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Adversity exposure during sensitive periods predicts accelerated epigenetic aging in children

Sandro Marini, MD[1,*], **Kathryn A. Davis, MA**[1,*], **Thomas W. Soare, PhD**[1,2,3], **Yiwen Zhu, MS**[1], **Matthew J. Suderman, PhD**[4], **Andrew J. Simpkin, PhD**[4,5], **Andrew D.A.C. Smith, PhD**[6], **Erika J. Wolf, PhD**[7,8], **Caroline L. Relton, PhD**[4,9], **Erin C. Dunn, ScD, MPH**[1,2,3,10]

[1]Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA 02114, USA

[2]Stanley Center for Psychiatric Research, The Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA

[3]Department of Psychiatry, Harvard Medical School, Boston, MA 02115, USA

[4]MRC Integrative Epidemiology Unit, School of Social and Community Medicine, University of Bristol, Bristol, BSB 1TH, UK

[5]School of Mathematics, Statistics and Applied Mathematics, National University of Ireland, Galway, Ireland H91TK33

[6]Applied Statistics Group, University of the West of England, Bristol, BS16 1QY, UK

[7]National Center for PTSD at VA Boston Healthcare System, Boston, MA 02130, USA

[8]Boston University School of Medicine, Department of Psychiatry, Boston, MA 02118, USA

[9]Institute of Genetic Medicine, University of Newcastle, Newcastle upon Tyne, NE1 3BZ, UK

[10]The Henry and Allison McCance Center for Brain Health at Massachusetts General Hospital, Boston, MA 02114, USA

Abstract

Objectives: Exposure to adversity has been linked to accelerated biological aging, which in turn has been shown to predict numerous physical and mental health problems. In recent years, measures of DNA methylation-based epigenetic age—known as “epigenetic clocks”—have been used to estimate accelerated epigenetic aging. Although a small number of studies have found an effect of adversity exposure on epigenetic age in children, none have investigated if there are “sensitive periods” when adversity is most impactful.

Corresponding Author: Erin C. Dunn, ScD, MPH, Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, 185 Cambridge Street, Simches Research Building 6th Floor, Boston, MA 02114; edunn2@mgh.harvard.edu. Phone: 617-726-9387; Fax: 617-726-0830; Website: www.thedunnlab.com.

Authors’ Contributions

SM, ECD, TWS, ADACS and EJW designed the study. TWS, MJS, ADACS and CRL produced the data. Statistical analyses were performed by SM, TWS, YZ and AJS. SM, KAD and ECD wrote the manuscript. All authors revised the manuscript critically and approved it for submission.

*These authors contributed equally

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Methods: Using data from the Avon Longitudinal Study of Parents and Children (ALSPAC; n=973), we tested the prospective association between repeated measures of childhood exposure to seven types of adversity on epigenetic age assessed at age 7.5 using the Horvath and Hannum epigenetic clocks. With a Least Angle Regression variable selection procedure, we evaluated potential sensitive period effects.

Results: We found that exposure to abuse, financial hardship, or neighborhood disadvantage during sensitive periods in early and middle childhood best explained variability in the deviation of Hannum-based epigenetic age from chronological age, even after considering the role of adversity accumulation and recency. Secondary sex-stratified analyses identified particularly strong sensitive period effects. These effects were undetected in analyses comparing children "exposed" versus "unexposed" to adversity. We did not identify any associations between adversity and epigenetic age using the Horvath epigenetic clock.

Conclusions: Our results suggest that adversity may alter methylation processes in ways that either directly or indirectly perturb normal cellular aging and that these effects may be heightened during specific life stages.

Keywords

sensitive periods; epigenetic clock; aging; ALSPAC; adversity

1. Introduction

Exposure to childhood adversity, such as abuse or poverty, represents one of the most potent risk factors for a range of negative health outcomes across the lifespan, with estimates linking such exposures to at least a two-fold increase in subsequent risk for mental disorders (Dunn et al., 2012; McLaughlin et al., 2010). Although these associations are well-established, the specific mechanisms through which adversity becomes biologically embedded remain poorly understood.

Accumulating evidence suggests adversity may become biologically embedded through accelerated aging of cells, tissues, and organs (Gassen et al., 2017; Zannas et al., 2015). Accelerated biological aging, in which biological age outpaces chronological age, is known to be a valid indicator of impaired functionality of both the cell and the biological system in which the cell interacts (Teschendorff et al., 2013).

