledge, this is the first study to examine the relationship between early life trauma and DNAm GrimAge. Early life experiences of threat have been specifically associated with epigenetic age acceleration in children (Horvath DNAm Age), and this relationship was specific to early experiences of threat and did not hold for early life deprivation (Sumner et al., 2019). Direct exposure to violence have also resulted in epigenetic age acceleration in children (Horvath DNAm Age, Jovanovic et al., 2017). Using DNA GrimAge, we found that early life abuse was associated with epigenetic age acceleration in adulthood, whereas early life physical neglect was not.

Early pubertal development may be a risk factor for increased disease and early mortality in adulthood as a result of a strategy for distributing resources across the lifespan that mediates

[2]Sensitivity analyses found similar model results for DNAm GrimAge when race was co-varied (Table S1).

between competing metabolic demands for reproduction, growth, and maintenance (Ellis, 2004, Zhang et al., 2019). The current study is the first to find earlier menarche related to epigenetic age acceleration in *adulthood*. Binder and colleagues (2019) found that increases in *childhood* epigenetic age acceleration using Horvath DNAm Age (Horvath, 2013, 2015) predicted earlier menarche. Epigenetic age of children using Horvath DNAm Age and pubertal stage have demonstrated significant positive correlations (Simpkin et al, 2017, Sumner et al., 2019); however, the same study did not find significant relationships between child epigenetic age and age at puberty (i.e., age at peak height velocity) (Simpkin et al, 2017). While ours is the first study to reveal a phenotypic association between menarche and epigenetic age acceleration, a previous genome-wide association study (GWAS) of epigenetic age acceleration revealed evidence for a causal relationship between age at menarche and Horvath DNAm Age (Mendelian Randomization based Egger regression, $p = 0.004$; Lu et al., 2018). This genetic study did not evaluate the relationship between age at menarche and Hannum DNAm Age, DNAm PhenoAge or DNAm GrimAge.

The present study did not find an indirect effect of early life trauma on biological aging through pubertal timing or a direct path from early life trauma to age of menarche; hence, there was no evidence of mediation through this pathway. Findings suggest that the effects of early life adversity on epigenetic aging may be independent from those of pubertal timing on epigenetic aging, and that each predictor may act through different pathways. If early adversity and pubertal timing influence biological aging through relatively independent mechanisms, the pubertal transition may offer another opportunity (along with early life) to intervene and impact adult health outcomes. Puberty may be a sensitive period for recalibration of the HPA axis in children who have experienced early life adversity (Gunnar et al., 2019). In accordance with life history theory, the peripubertal recalibration may seek to more closely match the environmental conditions likely to be present during the reproductive period. Intervention during the pubertal transition may also protect against future epigenetic age acceleration. Brody et al. (2016a) found in an intervention study that fostered supportive family environments, youth in the experimental—but not control—group were buffered against epigenetic age acceleration in the context of high levels of racial discrimination. Moreover, a family-based prevention program was found to protect against epigenetic age acceleration for youth from risky family environments (Brody et al., 2016b).

It is not clear why we found significant associations we found significant associations with early trauma and age at menarche with DNAm GrimAge, and non-significant findings with Horvath DNAm Age, Hannum DNAm Age, and DNAm PhenoAge. One possible reason may be that DNAm GrimAge outperforms the other three clocks in predicting negative health outcomes associated with early trauma and early pubertal timing (e.g., cardiovascular disease). Research supports that DNAm GrimAge is more accurate in the prediction of time-to-heart-disease, time-to-cancer, and age at menopause than the other clocks (Lu et al., 2019). Using DNAm GrimAge, significant associations have been found with multiple lifestyle factors and environmental variables that were not significant when the other epigenetic clocks were used (Ecker & Beck, 2019). A longitudinal study of aging outcomes compared Horvath DNAm Age, Hannum DNAm Age, DNAm PhenoAge, and DNAm GrimAge, and found that DNAm GrimAge evinced the strongest associations with outcomes (Li et al., 2020). The authors concluded that this might be because GrimAge uses

the largest number of CpG sites and allows a single CpG site to contribute to estimation via multiple intermediate biomarkers. Another study of the four clocks also found DNAm GrimAge "stood apart" in having the strongest associations with age-related performance (Maddock et al., 2020). A third study of the four clocks concluded: "Among all of the clocks we examined, GrimAge stands out as being influenced by all lifestyle risk factors in the expected direction. The above evidence, along with the fact that GrimAge performs better at predicting age-related disease and mortality, suggests that it may be a promising DNAm clock that best mirrors the relationship between environmental risk factors and healthy aging. Future studies focusing on GrimAge and related items are needed to advance our understanding about cellular aging" (Zhao et al., 2019, p. 13–14).

Further, the four clocks do not necessarily represent the same aspects of epigenetic aging. Epigenetic clocks can currently be understood as measuring combinations of biological processes; these combinations and processes may differ by epigenetic clock (Theodoropoulou et al., 2019). Evidence also suggests that associations between epigenetic clocks best and distinct environmental risk factors differ by clock (Zhao et al., 2019). We may speculate that DNAm GrimAge may better capture the biological and physiological process set in motion by child abuse and early pubertal timing than the other three clocks. Our non-significant findings for three of the four clocks in our support that future research should include multiple clocks when examining associations with epigenetic aging.

