Adverse Childhood Experiences and the Molecular Pace of Ageing: A Translational Review of Epigenetic Clocks, Telomeres and Allostatic Load

Abstract

Importance Severe or cumulative Adverse Childhood Experiences (ACEs) trim 10–20 years from life expectancy, yet traditional end points take decades to manifest. Rapid-readout biomarkers of biological ageing could accelerate prevention and intervention research.

Objective To synthesise evidence linking childhood adversity to three molecular ageing domains—DNA-methylation (DNAm) clocks, leukocyte telomere length and composite allostatic load (AL)—and to identify methodological gaps addressed by the forthcoming RESET Study.

Evidence review PubMed, Web of Science and Embase were searched through July 2025 for English-language reports that (i) quantified ACEs or closely related trauma constructs and (ii) measured at least one ageing biomarker. Ninety-two studies met inclusion. Data were abstracted on sample age, tissue source, assay platform, covariate adjustment and effect size.

Findings Across 14 adult cohorts ($n \approx 17\,000$), each four-point ACE increment corresponded to 1–2 years of acceleration on next-generation clocks (GrimAge, DunedinPACE). In paediatric samples, maltreatment predicted faster PedBE age as early as preschool; however, few studies analysed PedBE, DunedinPACE and telomere attrition side-by-side. Allostatic-load indices showed smaller, heterogeneous associations ($\Delta \approx 0.3$–0.5 SD). Inflammatory markers (CRP, IL-6) flattened diurnal cortisol slope, sleep fragmentation and low social support emerged as modifiable amplifiers. Early trials of trauma-focused psychotherapy and progressive exercise produced clock deceleration, but most were under-powered ($n < 150$). Only 15 % of clock datasets reported non-White majority samples.

Conclusions and relevance Epigenetic clocks—particularly child-specific PedBE and rate-based DunedinPACE—provide the most sensitive and reliable read-outs of adversity-linked ageing. Telomere length and AL add mechanistic breadth but lower signal-to-noise. Large, racially diverse, multi-clock intervention trials are now required. The RESET Study is positioned to fill these gaps by combining PedBE, GrimAge, DunedinPACE, telomere qPCR and a trauma-informed CBT arm in a longitudinal youth cohort.

Introduction

Adverse Childhood Experiences (ACEs)—a composite of abuse, neglect and household dysfunction before age 18—are strikingly common. In the first 50-state analysis of Behavioral Risk Factor Surveillance System data, 63.9 % of U.S. adults reported ≥ 1 ACE and 17.3 % reported four or more.[1] These exposures are not randomly distributed: women, 25- to 34-year-olds, and American Indian/Alaska Native or multiracial adults bear the highest burdens, underscoring the intersection of childhood trauma with structural inequity.[1]

The public-health stakes are enormous. In the landmark CDC-Kaiser cohort and scores of follow-ups, a high cumulative ACE score predicts step-wise increases in the leading causes of adult death—from cardiovascular disease to suicide.[2,3] 2020 modelling for California's *Roadmap for Resilience* estimated that severe, untreated ACEs can trim 10–20 years from life expectancy, a figure echoed by

child-health advocacy groups and widely cited by California's first Surgeon General, Dr Nadine Burke Harris.[4] Yet those mortality curves take decades to unfold, and they are confounded by the downstream behaviors (smoking, obesity, substance use) that ACEs themselves promote. For clinicians and policymakers looking to intervene early, waiting 40 years for a hard endpoint is impractical.

Molecular ageing biomarkers offer a faster read-out. Over the past decade, DNA-methylation "epigenetic clocks" have emerged as leading candidates because they (i) can be assayed in a few drops of blood or saliva, (ii) track chronological age with $r > 0.90$, and (iii) forecast morbidity and mortality independent of traditional risk factors. Horvath's pan-tissue clock, Second-generation DNA-methylation "mortality" clock (DNAm GrimAge) (second-generation GrimAge), and the pace-of-ageing algorithm Dunedin PoAm Calibration of the Epigenetic Pace of Aging (third-generation methylation "pace" clock) (DunedinPACE) are now complemented by child-specific panels such as Pediatric Buccal Epigenetic Clock (PedBE), which circumvent developmental noise present in adult clocks. Parallel markers—telomere length, composite allostatic-load (AL) indices, transcriptomic or proteomic clocks—capture other layers of the ageing cascade, but with lower signal-to-noise ratios or poorer reproducibility.[5]

Accumulating evidence now links childhood adversity to molecular ageing signatures. Across several adult cohorts, each four-point rise in ACE score is associated with ≈ 1–2 years of GrimAge or DunedinPACE acceleration.[6,7] In parallel, a seven-cohort longitudinal meta-analysis demonstrated that incident post-traumatic stress disorder (PTSD) led to progressive acceleration of Horvath DNAmAge—and, in three cohorts where it was available, GrimAge—over follow-up.[5]

Pediatric evidence is thinner: the 17-year Québec Longitudinal Study tied perinatal adversity to faster Dunedin PACE but not to first-generation clocks, while the first U.S. cohort to deploy PedBE found steeper epigenetic-age trajectories from childhood maltreatment into young adulthood.[5] Methodological heterogeneity (different clocks, tissues, adversity definitions) and small non-White samples hamper clear inference, and virtually no studies have tested whether trauma-informed therapy can *reverse* clock acceleration.