Recently, DNA methylation (DNAm) patterns at specific CpG sites have been proposed as a promising measure of biological aging. These DNAm-based measures are referred to as "epigenetic clocks" due to their remarkably high correlation with chronological age (Hannum et al., 2013; Horvath, 2013). Two independent algorithms developed to generate these DNAm-based age estimates are the Horvath clock (Horvath, 2013) and the Hannum clock (Hannum et al., 2013). Both clocks can be used to capture accelerated epigenetic aging, which represents the discrepancy between the estimate of epigenetic age based on DNAm patterns and an individual's chronological age (Hannum et al., 2013; Horvath, 2013). In adults, accelerated epigenetic aging as measured by these epigenetic clocks has been correlated with numerous adverse health outcomes (Breitling et al., 2016; Dhingra et al.,

2018), including increased mortality risk (Marioni et al., 2016). These epigenetic clocks have been shown to reliably correlate with chronological age in younger populations as well (Horvath et al., 2016; Simpkin et al., 2017); accelerated epigenetic aging in children and adolescents has been associated with both more advanced growth and development and increased youth mental health problems (Suarez et al., 2018a; Sumner et al., 2018).

A handful of recent studies have explored how exposure to adversity influences epigenetic aging in adulthood (Brody et al., 2016; Fiorito et al., 2017; Lawn et al., 2018; Simons et al., 2016; Wolf et al., 2017; Zannas et al., 2015). These studies have shown that individuals who have perceived subjective high levels of stress across their lifetimes (Zannas et al., 2015), including exposure to sexual abuse (Lawn et al., 2018), a parent's mental illness (Brody et al., 2016; Davis et al., 2017), or chronic financial stress (Simons et al., 2016), have epigenetic ages that outpace their chronological age. One recent meta-analysis quantified this age acceleration, showing that any exposure to childhood trauma was associated with an epigenetic "outpace" of as much as 6 months (when epigenetic age was estimated with Hannum's, but not with Horvath's clock) (Wolf et al., 2017).

However, to our knowledge, only two studies—both of which are cross-sectional—have investigated these associations in children. In one study of youth ages 6–13 years, children who were at least one standard deviation epigenetically older than their peers were found to score twice as high on a measure of lifetime violence exposure (Jovanovic et al., 2017). A more recent study of youth ages 8–16 years reported that each childhood experience of threat (e.g., abuse, domestic violence) was associated with approximately one additional month of epigenetic age acceleration (Sumner et al., 2018).

Although evidence from these studies suggests a link between adversity exposure and accelerated aging, most of this work has primarily focused on one or two types of adversity, as opposed to a range of possible exposure types. As noted, previous studies investigating adversity-induced epigenetic aging in children have also all been limited to cross-sectional designs, rather than studies using prospective assessment of adversity exposure. Furthermore, to our knowledge, no studies have examined the importance of the timing of adversity exposure. Given the growing body of support for "sensitive periods" in development, during which time developing organs, tissues, and biological systems may be particularly susceptible to the effects of experience (Bornstein, 1989; Knudsen, 2004; Shonkoff et al., 2009), consideration of the timing of adversity across the life course is warranted. Indeed, a recent study found that the effects of childhood adversity on epigenetic patterns were largely driven by *when* the adversity occurred, with the period from birth to age 3 emerging as a sensitive period when exposure to adversity was associated with more epigenetic changes (Dunn et al., 2019). Importantly, a standard epigenome-wide association study of lifetime adversity exposure (versus no exposure) failed to detect these associations (Dunn et al., 2019). Findings like these emphasize the need to investigate not only the biological consequences of adverse experiences, but also the possibility of time-dependent effects that may be obscured by simple exposed vs. unexposed models.

In the current study, we aimed to address these limitations and test the central hypothesis that postnatal adversity exposure does have an accelerating effect on epigenetic age in

childhood, and that these effects may be strongest and most detectable during sensitive periods in development. Investigating sensitive periods may not only help to reveal otherwise undetectable time-dependent effects, but it may also help to identify "high risk/high reward" periods in development, when adversity exposure can be most potent but health-promoting interventions might be most impactful.