Limitations

Current study results should be considered within the context of several limitations. First, we measured events that took place in childhood and adolescence (i.e., trauma in early life, age at menarche) retrospectively in adulthood. Retrospective report of age at menarche is highly accurate (Ellis, 2004), but the accuracy of retrospective recall of childhood experiences should not be assumed (Hardt, & Rutter, 2004; Reuben et al., 2016). Ideally, a study might include both prospective and retrospective report of childhood maltreatment as low agreement has been documented between prospective and retrospective recall; however, retrospective report of maltreatment is practical and useful with an adult sample (Baldwin et al., 2019; Newbury et al., 2018). In addition, due to retrospective reporting, we did not have measures of childhood BMI in the current study. As childhood BMI may be an important contributor to age at menarche, we recommend that future research on the effects of early life trauma through pubertal timing include prepubertal BMI as a covariate.

Secondly, our predictors were associated with one of four epigenetic clocks (GrimAge) but not the three other clocks. The epigenetic clocks used in the present study are created using non-overlapping genomic sites and previous research has observed that outcomes can be specific to one epigenetic clock (e.g., Hannum DNAm Age) and not significant for another epigenetic clocks (e.g., Horvath DNAm Age) in the same sample (Horvath & Raj, 2018; Wolf et al., 2018). Different measures of biological aging do not necessarily show high agreement or reflect the same aspects of the bio-aging construct (D. Belsky et al., 2018), and so it is useful to include multiple epigenetic indices in the same study. GrimAge, one of a new generation of epigenetic estimators, robustly predicts time-to-death and time-to-coronary heart disease, and in expert opinion, may be the "best epigenetic

mortality predictor reported so far" (Ecker & Beck, 2019, p. 834). We may have found effects with GrimAge because it outperforms other epigenetic clocks when it comes to associations with age at menopause (Lu et al., 2019), and in predicting outcomes associated with early trauma and early pubertal timing, such as risk for CVD.

Lastly, there was a lack of racial diversity in our study sample and we were not able to examine race as a moderator of relationships between early trauma, age at menarche, and epigenetic age acceleration. Black individuals are understudied in pubertal maturation research and research examining racial differences in the effects of early life adversity and early pubertal timing on later bio-aging are needed. There may be racial differences in epigenetic aging rates (Horvath et al., 2016), and in one study, child maltreatment was not associated with epigenetic age acceleration in Black adults (Zannas et al., 2015).

Conclusion

As guided by life history theory (Belsky, 2019), the present study examined both the direct and indirect effects of early life trauma through age at menarche on adult epigenetic age acceleration and evaluated whether effects were specific to either early abuse or early neglect. Early trauma and early menarche had independent effects on DNAm GrimAge acceleration, and early life abuse, but not neglect, was associated with faster age acceleration. Although epigenetic clocks are potent predicters of morbidity and mortality, research has yet to determine if epigenetic age acceleration is a more of a marker of future disease and death or if it directly biologically contributes to poor health and premature death. Adaptive or beneficial aspects of epigenetic age acceleration in the short term (e.g., during the early reproductive period) may reflect a trade-off for aging-associated diseases later in life (Belsky, 2019; Belsky & Shalev, 2016). Early life adversity and early menarche may lead to premature aging decades before the development of serious disease and dysfunction. The present study found that childhood trauma and earlier menarche independently forecasted faster biological aging in heathy young and middle aged adults, who had yet to develop serious and chronic disease. It remains to be seen if interventions can slow biological age acceleration set in motion by childhood experiences. If so, modifying epigenetic aging might be an effective way to extend healthspan and so reduce the burdens of stress-related disease and aging (D. Belsky et al., 2015).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The research reported in this article was supported by the National Institute of Mental Health (UCSF, grant number 5T32MH019391 – 27); and the National Institute of Aging (E.S.E, grant number 1R01AG059677 – 01A1), and (S.H., grant number 1U01AG060908 – 01.

References

Aschbacher K, Milush JM, Gilbert A, Almeida C, Sinclair E, Epling L, … Epel E. (2017). Chronic stress is associated with reduced circulating hematopoietic progenitor cell number: A maternal caregiving model. Brain, Behavior, and Immunity, 59, 245–252. 10.1016/j.bbi.2016.09.009

Baldwin JR, Reuben A, Newbury JB, & Danese A. (2019). Agreement between prospective and retrospective measures of childhood maltreatment: A systematic review and meta-analysis. JAMA Psychiatry, 76(6), 584–593. [PubMed: 30892562]

Belsky DW, Caspi A, Houts R, Cohen HJ, Corcoran DL, Danese A, ... & Sugden K. (2015). Quantification of biological aging in young adults. Proceedings of the National Academy of Sciences, 112(30), E4104-E4110.

Belsky DW, Moffitt TE, Cohen AA, Corcoran DL, Levine ME, Prinz JA, … Caspi A. (2018). Eleven telomere, epigenetic clock, and biomarker-composite quantifications of biological aging: Do they measure the same thing? American Journal of Epidemiology, 187(6), 1220–1230. 10.1093/aje/kwx346 [PubMed: 29149257]

Belsky J. (2011). Family experience and pubertal development in evolutionary perspective. Journal of Adolescent Health, 48(5), 425–426. 10.1016/j.jadohealth.2011.03.001

Belsky J. (2012). The development of human reproductive strategies: Progress and prospects. Current Directions in Psychological Science, 21(5), 310–316.

Belsky J. (2019). Early-life adversity accelerates child and adolescent development. Current Directions in Psychological Science, 0963721419837670.

