



Research Letter | Public Health

Epigenetic Clock Analysis of Biological Aging in Adults With Documented Childhood Maltreatment

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Introduction

Childhood maltreatment is associated with increased risk of chronic disease and premature mortality.¹ One hypothesized mechanism is accelerated biological aging. DNA methylation-based epigenetic clocks represent the cutting-edge of measurement technology to quantify impacts of environmental exposures on biological aging.² Prior studies based on retrospective self-reports of childhood maltreatment made by adults report small to moderate effect size associations with epigenetic clock measures of biological aging.³ We tested whether adults with court documented histories of childhood maltreatment exhibited signs of accelerated biological aging at the end of their sixth decade of life as compared with controls matched on demographic factors and childhood socioeconomic circumstances.

Methods

Participants for this cohort study were drawn from a prospective cohort of individuals with substantiated childhood maltreatment documented in court records (1967 to 1971) and demographically matched controls recruited from elementary schools registers and birth hospitals of the exposed cases.⁴ The maltreatment group included court documented cases of childhood physical and sexual abuse and neglect (physical abuse, 17%; neglect, 82%; sexual abuse, 14%). At follow-up in 2022-2023,⁵ participants provided saliva DNA for methylation analysis with EPIC version 1 array (Illumina).

Biological aging was quantified using the epigenetic clocks best validated for measuring cumulative burden of aging-related biological damage across the lifetime, GrimAge,⁶ and current rate of aging-related biological deterioration, DunedinPACE.⁷ We selected these blood-based clocks in preference to clocks designed for saliva because those clocks lack a track record of association with either health-risk exposures or later-life health outcomes. Clock values were residualized for technical covariates, including estimated proportion of buccal epithelial cells and standardized to z scores for analysis (mean [SD], 0 [1]). In the case of GrimAge, which includes calendar age and sex in its calculation, the clock was additionally residualized on these variables prior to standardization. The z scores have the interpretation that values above zero indicate older biological age (GrimAge) or faster pace of aging (DunedinPACE) relative to the sample norm.

We tested differences in biological aging between participants with court documented maltreatment histories and controls using linear regression with covariate adjustment for age, sex, and self-reported race and ethnicity (stratified as White and additional groups). Additional models included covariates for smoking and body mass index and applied inverse probability weighting to account for differential attrition. Weights were defined from logistic regression of saliva study participation on sex, body mass index (calculated as weight in kilograms divided by height in meters squared), and oral health problems. We focused primary hypothesis testing on the minimally adjusted models implemented without inverse probability weighting. Additional models should be

+ Supplemental content

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interpreted as sensitivity analyses. Results were calculated with the PC-Clocks (Morgan Levine Lab) and DunedinPACE packages in R version 4.5.0 (R Project for Statistical Computing) and in Stata version 18 (StataCorp LLC). The threshold for significance was $\alpha = .05$. Further details are provided in the eMethods in [Supplement 1](#).

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. Institutional review board approval was obtained from the Human Research Protection Program at The City University of New York (protocol No. 2015-0133). Participants signed a consent form acknowledging that they were participating voluntarily.

Results

A total of 276 participants provided saliva for analysis during follow-up; 112 in the control group (mean [SD] age, 60.0 [3.7] years; 53 male [47%]) and 164 in the maltreated group (mean [SD] age, 60.0 [3.6] years; 69 male [42%]) (eTable in [Supplement 1](#)). Participants with court documented histories of childhood maltreatment exhibited older GrimAge and faster DunedinPACE than controls, but differences were small and not statistically different from zero at the $\alpha = .05$ threshold (GrimAge: Cohen $d = 0.25$; 95% CI, -0.01 to 0.50 ; $P = .06$; DunedinPACE: $d = 0.18$; 95% CI, -0.06 to 0.43 ; $P = .14$) (Table; Figure). Effect sizes were attenuated following adjustment for smoking and body mass index. Results were unchanged with inverse-probability weighting to account for differential attrition.

Table. Effect Size Estimates for Regression Analysis of Maltreatment Exposure Associations With Epigenetic Clocks