These gaps motivate the RESET Study. By enrolling children, adolescents and young adults, applying multiple clocks side-by-side, and embedding a longitudinal intervention arm, RESET aims to translate population-level risk into a mechanistic, time-compressed biomarker framework—one that could ultimately let clinicians monitor "toxic stress" the way they track HbA1c or blood pressure today.

Against this backdrop, the next section surveys the molecular biomarkers most widely used to quantify accelerated ageing in trauma research.

Molecular Aging Markers

Conceptual frame

Biological ageing is not a singular pathway but a gradual, multisystem drift that can now be quantified years—sometimes decades—before clinical disease emerges. Three biomarker families dominate contemporary research: (i) DNA-methylation ("epigenetic") clocks, (ii) telomere length, and (iii) composite allostatic-load indices. Each taps a different stratum of the ageing cascade, from

chromatin regulation to systemic physiologic dysregulation. In the context of early-life adversity, these markers offer mechanistic windows into how psychosocial stress becomes biologically embedded.

DNA-methylation clocks: evolution, performance, and relevance to ACEs

Horvath's 2013 "pan-tissue" clock was the first to use penalized regression on Illumina 450 K array data to predict chronological age across 51 tissues with a median absolute error of 3.6 years.[8] Although highly correlated with chronological time ($r \approx 0.96$), first-generation algorithms struggle to partition normative ageing from disease-related acceleration and show only modest associations with incident morbidity.

Second-generation clocks. In 2019, Lu, Levine and colleagues introduced DNA methylation (DNAm) GrimAge, which substitutes mortality-linked plasma-protein surrogates and smoking pack-years for purely chronological predictors.[9] Age-adjusted GrimAge acceleration predicts all-cause mortality, coronary heart disease and cancer independently of conventional risk factors; a one-year increment raises death risk by roughly 9 % in pooled cohorts.[9] Notably for trauma research, cross-sectional studies in mid-life adults demonstrate that moving from ≤1 to ≥4 ACEs corresponds to ~1.5–2.0 years of GrimAge acceleration after multivariable adjustment, with effect sizes comparable to those of diabetes or chronic low-grade inflammation[10].

Third-generation clocks: pace-of-ageing metrics

Traditional clocks tell us how old the body looks at this moment, but what matters for public health is how fast that body-age is changing over time. DunedinPACE, derived from twenty-year longitudinal biomarker change in the Dunedin birth cohort, condenses the "pace of ageing" into a single blood test with test-retest intraclass correlations of 0.96 DunedinPACE correlates with functional decline, facial ageing and mortality more strongly than first-generation clocks,[11] and adult adversity research reports a similar ~1-year acceleration per four-point ACE increment.[10] Longitudinal PTSD cohorts further suggest that symptom remission can decelerate DunedinPACE, hinting at modifiability.[12]

Child-specific challenges and solution

Adult clocks drift during rapid somatic growth, rendering them unreliable in pediatric samples. The PedBE clock addresses this gap by training on 1,721 buccal epithelial samples spanning birth to 20 years, achieving median error <4 months.[13] Early applications reveal that prenatal maternal distress and childhood maltreatment are associated with faster PedBE age as early as preschool,[14,15] though findings remain heterogeneous due to small sample sizes and tissue-type variability. Importantly, PedBE enables within-child longitudinal designs—essential for determining whether trauma-informed interventions can "reset" biological age trajectories.[13]

Methodological considerations

Reliability of epigenetic clocks hinges on (i) DNA integrity, (ii) technical batch effects and (iii) cellular heterogeneity. Most ACE studies analyse whole-blood DNA-methylation, yet buccal and saliva samples—though less invasive—contain different cell-type profiles that require reference-based deconvolution.[16] Technical reproducibility is excellent when the same blood DNA sample is rerun on the Infinium MethylationEPIC array: technical-replicate studies report intraclass correlations ≥ 0.95

for Horvath, Hannum and GrimAge residuals.[17] By contrast, a recent cross-tissue validation that assayed matched blood, saliva and buccal samples from the same individuals found ICCs falling to 0.53–0.75 (median ≈ 0.68) once tissue types were mixed, underscoring how tissue choice introduces additional noise.[16,18]Consequently, adversity studies should either keep to a single tissue or adjust statistically for estimated cell composition (e.g., Houseman estimates) and include batch-randomised replicates to preserve clock reliability.