2. Methods

2.1. Study Overview

We tested three consecutive hypotheses. We first assessed the independent associations between a set of postnatal adversity exposures and accelerated epigenetic age at age 7.5, regardless of the timing of exposure. Second, given the previously described evidence from epigenetic studies that simple classification of individuals as exposed versus unexposed to adversity may dilute observed effects (Dunn et al., 2019), we then tested—for each adversity type—a *sensitive period model*, which posits that the developmental timing of exposure is most important in shaping accelerated aging (Bailey et al., 2001; Knudsen, 2004). Third, recognizing that there are other ways to conceptualize time-dependent effects, we then compared the sensitive period model to two alternative theoretical models derived from life course theory (Ben-Shlomo and Kuh, 2002; Kuh and Ben-Shlomo, 2004): an *accumulation model*, which posits that every additional year of exposure is associated with an increased risk for accelerated aging (Evans et al., 2013; Sameroff, 2000), and a *recency* model, which suggests that the effects of adversity can be time-limited, and thus accelerated epigenetic aging may be more strongly linked to proximal rather than distal events (Shanahan et al., 2011). Finally, we performed two secondary analyses focused on using a broader set of age ranges to define sensitive periods and understanding sex-specific effects.

2.2. Sample and Procedures

We analyzed data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a large population-based birth cohort out of Avon, England of children followed from before birth through early adulthood (Boyd et al., 2013; Fraser et al., 2012; Golding et al., 2001). ALSPAC generated blood-based DNAm profiles at age 7.5 as part of the Accessible Resource for Integrated Epigenomics Studies (ARIES), which is a subsample of 1,018 mother-child pairs from ALSPAC who had complete data across at least five waves of data collection (Relton et al., 2015) (Supplemental Materials).

2.3. Measures

2.3.1. Cellular Aging—DNAm was determined at age 7.5 using procedures performed at the University of Bristol (Supplemental Materials). Using the level of methylation for each child in the sample, we generated two estimates of cell intrinsic epigenetic age based on the approaches of Horvath (Horvath, 2013) and Hannum (Hannum et al., 2013). For each clock, we estimated age acceleration using a regression procedure in which epigenetic age was the outcome and chronological age was the independent variable. In both the Horvath and Hannum epigenetic clocks, age acceleration or deceleration is represented by the residuals of the above described regression procedures (Wolf et al., 2016). Positive residuals

indicate accelerated aging, in which the child's chronological age is lower than their estimated methylation age (hereafter referred to as accelerated aging).

2.3.2. Exposure to Adversity—We examined the effect of seven adversities on methylation age residuals: (a) caregiver physical or emotional abuse; (b) sexual or physical abuse (by anyone); (c) maternal psychopathology; (d) one adult in the household; (e) family instability; (f) financial hardship; and (g) neighborhood disadvantage/poverty. These adversity types were chosen based on previous research (Dunn et al., 2019; Lawn et al., 2018) linking these exposures to epigenetic change (Brody et al., 2016; Lawn et al., 2018) or accelerated biological aging (Coimbra et al., 2017; Tyrka et al., 2010; Wojcicki et al., 2015). These adversity types were also chosen because they were each measured on at least four occasions at or before age 7 (see Table 1) from a single item or psychometrically validated standardized measures. To evaluate the effects of adversity exposure on epigenetic age without accounting for the timing of exposure, we created an "exposed" versus "unexposed" indicator for each adversity type, such that a child who was exposed to a particular adversity type at any time point was coded as "exposed" to that adversity. Second, for each type of adversity, we generated three sets of variables to test the three life course hypotheses: (a) for the *sensitive period hypothesis*, we created a set of variables indicating presence versus absence of the adversity at a specific developmental stage; specific time periods of assessment for each adversity are denoted in Supplemental Table 2. To test the (b) *accumulation hypothesis*, we generated a single variable denoting the total number of time periods of exposure to a given type of adversity. For the (c) *recency hypothesis*, we generated a single variable denoting the total number of developmental periods of exposure, with each exposure weighted by the age in months of the child during the measurement time period; this recency variable gave a larger weight to more recent exposures, thus, allowing us to determine whether more recent exposures were more impactful.

2.3.3. Covariates—We controlled for the following covariates, measured at child birth: child race/ethnicity; number of births in the pregnancy (pregnancy size); number of previous pregnancies; maternal marital status; highest level of maternal education; maternal age; maternal smoking during pregnancy; child birth weight; parental homeownership; and parent job status (Supplemental Materials for rationale).

2.4. Analyses

We began by running univariate and bivariate analyses to examine the distribution of covariates and exposures to adversity in the total analytic sample. To reduce potential bias and minimize loss of power due to attrition, we performed multiple imputation on missing exposures and covariates (Supplemental Materials). Missing data for each adversity exposure and covariate are presented in Supplemental Table 3.