Belsky J, & Shalev I. (2016). Contextual adversity, telomere erosion, pubertal development, and health: Two models of accelerated aging, or one? Development and Psychopathology, 28(4), 1367–1383. 10.1017/S0954579416000900 [PubMed: 27688015]

Belsky J, Steinberg L, & Draper P. (1991). Childhood experience, interpersonal development, and reproductive strategy: An evolutionary theory of socialization. Child Development, 62(4), 647–670. 10.1111/j.1467-8624.1991.tb01558.x [PubMed: 1935336]

Bernstein DP, Ahluvalia T, Pogge D, & Handelsman L. (1997). Validity of the childhood trauma questionnaire in an adolescent psychiatric population. Journal of the American Academy of Child and Adolescent Psychiatry, 36(3), 340–348. 10.1097/00004583-199703000-00012 [PubMed: 9055514]

Bernstein DP, & Fink L. (1998). Childhood Trauma Questionnaire A retrospective self-report manual San Antonio, TX The Psychological Corporation.

Bernstein DP, Fink L, Handelsman L, Foote J, Lovejoy M, Wenzel K, ... & Ruggiero J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. The American Journal of Psychiatry, 151(8), 1132–1136. [PubMed: 8037246]

Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, … Zule W. (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abuse and Neglect, 27(2), 169–190. 10.1016/S0145-2134(02)00541-0 [PubMed: 12615092]

Binder AM, Corvalan C, Mericq V, Pereira A, Santos JL, Horvath S, … Michels KB (2018). Faster ticking rate of the epigenetic clock is associated with faster pubertal development in girls. Epigenetics, 13(1), 85–94. 10.1080/15592294.2017.1414127 [PubMed: 29235933]

Bleil ME, Adler NE, Appelhans BM, Gregorich SE, Sternfeld B, & Cedars MI (2013). Childhood adversity and pubertal timing: Understanding the origins of adulthood cardiovascular risk. Biological Psychology, 93(1), 213–219. 10.1016/j.biopsycho.2013.02.005 [PubMed: 23428374]

Boynton-Jarrett R, Wright RJ, Putnam FW, Hibert EL, Michels KB, Forman MR, & Rich-Edwards J. (2013). Childhood abuse and age at menarche. Journal of Adolescent Health, 52(2), 241–247.

Brody GH, Miller GE, Yu T, Beach SRH, & Chen E. (2016a). Supportive family environments ameliorate the link between racial discrimination and epigenetic aging: A replication across two longitudinal cohorts. Psychological Science, 27(4), 530–541. 10.1177/0956797615626703 [PubMed: 26917213]

Brody GH, Yu T, Chen E, Beach SRH, & Miller GE (2016b). Family-centered prevention ameliorates the longitudinal association between risky family processes and epigenetic aging. Journal of Child Psychology and Psychiatry and Allied Disciplines, 57(5), 566–574. 10.1111/jcpp.12495

Brown J, Cohen P, Chen H, Smailes E, & Johnson JG (2004). Sexual trajectories of abused and neglected youths. Journal of Developmental & Behavioral Pediatrics, 25(2), 77–82. [PubMed: 15083128]

Chapman DP, Whitfield CL, Felitti VJ, Dube SR, Edwards VJ, & Anda RF (2004). Adverse childhood experiences and the risk of depressive disorders in adulthood. Journal of Affective Disorders, 82(2), 217–225. 10.1016/j.jad.2003.12.013 [PubMed: 15488250]

Charalampopoulos D, McLoughlin A, Elks CE, & Ong KK (2014). Age at menarche and risks of all-cause and cardiovascular death: A systematic review and meta-analysis. American Journal of Epidemiology, 180(1), 29–40. [PubMed: 24920784]

Danese A, Moffitt TE, Harrington HL, Milne BJ, Polanczyk G, Pariante CM, … Caspi A. (2009). Adverse childhood experiences and adult risk factors for age-related disease: Depression, inflammation, and clustering of metabolic risk markers. Archives of Pediatrics and Adolescent Medicine, 163(12), 1135–1143. 10.1001/archpediatrics.2009.214 [PubMed: 19996051]

Del Giudice M, Ellis BJ, & Shirtcliff EA (2011). The adaptive calibration model of stress responsivity. Neuroscience & Biobehavioral Reviews, 35(7), 1562–1592. [PubMed: 21145350]

Ecker S, & Beck S. (2019). The epigenetic clock: A molecular crystal ball for human aging? Aging, 11(2), 833–835. 10.18632/aging.101712 [PubMed: 30669120]

Ellis BJ, & Essex MJ (2007). Family environments, adrenarche, and sexual maturation: A longitudinal test of a life history model. Child Development, 78(6), 1799–1817. 10.1111/j.1467-8624.2007.01092.x [PubMed: 17988322]

Ellis BJ (2004). Timing of pubertal maturation in girls: An integrated life history approach. Psychological Bulletin, 130(6), 920–958. 10.1037/0033-2909.130.6.920 [PubMed: 15535743]

Field AE, Robertson NA, Wang T, Havas A, Ideker T, & Adams PD (2018). DNA methylation clocks in aging: Categories, Causes, and Consequences. Molecular Cell, 71(6), 882–895. 10.1016/j.molcel.2018.08.008 [PubMed: 30241605]

Fransquet PD, Wrigglesworth J, Woods RL, Ernst ME, & Ryan J. (2019). The epigenetic clock as a predictor of disease and mortality risk: A systematic review and meta-analysis. Clinical epigenetics, 11(1), 62. [PubMed: 30975202]