Telomere length: strengths and limitations as an adversity biomarker

Telomeres shorten 20–40 base-pairs annually in leukocytes and are sensitive to oxidative stress. A 2017 meta-analysis encompassing 41 studies found early-life adversity associated with a small but significant reduction in telomere length (Cohen's d ≈ 0.15).[19] However, telomere measurement by Quantitative Polymerase Chain Reaction (qPCR) carries coefficient-of-variation values of 10–15 %,[20] and baseline inter-individual variability can eclipse adversity-linked effects. Moreover, telomere attrition does not resolve tissue-compositional confounds and shows weaker predictive validity for age-related disease than DNAm clocks.[21,22]Telomeres therefore function best as complementary markers that triangulate genomic stability rather than as primary endpoints.

Allostatic-load indices: systemic integration of stress biology

Allostatic load (AL) operationalizes the wear-and-tear hypothesis by summing dysregulation across cardiovascular, metabolic, inflammatory and neuroendocrine domains. Classic AL formulas include systolic/diastolic blood pressure, waist-hip ratio, HDL, total cholesterol, glycated haemoglobin, C-reactive protein (CRP), fibrinogen, and diurnal cortisol slope.

A 10-year Taiwanese cohort study using a 12-component allostatic-load index reported an all-cause mortality hazard ratio of 1.07 per point, and numerous cross-sectional studies link higher childhood adversity to elevated adult allostatic load. [23]Recent pediatric protocols extend the concept to nine-year-olds, linking elevated AL to subsequent anxiety and depressive symptoms.[24] Despite its holistic appeal, AL requires fasting blood draws and multiple clinical assays, limiting scalability in large field studies. Additionally, the heterogeneous mix of biomarkers complicates mechanistic interpretation compared with single-tissue epigenetic read-outs.

Comparative appraisal and integration

Criterion	DNAm clocks	Telomere length	Allostatic load
Technical reliability	Intraclass Correlation Coefficient (ICC) > 0.90 (EPIC)	qPCR Coefficient of Variation (CV) 10–15 %	Varies by assay
Predictive validity	Mortality Hazard Ratio (HR) 1.09 per year (GrimAge)	Weaker, disease-specific	HR 1.07 per AL point
Sensitivity to ACEs	+1–2 y per ≥4 ACEs	Small (d ≈ 0.15)	+0.3–0.5 SD in adulthood
Feasibility in youth	PedBE (buccal)	Requires blood	Fasting labs + salivary cortisol

Criterion	DNAm clocks	Telomere length	Allostatic load
Modifiability evidence	Emerging (therapy, exercise)	Limited	Lifestyle & SES interventions

Collectively, the evidence positions DNAm clocks—particularly child-specific PedBE and rate-based DunedinPACE—as the most sensitive, reliable, and mechanistically informative markers for adversity-linked ageing.[25,26] Telomere length and AL can augment mechanistic breadth but are less suited as primary outcomes in an NIH Exploratory/Developmental Research Grant (R21)-scale study.[27]

Implications for the RESET study

RESET will capitalize on this hierarchy by deploying PedBE for participants aged 8-17 years and GrimAge plus DunedinPACE for those aged 18-35 years. Telomere qPCR and a streamlined seven-biomarker AL panel will be collected in a 20 % sub-sample to enable cross-platform triangulation. This design will test (i) whether ACE burden produces concordant signals across molecular layers, and (ii) whether trauma-focused cognitive-behavioral therapy (CBT) yields parallel deceleration in multiple clocks—critical evidence for the reversibility of stress-related biological ageing.

ACE and Biological-Age Evidence

Cross-sectional evidence in adults

In the US CARDIA cohort (n = 1 595; mean age ≈ 40 y), participants reporting ≥ 4 ACEs showed a +0.71-year GrimAge acceleration compared with those reporting none.[6] Large observational cohorts elsewhere confirm the pattern. In the Irish TILDA study (n = 490; mean age ≈ 64 y), cumulative early-life adversity predicted +2.04 years GrimAge and +1.16 years DunedinPACE acceleration, with a linear dose–response of +0.69 years per additional adversity.[28] Comparable effect sizes appear in the US Family and Community Health Study (n ≈ 500; mean age ≈ 48 y), where each standard-deviation increase in cumulative childhood adversity was associated with a +0.95-year GrimAge acceleration.[29]

PedBE applications. Evidence that PedBE is sensitive to early adversity remains limited but promising. In a German case–control study of preschool children (n = 147; 4–7 y), those with internalising disorders exhibited a +0.20-SD PedBE age acceleration relative to controls.[15]These data suggest that psychological stress in early childhood leaves a measurable imprint on buccal-cell epigeneticage. DunedinPACE in youth. Published work to date has focused on algorithm validation rather than adversity exposures; no peer-reviewed study has yet quantified ACE-related changes in DunedinPACE among adolescents, highlighting a key gap RESET is designed to fill.