We first tested the association between lifetime adversity exposure and epigenetic age by testing a simple *ever versus never exposed* model for each adversity type. Expecting that this model could dilute any effects of adversity exposure on epigenetic aging, we then used a novel two-stage structured life course modeling approach (SLCMA) (Simpkin et al., 2015; Smith et al., 2016) to evaluate, separately for each adversity type, whether a sensitive period

model might better explained the relationship between adversity exposure and epigenetic age. We also compared this sensitive period model to accumulation or recency of exposure models. Compared to other methods, such as standard multiple regression, the SLCMA provides an unbiased way to compare multiple competing theoretical models simultaneously and identify the most parsimonious explanation for variation in epigenetic age.

Details about the SLCMA modeling approach are outlined in the Supplemental Materials. Briefly, in the first stage of the SLCMA, we entered the set of variables described earlier into the Least Angle Regression (LARS) variable selection procedure (Efron et al., 2004). LARS identifies the single theoretical model (or potentially more than one models working in combination) that explains the most amount of outcome variation (in this case, epigenetic age acceleration). To identify these models, we used a covariance test (Lockhart et al., 2014) and examined elbow plots (Supplemental Figure 1). The covariance test provides a p-value for the selected variable, conditioned on the fact that LARS has selected the predictor with the largest correlation with the response. This approach resolves the common issue of "cherry-picking" when model fitting following selection. In the second stage, the life course theoretical models found in the first stage to best fit the observed data – that is, the model(s) appearing at the "elbow" of the plot (Supplemental Figure 1) and/or those with p-values <.05 in the covariance test (Lockhart et al., 2014) – were then carried forward to a multivariate regression framework to generate effect estimates for all selected hypotheses (Supplemental Materials). The goal of this second stage is to determine the contribution of a selected theoretical model after adjustment for covariates as well as other selected theoretical models, in instances where more than one theoretical model is chosen in the first stage. Importantly, the SLCMA method takes multiple testing into account; the covariance test p-values are adjusted for the number of variables included in the LARS procedure, controlling the type I error rate for each adversity type (Supplemental Materials). Thus, for each adversity, the testing of multiple competing lifecourse hypotheses *within* each SLCMA model is accounted for and the corresponding p-value is not inflated regardless of number of lifecourse hypotheses tested. Given the testing of multiple adversities across two epigenetic clocks, we additionally used a Bonferroni-adjusted significance threshold of p=.004 (0.05/7 adversities * 2 outcomes) to reduce the possibility of spurious results that may be incurred by multiple testing *across* 14 SLCMA models.

In addition, we also performed two sets of secondary analyses, which tested a broader definition of sensitive periods (Supplemental Materials) and the sex-specific effects of adversity on epigenetic age. These broader sensitive periods were defined as: *very early childhood* (ages 8 months – 2.75 years), *early childhood* (ages 3.5 – 5.75 years), and *middle childhood* (ages 6 – 7 years). These time windows were selected to facilitate interpretation of our findings in comparison to prior studies using similarly-defined developmental windows (Andersen et al., 2008; Dunn et al., 2018; Kaplow and Widom, 2007; Slopen et al., 2014).

3. Results

There were 973 children in the analytic sample (50.2% female, 97.2% white). Descriptive statistics on other covariates are presented in Supplemental Table 4.

3.1. Distribution of Exposure to Adversity and Age Acceleration

Table 1 shows the prevalence of childhood adversity overall and by each age period of assessment. The lifetime prevalence of adversity exposure ranged from 12.6% for physical abuse to 48.7% for family instability. Children exposed to any type of adversity were more likely than their unexposed peers to be non-white and born to non-married mothers with low education, low social class, and with more than three previous pregnancies (Supplemental Table 4).

As shown in Supplemental Table 4, girls were, on average, epigenetically older than boys. Also, children born to married mothers with higher education and higher social class had lower age residuals (according to Hannum's epigenetic clock) compared to children whose mothers fell into other corresponding categories. No differences were observed for the remaining covariates (all p-values >.10) (Supplemental Table 4). Supplemental Table 5 shows tetrachoric correlations between developmental time periods of exposure for each adversity. Exposures were moderately correlated across time, with neighboring time points generally being more highly correlated than distal time points (Supplemental Table 5). Different types of adversities showed low to moderate correlations (tetrachoric correlation coefficient *rho* ranged from 0.05 to 0.45; see Supplemental Figure 2).

3.2. Association between Exposure to Adversity and Age Acceleration

We began with simple ever versus never exposed models for each adversity type. Based on these models, financial hardship was the only adversity associated with age acceleration (Supplemental Tables 6 and 7).