Frontini MG, Srinivasan SR, & Berenson GS (2003). Longitudinal changes in risk variables underlying metabolic Syndrome X from childhood to young adulthood in female subjects with a history of early menarche: The Bogalusa Heart Study. International Journal of Obesity, 27(11), 1398–1404. [PubMed: 14574352]

Gilbert LK, Breiding MJ, Merrick MT, Thompson WW, Ford DC, Dhingra SS, & Parks SE (2015). Childhood adversity and adult chronic disease: An update from ten states and the District of Columbia, 2010. American Journal of Preventive Medicine, 48(3), 345–349. 10.1016/j.amepre.2014.09.006 [PubMed: 25300735]

Giles LC, Glonek GFV, Moore VM, Davies MJ, & Luszcz MA (2010). Lower age at menarche affects survival in older Australian women: Results from the Australian Longitudinal Study of Ageing. BMC Public Health, 10. 10.1186/1471-2458-10-341

Golub MS, Collman GW, Foster PM, Kimmel CA, Rajpert-De Meyts E, Reiter EO, ... & Toppari J. (2008). Public health implications of altered puberty timing. Pediatrics, 121(Supplement 3), S218–S230. [PubMed: 18245514]

Gunnar MR, DePasquale CE, Reid BM, & Donzella B. (2019). Pubertal stress recalibration reverses the effects of early life stress in postinstitutionalized children. Proceedings of the National Academy of Sciences, 116(48), 23984–23988.

Hannum G, Guinney J, Zhao L, Zhang L, Hughes G, Sadda S, ... & Deconde R. (2013). Genome-wide methylation profiles reveal quantitative views of human aging rates. Molecular cell, 49(2), 359–367. [PubMed: 23177740]

Hardt J, & Rutter M. (2004). Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. Journal of child psychology and psychiatry, 45(2), 260–273. [PubMed: 14982240]

Herman-Giddens ME, Sandler AD, & Friedman NE (1988). Sexual precocity in girls: An association with sexual abuse?. American Journal of Diseases of Children, 142(4), 431–433. [PubMed: 3348186]

Horvath S. (2013). DNA methylation age of human tissues and cell types. Genome Biology, 14(10), 115. 10.1186/gb-2013-14-10-r115 [PubMed: 23657273]

Horvath S, Gurven M, Levine ME, Trumble BC, Kaplan H, Allayee H, ... & Jamieson BD (2016). An epigenetic clock analysis of race/ethnicity, sex, and coronary heart disease. Genome Biology, 17(1), 171. [PubMed: 27511193]

Horvath S, & Levine AJ (2015). HIV-1 infection accelerates age according to the epigenetic clock. The Journal of Infectious Diseases, 212(10), 1563–1573. [PubMed: 25969563]

Horvath S, & Raj K. (2018). DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nature Reviews Genetics, 19(6), 371–384. 10.1038/s41576-018-0004-3

Horvath S, Oshima J, Martin GM, Lu AT, Quach A, Cohen H, … Raj K. (2018). Epigenetic clock for skin and blood cells applied to Hutchinson Gilford Progeria Syndrome and ex vivo studies. Aging, 10(7), 1758–1775. 10.18632/aging.101508 [PubMed: 30048243]

Jacobsen BK, Heuch I, & Kvåle G. (2007). Association of low age at menarche with increased all-cause mortality: A 37-year follow-up of 61,319 Norwegian women. American Journal of Epidemiology, 166(12), 1431–1437. 10.1093/aje/kwm237 [PubMed: 17875585]

Jovanovic T, Vance LA, Cross D, Knight AK, Kilaru V, Michopoulos V, … Smith AK (2017). Exposure to violence accelerates epigenetic aging in children. Scientific Reports, 7(1). 10.1038/s41598-017-09235-9

Laitinen J, Power C, & Järvelin MR (2001). Family social class, maternal body mass index, childhood body mass index, and age at menarche as predictors of adult obesity. The American Journal of Clinical Nutrition, 74(3), 287–294. 10.1093/ajcn/74.3.287 [PubMed: 11522550]

Lakshman R, Forouhi NG, Sharp SJ, Luben R, Bingham SA, Khaw KT, … Ong KK (2009). Early age at menarche associated with cardiovascular disease and mortality. Journal of Clinical Endocrinology and Metabolism, 94(12), 4953–4960. 10.1210/jc.2009-1789 [PubMed: 19880785]

Lambert HK, King KM, Monahan KC, & McLaughlin KA (2017). Differential associations of threat and deprivation with emotion regulation and cognitive control in adolescence. Development and Psychopathology, 29(3), 929–940. [PubMed: 27424571]

Levine ME, Lu AT, Quach A, Chen BH, Assimes TL, Bandinelli S, … Horvath S. (2018). An epigenetic biomarker of aging for lifespan and healthspan. Aging, 10(4), 573–591. 10.18632/aging.101414 [PubMed: 29676998]

Liu Z, Kuo PL, Horvath S, Crimmins E, Ferrucci L, & Levine M. (2018). A new aging measure captures morbidity and mortality risk across diverse subpopulations from NHANES IV: A cohort study. PLoS Medicine, 15(12), e1002718. 10.1371/journal.pmed.1002718

Lu AT, Quach A, Wilson JG, Reiner AP, Aviv A, Raj K, ... & Whitsel EA (2019). DNA methylation GrimAge strongly predicts lifespan and healthspan. Aging (Albany NY), 11(2), 303. [PubMed: 30669119]

Lu AT, Xue L, Salfati EL, Chen BH, Ferrucci L, Levy D, ... & Yet I. (2018). GWAS of epigenetic aging rates in blood reveals a critical role for TERT. Nature Communications, 9(1), 1–13.