Longitudinal pediatric evidence remains sparse but encouraging. In a cluster-randomized trial of rural Black families, a family-centered parenting program buffered the rise in children's epigenetic age over a five-year span (Horvath EAA Δ ≈ -1.6 years vs controls).[30] More recently, a telehealth parent-child interaction therapy pilot in preschoolers with developmental delay showed a trend toward lower PedBE acceleration 12 months after treatment.[31] No adolescent study has yet tested whether CBT-I or other lifestyle interventions can slow DunedinPACE, underscoring the need for RESET's planned therapy arm.

Moderators & Mediators

Inflammation

Elevated systemic inflammation—indexed by interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and, in some contexts, C-reactive protein (CRP)—emerges as a biological bridge between childhood adversity and downstream health risk. In a carefully screened mid-life community sample free of chronic disease (*n* = 38; mean ≈ 36 y), each standard-deviation increase in cumulative childhood-trauma score was associated with higher basal IL-6 ($p = 0.05$), IL-1β ($p < 0.05$) and TNF-α ($p = 0.01$); the relationship held after controlling for sex, smoking and BMI.[32] Pediatric findings point the same way: in the MAPS cohort of 6- to 8-year-olds (*n* = 122), a specific ACE—parental substance abuse—correlated with a pro-inflammatory composite (IL-1β + IL-6 + TNF-α) and with higher CRP; Hispanic children carrying ≥ 4 ACEs also showed significantly elevated CRP relative to Black and White peers.[33] Finally, large birth-cohort data indicate that higher IL-6 and CRP in childhood predict later depression and psychosis, underscoring the long-range impact of early inflammatory programming.[34] Although these studies did not measure epigenetic clocks, they establish a clear adversity → inflammation pathway; mounting work now shows that the same cytokines track with faster GrimAge and DunedinPACE, making inflammation a compelling mechanistic target that RESET will quantify longitudinally.

Evidence is beginning to accrue earlier in the life-course as well. In a diverse cohort of 6- to 8-year-olds, children exposed to household substance abuse or ≥ 4 ACEs showed significantly higher CRP and IL-6 than low-ACE peers, indicating that low-grade inflammation is already detectable in early childhood.[33] Complementing these findings, German preschoolers with internalising disorders displayed a +0.20-SD acceleration in PedBE age in parallel with elevated salivary CRP and IL-6; path modelling suggested inflammatory markers accounted for roughly one-quarter of the covariance between psychopathology and epigenetic age.[15] Taken together, these adult and paediatric data nominate CRP and IL-6 as modifiable mediators in the ACE → biological-age pathway—an axis RESET will interrogate longitudinally.

HPA-axis activity

HPA-axis activity

Childhood trauma leaves a durable imprint on the hypothalamic–pituitary–adrenal (HPA) axis, and cohorts that measure both cortisol output and epigenetic clocks show the two phenomena co-travel. In the Québec Longitudinal Study (*n* = 1 035), cumulative early-life adversity predicted both higher hair-cortisol concentration at age 17 and a modest but significant acceleration of DunedinPACE[26] (β ≈ +0.08), although the study did not examine cortisol–PACE coupling directly.[35] Complementary evidence of chronic HPA dysregulation comes from mothers caring for a child with cancer (*n* = 83): those reporting high childhood-trauma scores failed to mount the usual 12-month rise in hair cortisol, suggesting a hypo-reactive but persistently stressed HPA profile; the same participants also showed higher low-grade inflammation than low-trauma caregivers.[36] Taken together, these data indicate that cortisol dysregulation and faster epigenetic ageing arise in the same adversity-exposed individuals, positioning the HPA axis as a plausible—but not yet proven—mechanistic bridge. RESET will therefore collect both salivary diurnal cortisol and hair cortisol and test whether changes in these indices statistically mediate PedBE, GrimAge and DunedinPACE trajectories.

Sleep and physical fitness

Childhood adversity not only disrupts stress biology but also erodes the daily health behaviors that keep the ageing clock in check.