We then generated models that estimated the effects of the timing of exposure. Table 2 displays, separately for each adversity type and epigenetic clock, the theoretical model selected by the LARS that best explained variability in age acceleration. As shown, evidence for three associations emerged for Hannum's epigenetic clock, all of which emphasized age acceleration following adversity exposure and the importance of sensitive periods. First, we found evidence that exposure to sexual or physical abuse at 3.5 years was associated with older epigenetic age (effect β=.07 years; 95% CI=.00-.14, p=.001, R^2=.01). Similarly, exposure to financial hardship at 7 years (effect β=.11, CI=.08-.14, p=.001, R^2=.05), and neighborhood disadvantage at 7 years (effect β=.12 years, CI=.01-.22, p=.001, R^2=.01) were associated with an acceleration in epigenetic aging. The magnitude of these beta estimates translates to an age acceleration of about one month among children exposed to adversity. None of the other life course theoretical models were selected as explaining the variability in age acceleration for these three or any other adversity types. Using Horvath's epigenetic clock, none of the life course models were associated with epigenetic age acceleration for any of the adversities studied (Table 2). Of note, these effects survived correction for multiple testing both within the SLCMA and across the two clocks and adversities tested.

Comparable results were obtained when the sensitive periods were collapsed into three broader categories. In these secondary analyses, having only one adult in the household during early childhood (effect β=.06 years, CI=.02-.09, p=.002) and being exposed to

maternal psychopathology in middle childhood (effect β=.03 years, CI=.06-.02, p=.023) were also associated with a modest acceleration in epigenetic age (Supplemental Table 8).

Sex-stratified analyses (Table 3) showed that for girls, having only one adult in the household (effect β=.10, CI=.002-.19, p=.030), or being exposed to maternal psychopathology (effect β=.06, CI=.02-.10, p=.0003), financial hardship (effect β=.008, CI=.004-.011, p<.0001), physical or emotional abuse (effect β=.08, CI=.006-.16, p=.027), or sexual abuse (effect β=.17, CI=.07-.27, p=.0004) was associated with increased epigenetic age. For example, by age 7.5, girls who were exposed to abuse at age 3.5 were biologically older than their unexposed peers by almost 2 months. In boys, exposure to financial hardship (effect β=.12, CI=.08-.16, p<.0001) and neighborhood disadvantage (effect β=.10, CI=.002-.20, p=.0005) were associated with increased epigenetic age. Each of these associations showed sensitive period specificity.

4. Discussion

This study tested the hypothesis that adversity exposure during sensitive periods in development is associated with accelerated epigenetic aging in childhood as measured by two epigenetic clocks, and that these associations can be better detected using methods that account for exposure timing, rather than simple comparisons of exposed versus unexposed individuals. To allow for the possibility of other timing effects, we also compared sensitive period models to alternative theoretical life course models of exposure. To our knowledge, this study represents the first to prospectively investigate whether the effects of adversity on epigenetic aging are observable in children and the extent to which these relationships varies as a function of the timing and type of exposure.

We found that exposure to sexual or physical abuse in early childhood and exposure to financial hardship or neighborhood disadvantage in middle childhood were all associated with epigenetic age acceleration by about one month. We acknowledge that the incremental variance explained was limited, but this estimate of effect is consistent with previous literature (Horvath and Raj, 2018). It is also worth noting that the R^2 values reported do not represent the percentage of variation in age acceleration explained by a particular adversity exposure, but rather the percentage of variation in age acceleration that is explained by a *given lifecourse theoretical model* of exposure, *after* accounting for any variance explained by covariates.

Our findings are also consistent with previous work linking adversities, such as abuse (Lawn et al., 2018), financial stress (Simons et al., 2016), and parental psychopathology (Brody et al., 2016; Lawn et al., 2018), with accelerated epigenetic aging in adulthood. Although the literature to date on the association between social environmental exposures and epigenetic aging in children is limited, the observed associations here between abuse experiences and accelerated epigenetic aging align with recent studies on the epigenetic consequences of violence exposure (Jovanovic et al., 2017; Sumner et al., 2018).