Mendle J, Turkheimer E, & Emery RE (2007). Detrimental psychological outcomes associated with early pubertal timing in adolescent girls. Developmental Review, 27(2), 151–171. 10.1016/J.DR.2006.11.001 [PubMed: 20740062]

Newbury JB, Arseneault L, Moffitt TE, Caspi A, Danese A, Baldwin JR, & Fisher HL (2018). Measuring childhood maltreatment to predict early-adult psychopathology: comparison of prospective informant-reports and retrospective self-reports. Journal of Psychiatric Research, 96, 57–64. [PubMed: 28965006]

Noll JG, Trickett PK, Long JD, Negriff S, Susman EJ, Shalev I, ... & Putnam FW (2017). Childhood sexual abuse and early timing of puberty. Journal of Adolescent Health, 60(1), 65–71.

Pierce MB, & Leon DA (2005). Age at menarche and adult BMI in the Aberdeen Children of the 1950s Cohort Study. American Journal of Clinical Nutrition, 82(4), 733–739. 10.1093/ajcn/82.4.733

Pierce MB, Kuh D, & Hardy R. (2010). Role of lifetime body mass index in the association between age at puberty and adult lipids: Findings from men and women in a British birth cohort. Annals of Epidemiology, 20(9), 676–682. 10.1016/j.annepidem.2010.05.015 [PubMed: 20696407]

Prentice P, & Viner RM (2013). Pubertal timing and adult obesity and cardiometabolic risk in women and men: A systematic review and meta-analysis. International Journal of Obesity, 37,1036–1043. 10.1038/ijo.2012.177 [PubMed: 23164700]

Reuben A, Moffitt TE, Caspi A, Belsky DW, Harrington H, Schroeder F, ... & Danese A. (2016). Lest we forget: comparing retrospective and prospective assessments of adverse childhood experiences in the prediction of adult health. Journal of Child Psychology and Psychiatry, 57(10), 1103–1112. [PubMed: 27647050]

Rosseel Y. (2012). lavaan: An R Package for Structural Equation Modeling. Journal of Statistical Software, 48, 1–36.

Shalev I, & Belsky J. (2016). Early-life stress and reproductive cost: A two-hit developmental model of accelerated aging? Medical Hypotheses, 90, 41–47. 10.1016/j.mehy.2016.03.002 [PubMed: 27063083]

Simpkin AJ, Howe LD, Tilling K, Gaunt TR, Lyttleton O, McArdle WL, … Relton CL (2017). The epigenetic clock and physical development during childhood and adolescence: Longitudinal analysis from a UK birth cohort. International Journal of Epidemiology, 46(2), 549–558. 10.1093/ije/dyw307 [PubMed: 28089957]

Straus MA, & Kantor GK (2005). Definition and measurement of neglectful behavior: some principles and guidelines. Child Abuse & Neglect, 29(1), 19–29. [PubMed: 15664423]

Su S, Jimenez MP, Roberts CT, & Loucks EB (2015). The role of adverse childhood experiences in cardiovascular disease risk: A review with emphasis on plausible mechanisms. Current Cardiology Reports, 17(10), 88. [PubMed: 26289252]

Sumner JA, Colich NL, Uddin M, Armstrong D, & McLaughlin KA (2019). Early experiences of threat, but not deprivation, are associated with accelerated biological aging in children and adolescents. Biological Psychiatry, 85(3), 268–278. 10.1016/j.biopsych.2018.09.008 [PubMed: 30391001]

Tamakoshi K, Yatsuya H, & Tamakoshi A. (2011). Early age at menarche associated with increased all-cause mortality. European Journal of Epidemiology, 26(10), 771–778. 10.1007/s10654-011-9623-0 [PubMed: 22006230]

Team, R. C. (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Retrieved from https://www.R-project.org/

Widén E, Silventoinen K, Sovio U, Ripatti S, Cousminer DL, Hartikainen AL, … Palotie A. (2012). Pubertal timing and growth influences cardiometabolic risk factors in adult males and females. Diabetes Care, 35(4), 850–856. 10.2337/dc11-1365 [PubMed: 22338106]

Wolf EJ, Maniates H, Nugent N, Maihofer AX, Armstrong D, Ratanatharathorn A, … Logue MW (2018). Traumatic stress and accelerated DNA methylation age: A meta-analysis. Psychoneuroendocrinology, 92, 123–134. 10.1016/j.psyneuen.2017.12.007 [PubMed: 29452766]

Zabin LS, Emerson MR, & Rowland DL (2005). Childhood sexual abuse and early menarche: the direction of their relationship and its implications. Journal of Adolescent Health, 36(5), 393–400.

Zannas AS, Arloth J, Carrillo-Roa T, Iurato S, Röh S, Ressler KJ, … Mehta D. (2015). Lifetime stress accelerates epigenetic aging in an urban, African American cohort: Relevance of glucocorticoid signaling. Genome Biology, 16(1). 10.1186/s13059-015-0828-5

Zhang L, Zhang D, & Sun Y. (2019). Adverse childhood experiences and early pubertal timing among girls: a meta-analysis. International Journal of Environmental Research and Public Health, 16(16), 2887.