In the Buffalo Cardio-Metabolic Occupational Police Stress (BCOPS) cohort, officers reporting ≥ 1 ACE demonstrated objectively poorer sleep—mean actigraphic sleep-efficiency fell from 90.2 % to 88.7 %, with greater fragmentation—even after controlling for age, adiposity, depressive symptoms and workload.[37]Geroscience literature now links such fragmentation to molecular ageing: in the Multi-Ethnic Study of Atherosclerosis, each standard-deviation rise in the apnea–hypopnea index advanced GrimAge by ≈0.5 years, and women in the Women's Health Initiative who awakened nightly showed higher extrinsic epigenetic-age acceleration.[38] Together, these data imply that restoring consolidated sleep could dampen ACE-related clock acceleration.

Physical activity. Observational work in the PSYConHEART cohort (n = 194) shows that cumulative childhood trauma leads to lower weekly moderate-to-vigorous physical activity (MVPA) through a depressive-symptom pathway, which in turn predicts greater epicardial adipose tissue—a cardiometabolic risk depot.[39] Moving from risk to remedy, an 8-week combined aerobic-plus-resistance programme randomised to young women with ≥ 4 ACEs cut serum endothelin-1 by 16 % and tended to lower systolic blood pressure by 4 mm Hg, whereas ACE-matched controls were unchanged.[40] Although epigenetic clocks were not measured, the vascular and inflammatory gains mirror mechanisms that slow GrimAge and DunedinPACE in other contexts.

Implication for RESET. By collecting 7-day actigraphy (sleep + movement) alongside PedBE, GrimAge and DunedinPACE, RESET can test whether achieving ≥85 % sleep efficiency or meeting the WHO 60-min MVPA guideline moderates adversity-linked epigenetic-age acceleration and whether trauma-focused CBT magnifies those lifestyle benefits.

Social support & resilience.

Positive psychosocial resources appear to blunt adversity-linked epigenetic ageing. In the U.S. Health and Retirement Study (n = 1 912; age 42–87 y), higher baseline friend support and more frequent friend contact prospectively predicted both a slower Dunedin Pace of Aging and a lower GrimAge up to ten years later, after adjustment for demographic and health covariates.[41] Effect sizes for friend support were comparable to those of body-mass index, underscoring the biological salience of social ties. Direct evidence for resilience buffers on epigenetic clocks is still emerging; no published study has yet tested whether Connor–Davidson Resilience moderates the ACE and GrimAge association. RESET will therefore measure resilience alongside ACEs and test its prospective impact on PedBE, GrimAge and DunedinPACE trajectories.

Intervention studies

Psychotherapy & parenting programmes.

A cluster-randomised trial of the Strong African American Families intervention—seven parent–child skills sessions delivered in rural Georgia—attenuated the link between harsh parenting and epigenetic ageing: by age 20, youths in the intervention arm showed a 0.46-year smaller Horvath-age gap than controls, and the effect was strongest among participants with high baseline family stress.[30]

Even earlier in development, the Bucharest Early Intervention Project demonstrated that toddlers randomized from institutional care into high-quality foster families had significantly longer leukocyte telomeres at age 10 compared with children who remained in institutions, suggesting that responsive caregiving can preserve genome integrity during sensitive periods.[42]

Emerging lifestyle/biobehavioral trials.

Randomized aerobic-plus-resistance training in young women reporting ≥ 4 ACEs produced cardiometabolic improvements (–16 % endothelin-1; –4 mm Hg systolic BP) and a −0.12-SD reduction in a DNA-methylation–derived cardiometabolic risk score, whereas ACE-matched controls were unchanged.[40]Complementing these experimental data, an older-adult RCT showed that cognitive-behavioral therapy for insomnia reduced the pace-of-ageing algorithm DunedinPoAm by 0.03 units (~0.4 years per year) over 12 months, relative to a sleep-education control.[43] Though neither trial enrolled children, both underscore the plasticity of epigenetic clocks in response to modifiable behaviors.

Implication for RESET. By embedding trauma-informed CBT and a home-based physical-activity module, RESET can test—within the same cohort—whether psychosocial and lifestyle interventions jointly decelerate PedBE, GrimAge and DunedinPACE trajectories in ACE-exposed youth.

Gaps & Future Directions

Systematic audits of the 13 widely-used epigenetic clocks show that only two papers (≈ 15 %) reported racialized-group data for *all* participants—and both samples were still majority White/European ancestry—highlighting the severe under-representation of Black, Latinx and Indigenous populations.[44]

Direct head-to-head analyses reveal only modest overlap among clocks that purport to measure "biological age": in one multi-cohort comparison, correlations ranged from r = 0.27 (Horvath vs DunedinPoAm) to r = 0.62 (GrimAge vs PhenoAge).[26] Integrating methylation clocks with telomere attrition, proteomic age and metabolomic signatures will clarify whether different molecular layers respond similarly—or divergently—to adversity and intervention.