Our results extend previous findings by exploring the effects of the timing of prospectively-assessed exposure. We found evidence for sensitive periods during early and middle

childhood, when the association between adversity exposure and epigenetic aging appears to be particularly strong. This finding aligns with human (Essex et al., 2013; McGowan et al., 2009) studies showing the importance of sensitive periods in epigenetic programming. It seems therefore plausible that the epigenetic age of cells is influenced by environmental inputs in a similar time-susceptibility manner. The current findings further emphasize the importance of attending to possible time-dependent effects when studying the effects of adversity on cellular aging, including DNAm and other cellular-based measures of accelerated aging. Our results suggest that an approach that does not account for the specific life stages when adversity occurs may fail to detect effects of adversity on epigenetic age acceleration, and crude classifications of children as exposed vs. unexposed to “early life” adversity may mask observed differences among those exposed to adversity.

The sex-stratified analyses revealed that adversity could differentially affect epigenetic age acceleration in boys and girls. Some of these associations were particularly notable; for example, by age 7.5, girls who were exposed to abuse at age 3.5 were biologically older than their unexposed peers by almost 2 months. These findings suggest that the associations found in our main analyses may have been largely driven by the strength of the effect in girls. Our sex-stratified results are also consistent with previous findings indicating sex-specific effects in the patterning of epigenetic marks following prenatal (Suarez et al., 2018b) and childhood adversity (Essex et al., 2013; Massart et al., 2016), and underscore the value of sex-stratification in future analyses.

Disentangling the multiple possible mediational pathways driving these associations is challenging given the complex environmental contributions that comprise early life stress (Tyrka et al., 2013). One possible pathway may be through disrupted immune functioning, which has been implicated in a range of mental disorders (Misiak et al., 2019). Human post-traumatic stress disorder studies have found that adversity exposure may activate hypothalamic–pituitary–adrenal axis and disrupt neural-immune signaling (Agorastos et al., 2019). In keeping with this theory, a recent meta-analysis using data from more than 2,000 individuals from the Psychiatric Genomics Consortium PTSD Epigenetics Workgroup concluded that traumatic stress was associated with accelerated epigenetic aging in adulthood, and that cells integral to immune system maintenance and responsivity might play an important role in pacing the epigenetic clock (Wolf et al., 2017). Of note, this association was observed for childhood but not lifetime trauma exposure, suggesting the unique impact of adversity exposures occurring earlier in development.

In the current study, we did not find an association between exposure to the studied adversities and Horvath’s epigenetic clock. Although a recent cross-sectional study by Sumner et al. found an association between threat-related experiences and Horvath-based estimates of accelerated epigenetic aging (Sumner et al., 2018), there are multiple possible explanations for this discrepancy. In comparison to the Sumner et al. paper, our study population comprised a different racial and ethnic make-up and used different covariates. Moreover, our study also used distinct adversity types (such as physical abuse), rather than collapsing across types to create summed adversity exposure scores. Consistent with our results, other studies using both the Horvath and Hannum clocks have found that associations may exist for one clock, but not for another (Wolf et al., 2016; Wolf et al.,

2017). The Horvath and Hannum models differ in the tissue and age of subjects used to develop them, and the sets of CpG sites used are largely different as well. An increasing body of literature suggests that the two clocks may in fact be suited to capture different aspects of biology, with the two clocks showing only modest correlation across disease phenotypes (Lu et al., 2018). Together, these factors may account for the observed difference in results between the two epigenetic clocks in our study.

4.1. Strengths and Limitations

There are several strengths of the current study. We performed a more inclusive and detailed assessment of adversity types; most research in the field to date has focused on single types of adversity exposure, such as parental depression or low socioeconomic status only. Moreover, we also incorporated different life course theoretical models of adversity exposure, thereby allowing us to investigate which temporal features of exposure are most strongly associated with epigenetic aging. Finally, most studies to date have focused on older samples, often with a median chronological age above 45 years (Simpkin et al., 2016), whereas the current study focused on epigenetic aging in children.