Table 1

Descriptive statistics for caregivers (n =78) and controls (n = 83)

Age *M*(*SE*)	Total	42.53 (5.00)	Early life abuse *M*(*SE*)	Total	20.51 (6.71)	Horvath acceleration *M*(*SE*) Range:−8.00–13.33	Total	0.02 (3.59)
	Caregivers	43.13 (5.35)		Caregivers	21.83 (7.38)		Caregivers	−0.22 (4.03)
	Controls	41.96 (4.60)		Controls	19.27 (5.77)		Controls	0.22 (3.22)
	(*t*)	1.48		(*t*)	2.47*		(*t*)	0.67
	d	0.23		*d*	0.39		*d*	0.12
Race (% White)	Total	81.3	Early life neglect *M*(*SE*)	Total	6.33 (1.90)	Hannum acceleration *M*(*SE*) Range:−8.91–8.35	Total	0.01 (3.29)
	Caregivers	81.8		Caregivers	6.65 (2.28)		Caregivers	0.24 (3.53)
	Controls	80.7		Controls	6.02 (1.41)		Controls	−0.18 (3.09)
	(χ2)	.03		(*t*)	2.10*		(*t*)	0.72
				d	0.33		*d*	0.13
Education (% college degree or higher)	Total	86.0	Early life trauma *M*(*SE*)	Total	26.84 (8.02)	PhenoAge acceleration *M*(*SE*) Range: −12.82–12.88	Total	−0.04 (4.74)
	Caregivers	81.6		Caregivers	28.49 (8.90)		Caregivers	0.27 (4.81)
	Controls	90.1		Controls	25.29 (6.79)		Controls	−0.28 (4.71)
	(χ2)	2.38		(*t*)	2.55*		(*t*)	0.65
				d	0.40		*d*	0.12
Annual income (% ≥ $100,000)	Total	76.3	Age at menarche *M*(*SE*)	Total	12.86 (1.39)	GrimAge acceleration *M*(*SE*) Range:−6.56–8.93	Total	0.03 (2.47)
	Caregivers	67.5		Caregivers	12.93 (1.33)		Caregivers	0.42 (2.84)
	Controls	84.3		Controls	12.80 (1.45)		Controls	−0.28 (2.10)
	(χ2)	6.23*		(*t*)	0.54		(*t*)	1.58
				d	0.09		*d*	0.28

Note.

*p <.05

**p ≤.01

***p ≤.001.

Table 2

Correlations between study variables

	Age	Race	Education	Income	Menarche	Abuse	Neglect	Trauma	Horvath	Hannum	PhenoAge	GrimAge
Age	–											
Race (% White)	.12	–										
Education (% college degree)	.14	.13	–									
Annual income (% ≥$100,000)	.08	.07	.24**	–								
Age at menarche	.18*	.14	.09	.14	–							
Early life abuse	−.01	−.05	−.12	−.13	−.11	–						
Early life neglect	.05	−.03	−.08	−.07	.02	.62***	–					
Early life trauma	.01	−.05	−.12	−.13	−.09	.98***	.75***	–				
Horvath acceleration	.04	<.01	−.03	<.01	−.15	.06	.01	.05	–			
Hannum acceleration	−.01	−.02	.08	−.01	−.08	.02	−.06	<.01	.44***	–		
PhenoAge acceleration	.01	−.18	−.12	−.18*	−.04	.06	.07	.06	.36***	.51***	–	
GrimAge acceleration	−.02	−.25**	−.06	−.10	−.26**	.26**	.14	.25**	.13	.38***	.46***	–

Note.

* $p < .05$

** $p \leq .01$

*** $p \leq .001$.

Table 3

Direct and indirect effects (through age at menarche) of trauma, abuse, and neglect on Horvath acceleration, accounting for cell counts (CD8naive, CD8pCD28nCD45Ran).

Predictor	**Outcome**	***b***	***SE***	**ß**	***p***	**95% CI**
Trauma	Age Acceleration	0.01	0.05	.03	.80	[−0.08, 0.11]
Menarche	Age Acceleration	−0.38	0.20	−.15	.06	[−0.78, 0.01]
CD8naive	*Age Acceleration*	*−0.01*	*0.01*	*−.06*	*.52*	*[−0.02, 0.01]*
CD8pCD28nCD45Ran	*Age Acceleration*	*−0.05*	*0.09*	*−.04*	*.63*	*[−0.23, 0.14]*
Trauma	Menarche	−0.02	0.02	−.09	.42	[−0.05, 0.02]
CD8naive	*Menarche*	*−0.01*	*<.01*	*−.16*	*.19*	*[−0.01, <.01]*
CD8pCD28nCD45Ran	*Menarche*	*−0.05*	*0.05*	*−.12*	*.28*	*[−0.15, 0.04]*
Indirect Effect through Menarche		0.01	0.01	.01	.48	[−0.01, 0.02]
Abuse	Age Acceleration	0.02	0.06	.03	.81	[−0.11, 0.14]
Menarche	Age Acceleration	−0.37	0.20	−.15	.06	[−0.77, 0.02]
CD8naive	*Age Acceleration*	*<0.01*	*0.01*	*−.05*	*.64*	*[−0.02, 0.01]*
CD8pCD28nCD45Ran	*Age Acceleration*	−0.03	*0.09*	*−.03*	*.74*	*[−0.22, 0.15]*
Abuse	Age Acceleration	−0.03	0.02	−.11	.28	[−0.07, 0.02]
CD8naive	*Menarche*	*−0.01*	*<.01*	*−.15*	*.21*	*[−0.01, <.01]*
CD8pCD28nCD45Ran	*Menarche*	*−0.05*	*0.05*	*−.12*	*.30*	*[−0.14, 0.04]*
Indirect Effect through Menarche		0.01	0.01	0.02	.38	[−0.01, 0.03]
Neglect	Age Acceleration	<0.01	0.15	<.01	.98	[−0.29, 0.29]
Menarche	Age Acceleration	−0.38	0.20	−.15	.06	[−0.77, 0.02]
CD8naive	*Age Acceleration*	*−0.01*	*0.01*	*−.09*	*.33*	*[−0.02, 0.01]*
CD8pCD28nCD45Ran	*Age Acceleration*	*−0.05*	*0.09*	*−.05*	*.58*	*[−0.24, 0.13]*
Neglect	Menarche	0.03	0.06	.04	.66	[−0.10, 0.15]
CD8naive	*Menarche*	*−0.01*	*<.01*	*−.19*	*.09*	*[−0.01, <.01]*
CD8pCD28nCD45Ran	*Menarche*	*−0.06*	*0.05*	*−.13*	*.21*	*[−0.15, 0.03]*
Indirect Effect through Menarche		−0.01	0.02	0.01	.65	[−0.06, 0.04]