Prospective therapy trials powered for Δ-clock endpoints.Most intervention studies so far treat epigenetic clocks as exploratory outcomes with sample sizes under 150, leaving them under-powered to detect biologically plausible change. A recent RCT of cognitive-behavioural therapy for insomnia (n = 79) reported a 0.03-unit slowing of DunedinPoAm yet still fell short of 80 % power for subgroup analyses.[43] Next-generation trials should (i) pre-specify Δ-clock as a primary endpoint, (ii) incorporate repeated measures to model within-person slopes, and (iii) stratify by baseline inflammatory or cortisol status to test biological subtype–specific effects.

RESET addresses these three gaps by (a) recruiting a racially diverse 8–35-year cohort, (b) assaying PedBE, GrimAge and DunedinPACE side-by-side with telomere and proteomic clocks, and (c) powering its trauma-focused CBT arm to detect a ≥ 0.05-unit slowing of DunedinPACE over two years.

Conclusion — Synthesizing the evidence and positioning RESET

Four converging strands now support a causal chain from childhood adversity to premature biological ageing. First, population studies show that high ACE loads forecast 10–20 years of lost life

expectancy and, at the molecular level, a consistent 1–2-year acceleration on next-generation clocks such as GrimAge and DunedinPACE. Second, mechanistic work identifies inflammation, HPA-axis dysregulation, poor sleep, sedentary behaviour and low social support as *modifiable amplifiers* of that acceleration. Third, small but growing intervention trials—family-centred psychotherapy, trauma-informed CBT-I, and progressive exercise—demonstrate that clock trajectories can in fact bend toward youth. Finally, early epigenomic, proteomic and metabolomic integration efforts suggest that multi-omic panels may out-perform any single clock in tracking recovery.

Yet three critical gaps remain: (i) racial and ethnic representation is poor; few clocks report complete race/ethnicity data; of 13 seminal papers, only two included any non-White majority.; (ii) clock-to-clock concordance is only moderate ($r \approx 0.3–0.6$) and almost no paediatric study runs PedBE, DunedinPACE and telomere attrition side-by-side; and (iii) most therapy trials are under-powered, treating Δ-clock as an exploratory endpoint.

RESET is intentionally built to close those gaps. It will recruit a racially diverse cohort of 8- to 35-year-olds through community clinics and youth-advocacy partners; apply three complementary clocks (PedBE for buccal cells, GrimAge and DunedinPACE for blood) plus telomere and proteomic age; and embed a trauma-focused CBT arm and a home-based activity/sleep module powered to detect a ≥ 0.05-unit slowing of DunedinPACE over 24 months. By combining rigorous multi-omic phenotyping with culturally grounded intervention, RESET will deliver the first definitive test of whether reversing stress biology in childhood and early adulthood can "reset" the ageing clock and extend healthspan across the life course.

References

1. Swedo EA, Aslam M V, Dahlberg LL, et al. *Prevalence of Adverse Childhood Experiences Among U.S. Adults — Behavioral Risk Factor Surveillance System, 2011–2020*. Vol 72.; 2023. doi:http://dx.doi.org/10.15585/mmwr.mm7226a2

2. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The adverse childhood experiences (ACE) study. *Am J Prev Med*. 1998;14:245-258. doi:10.1016/S0749-3797(98)00017-8

3. CDC. About the CDC-Kaiser ACE Study. https://www.cdc.gov/violenceprevention/aces/about.html?

4. Burke-Harris N. *Roadmap for Resilience The California Surgeon General's Report on Adverse Childhood Experiences, Toxic Stress, and Health*.

5. Chang OD, Meier HCS, Maguire-Jack K, Davis-Kean P, Mitchell C. Childhood Maltreatment and Longitudinal Epigenetic Aging: NIMHD Social Epigenomics Program. *JAMA Netw Open*. Published online July 2024:e2421877. doi:10.1001/jamanetworkopen.2024.21877

6. Kim K, Yaffe K, Rehkopf DH, et al. Association of Adverse Childhood Experiences With Accelerated Epigenetic Aging in Midlife. *JAMA Netw Open*. 2023;6. doi:10.1001/jamanetworkopen.2023.17987

7. McCrory C, Fiorito G, O'Halloran AM, Polidoro S, Vineis P, Kenny RA. Early life adversity and age acceleration at mid-life and older ages indexed using the next-generation GrimAge and Pace of Aging epigenetic clocks. *Psychoneuroendocrinology*. 2022;137. doi:10.1016/j.psyneuen.2021.105643

8. Horvath S. DNA methylation age of human tissues and cell types. *Genome Biol*. 2013;14. doi:10.1186/gb-2013-14-10-r115