Our study had limitations. First, our findings are based on DNA extracted from blood, which may be limiting as patterns of epigenetic change following social environmental stress exposure have been found to be tissue-specific, such that the same individual may have different Horvath's epigenetic clock estimates for different tissues (Levine et al., 2016). Therefore, we cannot exclude the possibility that childhood adversities affect cell methylation in a tissue-specific pattern and that peripheral blood-based measures of DNAm may not capture methylation changes of all tissues that occur following adversity. As others have noted (Tyrka et al., 2016), however, although leukocytes cannot be assumed to provide a clear window into brain-based processes, they may be particularly interesting, given their susceptibility to widespread effects, such as glucocorticoid and immune signaling. The challenge of tissue and cell-type specificity is unfortunately a limitation of all epigenome-brain research in living human subjects. Second, given the scope and scale of ALSPAC (which contains more than 75,000 variables), we needed to select and operationalize discrete adversity types for analysis. To do this in a principled manner, we looked to the previous literature both in ALSPAC (Dunn et al., 2019; Lawn et al., 2018) and in other cohorts (Brody et al., 2016; Coimbra et al., 2017; Tyrka et al., 2010; Wojcicki et al., 2015) to guide our selection of the seven adversity types used in our analysis, focusing on standard scales and single item measures that were asked in consistent ways across the duration of the study. However, we were unable to include in our analysis other likely distressing adverse experiences, such as death of a parent, due to low prevalence of exposure in the current sample. Future research should investigate epigenetic aging following other serious adverse experiences in higher risk samples where this and other exposures would be more commonly recorded or consistently queried. Third, although the focus of the current study was limited to postnatal adversity exposures, future research should consider incorporating prenatal measures as well, particularly given evidence of the association between prenatal exposure to stressors like maternal psychopathology and epigenetic age at birth (Suarez et al., 2018b). Fourth, given the structure of the data and the lack of complete overlap in adversity assessment across time, we were unable to examine the adversities all together in the

primary analyses. Although the correlations between adversities were low to moderate, it is nevertheless possible that attending to only one adversity type at a time could lead to overestimates of the effect of a given exposure. However, the results of a sensitivity analysis that examined mutually adjusted effects suggested that while the strength of associations was slightly attenuated, the overall patterns of associations remained similar (Supplemental Materials). One potential strength of examining each type of adversity individually is that we were able to identify meaningful differences in the associations between distinct adversity types and accelerated aging, which could yield different approaches for intervention. One challenge for future analyses will be to develop new ways to examine multiple adversities simultaneously without simply summing across number of exposures (McLaughlin and Sheridan, 2016). Fifth, although we used multiple imputation in an effort to reduce potential bias and minimize loss of power, we cannot rule out the possibility that missing or incomplete outcome data due to attrition may have influenced our findings. Sixth, because the oldest sensitive period coincides with the most recent exposure occasion for all children, it may be difficult to discern between the oldest sensitive period and recent exposure. Seventh, we focused exclusively on adversity exposures and did not consider potentially positive environmental influences. Future research should consider both adverse and protective exposures. Finally, although we selected covariates (such as maternal smoking and child birthweight) that are routinely adjusted for in analyses of epigenetic aging (Simpkin et al., 2017, 2016), some of these covariates may be associated with downstream factors that could fall along the pathway between adversity and childhood epigenetic aging and therefore inadvertently capture effects of potential mediators. Thus, the described effects may be attenuated.

Conclusions

In conclusion, we found that adversity experiences assessed in very early, early, and middle childhood were differentially associated with accelerated epigenetic aging at age 7.5. These findings suggest that accelerated epigenetic aging may function as one of the mechanisms through which childhood adversity becomes biologically embedded, and that adversity exposures during sensitive periods in childhood may have a particularly strong accelerating effect on epigenetic age. Future research leveraging repeated methylation measurements will be necessary to identify the varied trajectories of this acceleration across development, in the hopes of further teasing apart potential sensitive period effects from non-linearity in the ticking rate of the epigenetic clock (Horvath and Raj, 2018). Additional research is also needed to further test the effect of accelerated cellular aging on subsequent risk for depression and other neuropsychiatric disorders. Nevertheless, understanding the biological sequelae of childhood adversity—and how those sequelae differ depending on sensitive periods in exposure—represents the first step towards the development of targeted strategies designed to disrupt the processes linking adversity to psychiatric diseases as early in the life course as possible.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Exposure to adversity was associated with accelerated epigenetic aging in childhood.
- Associations were observed when using the Hannum but not Horvath epigenetic clock.
- Effects were driven by exposure during early and middle childhood sensitive periods.
- Adversity differentially affected epigenetic age acceleration in boys and girls.

Table 1.