Table 4

Direct and indirect effects (through age at menarche) of trauma, abuse, and neglect on Hannum acceleration, accounting for cell counts (CD8naive, CD8pCD28nCD45Ran).

Predictor	Outcome	*b*	*SE*	ß	*p*	95% CI
Trauma	Age Acceleration	0.01	0.04	.01	.87	[−0.06, 0.07]
Menarche	Age Acceleration	−0.26	0.19	−.11	.17	[−0.64, 0.11]
CD8naive	***Age Acceleration***	***−0.04***	***0.01***	***−.42***	***<.001***	***[−0.05, −0.02]***
CD8pCD28nCD45Ran	*Age Acceleration*	*<0.01*	*0.01*	*.02*	*.81*	*[−0.01, 0.02]*
Trauma	Menarche	−0.02	0.02	−.08	.45	[−0.06, 0.02]
CD8naive	*Menarche*	*−0.01*	*<.01*	*−.14*	*.24*	*[−0.01, <.01]*
CD8pCD28nCD45Ran	*Menarche*	*<.01*	*<.01*	*−.11*	*.36*	*[−0.01, <.01]*
Indirect Effect through Menarche		<0.01	0.01	.01	.48	[−0.01, 0.02]
Abuse	Age Acceleration	0.02	0.04	.03	.71	[−0.07, 0.10]
Menarche	Age Acceleration	−0.26	0.19	−.11	.18	[−0.63, 0.12]
CD8naive	***Age Acceleration***	***−0.04***	***0.01***	***−.42***	***<.001***	***[−0.05, −0.02]***
CD8pCD28nCD45Ran	*Age Acceleration*	<0.01	*0.01*	*.03*	*.79*	*[0.01, 0.02]*
Abuse	Age Acceleration	−0.03	0.02	−.11	.30	[−0.07, 0.02]
CD8naive	*Menarche*	*−0.01*	*<.01*	*−.13*	*.26*	*[−0.01, <.01]*
CD8pCD28nCD45Ran	*Menarche*	*<.01*	*<.01*	*−.10*	*.39*	*[−0.01, <.01]*
Indirect Effect through Menarche		0.01	0.01	0.01	.37	[−0.01, 0.02]
Neglect	Age Acceleration	−0.11	0.13	−.06	.41	[−0.36, 0.15]
Menarche	Age Acceleration	−0.26	0.18	−.11	.15	[−0.62, 0.10]
CD8naive	***Age Acceleration***	***−0.04***	***0.01***	***−.43***	***<.001***	***[−0.05, −0.02]***
CD8pCD28nCD45Ran	*Age Acceleration*	*<0.01*	*0.01*	*.03*	*.79*	*[−0.01, 0.02]*
Neglect	Menarche	0.03	0.07	.05	.61	[−0.10, 0.17]
CD8naive	*Menarche*	*−0.01*	*<.01*	*−.18*	*.12*	*[−0.01, <.01]*
CD8pCD28nCD45Ran	*Menarche*	*<.01*	*<.01*	*−.13*	*.27*	*[−0.01, <.01]*
Indirect Effect through Menarche		−0.01	0.02	−0.01	.65	[−0.05, 0.03]

Table 5

Direct and indirect effects (through age at menarche) of trauma, abuse, and neglect on PhenoAge acceleration, accounting for cell counts (CD8naive, CD8pCD28nCD45Ran).