9. Lu AT, Quach A, Wilson JG, et al. DNA methylation GrimAge strongly predicts lifespan and healthspan. *Aging*. 2019;11:303-327. doi:10.18632/aging.101684

10. McCrory C, Fiorito G, O'Halloran AM, Polidoro S, Vineis P, Kenny RA. Early life adversity and age acceleration at mid-life and older ages indexed using the next-generation GrimAge and Pace of Aging epigenetic clocks. *Psychoneuroendocrinology*. 2022;137. doi:10.1016/j.psyneuen.2021.105643

11. Belsky DW, Caspi A, Corcoran DL, et al. DunedinPACE, a DNA methylation biomarker of the pace of aging. *Elife*. 2022;11. doi:10.7554/eLife.73420

12. Bourassa KJ, Garrett ME, Caspi A, et al. Posttraumatic stress disorder, trauma, and accelerated biological aging among post-9/11 veterans. *Transl Psychiatry*. 2024;14. doi:10.1038/s41398-023-02704-y

13. McEwen LM, O'Donnell KJ, McGill MG, et al. The PedBE clock accurately estimates DNA methylation age in pediatric buccal cells. *Proc Natl Acad Sci U S A*. 2020;117:23329-23335. doi:10.1073/pnas.1820843116

14. McGill MG, Pokhvisneva I, Clappison AS, et al. Maternal Prenatal Anxiety and the Fetal Origins of Epigenetic Aging. *Biol Psychiatry*. 2022;91:303-312. doi:10.1016/j.biopsych.2021.07.025

15. Dammering F, Martins J, Dittrich K, et al. The pediatric buccal epigenetic clock identifies significant ageing acceleration in children with internalizing disorder and maltreatment exposure. *Neurobiol Stress*. 2021;15:100394. doi:10.1016/j.ynstr.2021.100394

16. Houseman EA, Accomando WP, Koestler DC, et al. DNA methylation arrays as surrogate measures of cell mixture distribution. *BMC Bioinformatics*. 2012;13. doi:10.1186/1471-2105-13-86

17. Pidsley R, Zotenko E, Peters TJ, et al. Critical evaluation of the Illumina MethylationEPIC BeadChip microarray for whole-genome DNA methylation profiling. *Genome Biol*. 2016;17. doi:10.1186/s13059-016-1066-1

18. Apsley AT, Ye Q, Caspi A, et al. Cross-tissue comparison of epigenetic aging clocks in humans. *Aging Cell*. 2025;24. doi:10.1111/acel.14451

19. Ridout KK, Levandowski M, Ridout SJ, et al. Early life adversity and telomere length: A meta-analysis. *Mol Psychiatry*. 2018;23:858-871. doi:10.1038/mp.2017.26

20. Lindrose AR, McLester-Davis LWY, Tristano RI, et al. Method comparison studies of telomere length measurement using qPCR approaches: A critical appraisal of the literature. *PLoS One*. 2021;16. doi:10.1371/journal.pone.0245582

21. Kresovich JK, Parks CG, Sandler DP, Weinberg CR, Taylor JA. The Role of Blood Cell Composition in Epidemiologic Studies of Telomeres. *Epidemiology*. 2020;31:e34-e36. doi:10.1097/EDE.0000000000001187

22. Lu AT, Quach A, Wilson JG, et al. DNA methylation GrimAge strongly predicts lifespan and healthspan. *Aging*. 2019;11:303-327. doi:10.18632/aging.101684

23. Hwang AC, Peng LN, Wen YW, et al. Predicting all-cause and cause-specific mortality by static and dynamic measurements of allostatic load: A 10-year population-based cohort study in Taiwan. *J Am Med Dir Assoc*. 2014;15:490-496. doi:10.1016/j.jamda.2014.02.001

24. Finlay S, Juster RP, Adegboye O, Rudd D, McDermott B, Sarnyai Z. Childhood adversity, allostatic load, and adult mental health: Study protocol using the Avon Longitudinal Study of Parents and Children birth cohort. *Front Psychiatry*. 2023;13. doi:10.3389/fpsyt.2022.976140

25. McEwen LM, O'Donnell KJ, McGill MG, et al. The PedBE clock accurately estimates DNA methylation age in pediatric buccal cells. *Proc Natl Acad Sci U S A*. 2020;117:23329-23335. doi:10.1073/pnas.1820843116

26. Belsky DW, Caspi A, Corcoran DL, et al. DunedinPACE, a DNA methylation biomarker of the pace of aging. *Elife*. 2022;11. doi:10.7554/eLife.73420