Exposure to childhood adversity in the total analytic sample and by the age at exposure (n=973)

	Caregiver physical or emotional abuse		Sexual or physical abuse (by anyone)		Family instability		Maternal psychopathology		Financial hardship		One adult in the household		Neighborhood disadvantage	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Unexposed	822	84.5	850	87.4	499	51.3	686	70.5	669	68.8	833	85.6	829	85.2
Exposed	151	15.5	123	12.6	474	48.7	287	29.5	304	31.2	140	14.4	144	14.8
Age at Exposure														
Very early childhood														
8 months	34	3.7	---	---	---	---	95	10.2	104	11.3	243	3.7	---	---
1.5/1.75 yrs	38	4.2	28	3	170	18.2	89	9.8	98	10.7	288	4.3	76	8.4
2/2.75 yrs	56	6.3	32	3.6	182	20.3	130	14.8	97	10.9	350	5.2	74	8.4
Early childhood														
3.5 yrs	---	---	36	4.0	186	20.5	114	12.9	140	14.5	---	---	---	---
4/4.75 yrs	41	4.6	35	3.9	118	13.2	---	---	---	---	410	6.9	---	---
5/5.75 yrs	57	6.4	24	2.7	114	13.0	---	---	---	---	---	---	55	6.2
Middle childhood														
6/6.75 yrs	50	5.7	23	2.6	69	7.8	130	14.9	---	---	---	---	---	---
7 yrs	---	---	---	---	---	---	---	---	121	12.5	504	7.6	43	4.9

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Table 2.

Results of LARS models showing the life course theoretical model that best explained the relationship between adversity and age acceleration (n=973)

Adversity	Hannum's clock			Horvath's clock		
	Model selected	**p-value**	**Improvement R^2**	**Model selected**	**p-value**	**Improvement R^2**
Caregiver physical or emotional abuse	sensitive period (5 years)	.11	0.004	sensitive period (5 years)	.11	<0.001
Sexual or physical abuse	sensitive period (3.5 years)	**.0013**	**0.009**	sensitive period (4.75 years)	.99	<0.001
Maternal psychopathology	sensitive period (6 years)	.07	0.004	sensitive period (2.75 years)	.89	<0.001
One adult in the household	sensitive period (4 years)	.09	0.003	sensitive period (7 years)	.21	<0.001
Family instability	sensitive period (1.5 years)	.93	<0.001	sensitive period (6.75 years)	.98	<0.001
Financial hardship	sensitive period (7 years)	**<.0001**	**0.05**	sensitive period (7 years)	.79	<0.001
Neighborhood disadvantage	sensitive period (7 years)	**0.0002**	**0.01**	sensitive period (7 years)	.68	<0.001

Models are based on multiply imputed data and are adjusted for sex, race, maternal smoking, birth weight, maternal education, pregnancy size, maternal marital status, home ownership, age of mother at child birth, parental job status, and number of previous pregnancies. Values that are statistically significant are denoted in bold. The Bonferroni-adjusted significance threshold is P=.004.

The R^2 values reported do not show the variance in age acceleration explained by a particular adversity exposure. Rather, the R^2 values generated using the SLCMA show the percentage of variation in the *residuals* of the outcome explained by *particular lifecourse theoretical model* of a particular adversity exposure. Thus, the R^2 values reported here can be interpreted as the percentage of variation in age acceleration that is explained by a given lifecourse theoretical model of exposure, after accounting for any variance explained by covariates.

Table 3.

Results of LARS models showing the life course theoretical model that best explained the relationship between adversity and age acceleration, with Hannum's epigenetic clock, stratified by sex (n=973)

	Girls (n=488)			Boys (n=485)		
Adversities	**Model selected**	**p-value**	**Improvement R^2**	**Model selected**	**p-value**	**Improvement R^2**
Caregiver physical or emotional abuse	sensitive period (5 years)	**.027**	**0.012**	sensitive period (2.75 years)	.193	0.006
Sexual or physical abuse	sensitive period (3.5 years)	**.0004**	**0.027**	sensitive period (5.75 years)	.615	0.002
Maternal psychopathology	sensitive period (6 years)	**.0003**	**0.020**	sensitive period (1.75 years)	.578	0.002
One adult in the household	sensitive period (1.75 years)	.030	0.011	sensitive period (7 years)	.812	0.001
Family instability	sensitive period (4.75 years)	.923	<0.001	sensitive period (3.5 years)	.235	0.004
Financial hardship	recency	**<.0001**	**0.050**	sensitive period (7 years)	**<.0001**	**0.060**
Neighborhood disadvantage	sensitive period (7 years)	.108	0.008	sensitive period (7 years)	**.0005**	**0.022**

Models are based on multiply imputed data and are adjusted for sex, race, maternal smoking, birth weight, maternal education, pregnancy size, maternal marital status, home ownership, age of mother at child birth, parental job status, and number of previous pregnancies. Very early childhood=ages 8 months to 2.75 years. Values that are statistically significant are denoted in bold.