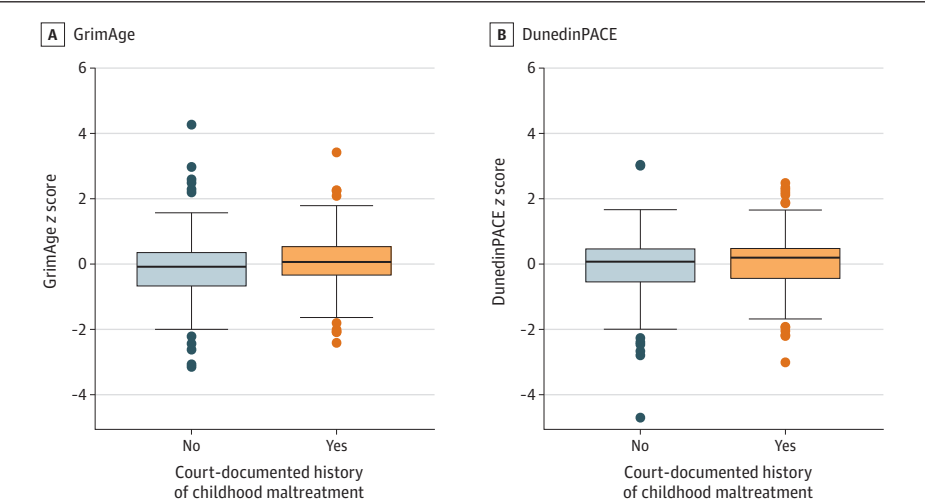
Model	Interview 5 sample, Cohen <i>d</i> (95% CI) ^a	<i>P</i> value	Analysis sample, Cohen <i>d</i> (95% CI) ^{a,b}	<i>P</i> value
Base model				
PC GrimAge	0.25 (−0.013 to 0.503)	.06	0.23 (−0.028 to 0.491)	.08
DunedinPACE	0.18 (−0.062 to 0.429)	.14	0.19 (−0.061 to 0.437)	.14
Smoking adjusted				
PC GrimAge	0.05 (−0.194 to 0.287)	.70	0.05 (−0.195 to 0.286)	.71
DunedinPACE	0.08 (−0.166 to 0.333)	.51	0.09 (−0.162 to 0.346)	.48
BMI adjusted				
PC GrimAge	0.23 (−0.033 to 0.499)	.09	0.21 (−0.064 to 0.478)	.13
DunedinPACE	0.13 (−0.126 to 0.386)	.32	0.13 (−0.133 to 0.390)	.33

Abbreviation: BMI, body mass index.

^a All regression models included covariates for participant age, sex, and racial identity (White and additional groups). Results are shown for standard regression models and models including inverse-probability weights to account for selective nonparticipation in DNA sampling.

^b Inverse probability weights were defined from a logistic regression comparing Interview 5 participants who provided saliva specimens to those who did not on sex, BMI, and oral health problems.

Figure. Box and Whisker Plot of Saliva PC GrimAge and DunedinPACE in Participants



The graph shows box plots of GrimAge and DunedinPACE z scores. In these plots, the dark line in the center of the boxes shows the median value of the data, the box borders show the 25th and 75th percentiles of the distribution of values, the whiskers extend beyond these boundaries by 1.5 times the interquartile range, and plotted points show data with values beyond range of the whiskers.

Discussion

In this prospective longitudinal cohort study comparing late-midlife adults with court documented childhood maltreatment to matched controls, we found only small differences in biological age and pace of aging that did not reach the level of statistical significance. Effect sizes were consistent with prior studies using retrospective exposure ascertainment, suggesting that reporting bias is unlikely to explain previously observed associations. Despite the likely greater severity of court documented maltreatment, findings indicate that childhood maltreatment is not associated with large differences in aging trajectories through the sixth decade of life.

Findings have implications for public health research and practice. Small effect sizes also caution against clinical use of epigenetic clocks to assess individual health risk associated with maltreatment and indicate that large samples are required for policy or intervention evaluation using these biomarkers. Results no longer being significant following adjustment for smoking and body mass index suggests behavioral pathways may play a role in long-term differences in aging.

The chief limitation of our study is the small number of participants with biomarker data, which limits our ability to explore heterogeneity in long-term impacts of childhood maltreatment across demographic and life history subgroups. A further limitation is that GrimAge and DunedinPACE are imperfect measurements of biological aging; more precise or sensitive measurements may reveal larger effects. Moreover, GrimAge and DunedinPACE were designed for analysis of blood and are here applied in saliva. Effect estimates may therefore represent a lower bound. Studies using similar designs with access to blood samples are needed, as are efforts to develop DNA methylation biomarkers of aging optimized for saliva DNA. Overall, findings support lasting but modest associations between childhood maltreatment and biological aging.

ARTICLE INFORMATION

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Author Contributions: Dr Belsky had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Belsky, Courtney, Graf, Champagne, Widom.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Belsky, Courtney, Indik, Widom.

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Statistical analysis: Belsky, Courtney, Lapp, Ryan.

Obtained funding: Champagne, Widom.

Administrative, technical, or material support: Belsky, Bellatin, Courtney, Ryan, Champagne, Widom.

Supervision: Belsky, Champagne.

Conflict of Interest Disclosures: Dr Belsky reported a license agreement for commercial applications as inventor of the DunedinPACE epigenetic clock to Tru Diagnostic through Duke University and the University of Otago; he reported a fellowship with the CIFAR Child & Brain Development network outside the submitted work; and he reported service on scientific advisory boards for Hundred Health, WNDRLTH, Hooke Clinic, and X-Prize Healthspan. Dr Lapp reported grants from Brain and Behavior Research Foundation outside the submitted work. No other disclosures were reported.

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Data Sharing Statement: See [Supplement 2](#).

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SUPPLEMENT 1.

eMethods.

SUPPLEMENT 2.

Data Sharing Statement