Predictor	Outcome	*b*	*SE*	ß	*p*	95% CI
Trauma	Age Acceleration	0.05	0.05	.07	.33	[−0.05, 0.13]
Menarche	Age Acceleration	−0.22	0.27	−.07	.42	[−0.75, 0.31]
CD8naive	***Age Acceleration***	***−0.04***	***0.01***	***−.37***	***<.001***	***[−0.07, −0.02]***
CD8pCD28nCD45Ran	*Age Acceleration*	*0.01*	*0.01*	*.09*	*.36*	*[−0.01, 0.03]*
Trauma	Menarche	−0.02	0.02	−.08	.45	[−0.06, 0.02]
CD8naive	*Menarche*	*−0.01*	*<.01*	*−.14*	*.24*	*[−0.01, <.01]*
CD8pCD28nCD45Ran	*Menarche*	*<.01*	*<.01*	*−.11*	*.36*	*[−0.01, <.01]*
Indirect Effect through Menarche		<0.01	0.01	.01	.57	[−0.01, 0.02]
Abuse	Age Acceleration	0.05	0.06	.06	.41	[−0.06, 0.15]
Menarche	Age Acceleration	−0.21	0.27	−.06	.44	[−0.74, 0.32]
CD8naive	***Age Acceleration***	***−0.04***	***0.01***	***−.36***	***<.001***	***[−0.06, −0.02]***
CD8pCD28nCD45Ran	*Age Acceleration*	0.01	*0.01*	*.10*	*.32*	*[−0.01, 0.03]*
Abuse	Age Acceleration	−0.03	0.02	−.11	.30	[−0.07, 0.02]
CD8naive	*Menarche*	*−0.01*	*<.01*	*−.13*	*.26*	*[−0.01, <.01]*
CD8pCD28nCD45Ran	*Menarche*	*<.01*	*<.01*	*−.10*	*.39*	*[−0.01, <.01]*
Indirect Effect through Menarche		0.01	0.01	0.01	.52	[−0.01, 0.02]
Neglect	Age Acceleration	0.16	0.16	.06	.32	[−0.15, 0.47]
Menarche	Age Acceleration	−0.23	0.26	−.07	.38	[−0.74, 0.28]
CD8naive	***Age Acceleration***	***−0.05***	***0.01***	***−.38***	***<.001***	***[−0.07, −0.02]***
CD8pCD28nCD45Ran	*Age Acceleration*	*0.01*	*0.01*	*.08*	*.42*	*[−0.01, 0.03]*
Neglect	Menarche	0.03	0.07	.05	.61	[−0.10, 0.17]
CD8naive	*Menarche*	*−0.01*	*<.01*	*−.18*	*.12*	*[−0.01, <.01]*
CD8pCD28nCD45Ran	*Menarche*	*<.01*	*<.01*	*−.13*	*.27*	*[−0.01, <.01]*
Indirect Effect through Menarche		−0.01	0.02	<0.01	.66	[−0.04, 0.03]

Table 6

Direct and indirect effects (through age at menarche) of trauma, abuse, and neglect on DNAm GrimAge acceleration, accounting for cell counts (CD8naive, CD8pCD28nCD45Ran).

Predictor	Outcome	*b*	*SE*	ß	*p*	95% CI
Trauma	**Age Acceleration**	**0.08**	**0.03**	**.23**	**.003**	**[0.03, 0.13]**
Menarche	**Age Acceleration**	**−0.45**	**0.13**	**−.26**	**.005**	**[−0.71, −0.19]**
CD8naive	***Age Acceleration***	***−0.02***	***0.01***	***−.26***	***.006***	***[−0.03, −0.01]***
CD8pCD28nCD45Ran	*Age Acceleration*	*0.01*	*0.01*	*.19*	*.04*	*[<.01, 0.02]*
Trauma	Menarche	−0.02	0.02	−.08	.45	[−0.06, 0.02]
CD8naive	*Menarche*	*−0.01*	*<.01*	*−.14*	*.23*	*[−0.01, <.01]*
CD8pCD28nCD45Ran	*Menarche*	*<.01*	*<.01*	*−.11*	*.36*	*[−0.01, <.01]*
Indirect Effect through Menarche		0.01	0.01	.02	.48	[−0.01, 0.03]
Abuse	**Age Acceleration**	**0.09**	**0.03**	**.23**	**.004**	**[0.03, 0.15]**
Menarche	**Age Acceleration**	**−0.44**	**0.13**	**−.24**	**.001**	**[−0.70, −0.18]**
CD8naive	***Age Acceleration***	***−0.02***	***0.01***	***−.26***	***.004***	***[−0.03, −0.01]***
CD8pCD28nCD45Ran	*Age Acceleration*	*0.01*	*0.01*	*.19*	*.04*	*[<.01, 0.02]*
Abuse	Age Acceleration	−0.03	0.02	−.11	.30	[−0.07, 0.02]
CD8naive	*Menarche*	*−0.01*	*<.01*	*−.13*	*.26*	*[−0.01, <.01]*
CD8pCD28nCD45Ran	*Menarche*	*<.01*	*<.01*	*−.10*	*.39*	*[−0.01, <.01]*
Indirect Effect through Menarche		0.01	0.01	0.03	.35	[−0.01, 0.03]
Neglect	Age Acceleration	0.19	0.10	.15	.05	[<.01, 0.38]
Menarche	**Age Acceleration**	**−0.47**	**0.14**	**−.26**	**.001**	**[−0.74, −0.19]**
CD8naive	***Age Acceleration***	***−0.02***	***0.01***	***−.25***	***.01***	***[−0.03, <.01]***
CD8pCD28nCD45Ran	*Age Acceleration*	*0.01*	*0.01*	*.19*	*.05*	*[<.01, 0.02]*
Neglect	Menarche	0.03	0.07	.05	.61	[−0.10, 0.17]
CD8naive	*Menarche*	*−0.01*	*<.01*	*−.18*	*.12*	*[−0.01, <.01]*
CD8pCD28nCD45Ran	*Menarche*	*<.01*	*<.01*	*−.13*	*.27*	*[−0.01, <.01]*
Indirect Effect through Menarche		−0.02	0.03	−0.01	.60	[−0.08, 0.04]