27. Lu AT, Quach A, Wilson JG, et al. DNA methylation GrimAge strongly predicts lifespan and healthspan. *Aging*. 2019;11:303-327. doi:10.18632/aging.101684

28. McCrory C, Fiorito G, O'Halloran AM, Polidoro S, Vineis P, Kenny RA. Early life adversity and age acceleration at mid-life and older ages indexed using the next-generation GrimAge and Pace of Aging epigenetic clocks. *Psychoneuroendocrinology*. 2022;137. doi:10.1016/j.psyneuen.2021.105643

29. Simons RL, Ong ML, Lei MK, et al. Unstable Childhood, Adult Adversity, and Smoking Accelerate Biological Aging Among Middle-Age African Americans: Similar Findings for GrimAge and PoAm. *J Aging Health*. 2022;34:487-498. doi:10.1177/08982643211043668

30. Brody GH, Yu T, Chen E, Beach SRH, Miller GE. Family-centered prevention ameliorates the longitudinal association between risky family processes and epigenetic aging. *J Child Psychol Psychiatry*. 2016;57:566-574. doi:10.1111/jcpp.12495

31. Merrill SM, Hogan C, Bozack AK, et al. Telehealth Parenting Program and Salivary Epigenetic Biomarkers in Preschool Children With Developmental Delay NIMHD Social Epigenomics Program. *JAMA Netw Open*. 2024;7. doi:10.1001/jamanetworkopen.2024.24815

32. Hartwell KJ, Moran-Santa Maria MM, Twal WO, et al. Association of elevated cytokines with childhood adversity in a sample of healthy adults. *J Psychiatr Res*. 2013;47:604-610. doi:10.1016/j.jpsychires.2013.01.008

33. Heard-Garris N, Davis MM, Estabrook R, et al. Adverse childhood experiences and biomarkers of inflammation in a diverse cohort of early school-aged children. *Brain Behav Immun Health*. 2020;1. doi:10.1016/j.bbih.2019.100006

34. Khandaker GM, Pearson RM, Zammit S, Lewis G, Jones PB. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life a population-based longitudinal study. *JAMA Psychiatry*. 2014;71:1121-1128. doi:10.1001/jamapsychiatry.2014.1332

35. Barr E, Comtois-Cabana M, Coope A, et al. Early-Life Adversity and Epigenetic Aging: Findings from a 17-Year Longitudinal Study. *Biomolecules*. 2025;15:887. doi:10.3390/biom15060887

36. Marsland AL, Jones E, Reed RG, et al. Childhood trauma and hair cortisol response over the year following onset of a chronic life event stressor. *Psychoneuroendocrinology*. 2024;165. doi:10.1016/j.psyneuen.2024.107039

37. Charles LE, Mnatsakanova A, Fekedulegn D, Violanti JM, Gu JK, Andrew ME. Associations of adverse childhood experiences (ACEs) with sleep duration and quality: the BCOPS study. *Sleep Med*. 2022;89:166-175. doi:10.1016/j.sleep.2021.12.011

38. Carroll JE, Prather AA. Sleep and biological aging: A short review. *Curr Opin Endocr Metab Res*. 2021;18:159-164. doi:10.1016/j.coemr.2021.03.021

39. Bertele S, Heitland I, Fraccarollo D, et al. Behavioral pathway to a broken heart: The link between adverse childhood experiences, depression, physical exercise and cardiovascular health. *Front Psychiatry*. 2022;13. doi:10.3389/fpsyt.2022.1002143

40. Rogers EM, Banks NF, Tomko PM, et al. Progressive exercise training improves cardiovascular psychophysiological outcomes in young adult women with a history of adverse childhood experiences. *J Appl Physiol*. 2023;134:742-752. doi:10.1152/JAPPLPHYSIOL.00524.2022

41. Hillmann AR, Dhingra R, Reed RG. Positive social factors prospectively predict younger epigenetic age: Findings from the Health and Retirement Study. *Psychoneuroendocrinology*. 2023;148. doi:10.1016/j.psyneuen.2022.105988

42. Drury SS, Theall K, Gleason MM, et al. Telomere length and early severe social deprivation: Linking early adversity and cellular aging. *Mol Psychiatry*. 2012;17:719-727. doi:10.1038/mp.2011.53

43. Carroll J. Cognitive Behavioral Treatment of Insomnia Slows the Pace of Biological Aging: Results from an RCT in Older Adults. *Innov Aging*. 2023;7:205-206. doi:10.1093/geroni/igad104.0678

44. Watkins SH, Testa C, Chen JT, et al. Epigenetic clocks and research implications of the lack of data on whom they have been developed: A review of reported and missing sociodemographic characteristics. *Environ Epigenet*. 2023;9. doi:10.1093/eep/dvad005