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The Impact of Early Life Adversity on Peripubertal Accelerated Epigenetic Aging and Psychopathology

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Objective: To examine longitudinal associations between early life threat and deprivation on epigenetic age acceleration at ages 9 and 15 years, and to examine associations of age acceleration on later internalizing and externalizing symptoms.

Method: The study examines a large (n = 2,039) and racially diverse (Black/African American = 44%, Latino = 18%, White = 5%) sample from a national dataset. Epigenetic age acceleration was estimated using the pediatric buccal epigenetic clock. Early life threat and deprivation were measured using composites from the Parent–Child Conflict Tactics Scale and county-level violent and property crime rate data. Internalizing and externalizing symptoms came from parent-reported Child Behavior Checklist. Path analysis models examined associations of threat and deprivation at age 3 years on epigenetic age acceleration at ages 9 and 15. Experiences of threat were further broken down into threat experienced in the home and in the community.

Results: Home threat experienced at age 3 years predicted age acceleration at 9 and 15, and community threat experienced at 3 predicted age acceleration at 15, but not at 9. Deprivation was not a significant predictor of accelerated aging. Age acceleration at age 9 predicted externalizing, but not internalizing, symptoms at age 15. Community threat had a direct effect on externalizing. No association emerged with internalizing.

Conclusion: Findings revealed that threat, not deprivation, was predictive of age acceleration, demonstrating support for this pattern longitudinally, using an epigenetic clock that is accurate in children. The findings provide critical nuance to the examination of threat, and highlight associated risks and possible intervention points for externalizing symptoms.

Plain language summary: This paper used publicly available data from the Future of Families and Child Wellbeing Study, a study that collected data from 2,039 children and families from early childhood to adolescence. The authors examined how early life experiences of adversity, such as threat and deprivation, are associated with increased epigenetic aging, a phenomenon where one's DNA ages faster than one's chronological age. Results demonstrated that early childhood experiences of threat in the home and in the community predicted increased epigenetic age acceleration, but that experiences of deprivation did not. Epigenetic age acceleration also predicted later externalizing, but not internalizing, symptoms. These findings support the potential for early childhood being a sensitive period for adversity and for further research on the nuances of the type of trauma and behavioral symptoms associated with long-lasting negative impacts.

Key words: pediatric buccal epigenetic clock; threat; deprivation; internalizing; externalizing

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Early life adversity (ELA) is associated with long-term health risks, such as poorer immune health via increased allostatic load,[1] increased risk of mental health problems,[2] and worsened global physical health.[3] Research has shown that ELA is common, as approximately half of children in the United States will experience at least one form of adversity by adulthood.[4] Researchers have begun to examine how this association between ELA and future health phenotypes may be reflected at the molecular level. One possibility is that ELA may "get under the skin" through epigenetics, or modifications to DNA without affecting the underlying genetic sequence, especially DNA methylation.[5] DNA methylation is a stable epigenetic mark that has the capacity to be maintained across the life course, is associated with health phenotypes, and is particularly sensitive to early life environments.[6] DNA methylation also changes reliably with age, reflecting the cellular aging process, and measurement of these changes is known as epigenetic age.[7] Epigenetic age is calculated using the percentage of DNA methylation on key genetic sites associated with aging. Thus, aging faster epigenetically than expected chronologically is known as increased epigenetic age acceleration. Increased epigenetic age acceleration shows critical associations with ELA; it has also been predicted by exposure to ELA such as trauma[8] and poverty[9] in children and adolescents, both directly and through other associated risks such as earlier menarche in girls.[10]

Despite these critical associations between ELA and accelerated biological aging, many studies investigating adversity have examined the construct in broad and

nonspecific terms,[11] combining distinct experiences that may have differing impacts on biological aging—specifically, biological aging as measured with epigenetic age.[12] Because adversity refers to a wide range of negative experiences (abuse, neglect, poverty, bullying, or parental psychopathology),[13] this approach fails to capture the unique differences in biological risk that are associated with each of those experiences.[14] Recent work has instead attempted to quantify individual differences in the amount of exposure to distinct "types" of adversity, breaking down adversity into experiences of threat and deprivation. For example, in McLaughlin and Sheridan's Dimensional Model of Adversity and Psychopathology, threat-related adversity refers to the presence of negative experiences that threaten the well-being of the child or someone close to them either physically or psychologically (physical abuse, neighborhood violence exposure, emotional abuse, and witnessing intimate partner violence).[14,15] In contrast, deprivation-related adversity refers to the absence of developmentally expected experiences caused by caregivers who are physically and/or psychologically not present (physical and emotional neglect and poverty, often characterized by a lack of cognitive, social, and emotional stimulation).[11]

With this enhanced clarity in defining adversity, nascent research has demonstrated differential associations between threat and deprivation with accelerated aging. For example, a recent study demonstrated that both threat- and deprivation-related ELA were associated with earlier age of pubertal onset, but that only greater exposure to threat was associated with accelerated aging.[16] Disparate outcomes are similarly demonstrated in related research, such that threat-related but not deprivation-related ELA has shown associations with accelerated aging,[17] a pattern that has also been noted in a meta-analysis of the influence of threat and deprivation on epigenetic aging.[18] Although existing research suggests that deprivation may be less clearly associated with epigenetic aging, few studies have examined epigenetic age using the Pediatric Buccal Epigenetic Clock (PedBE), which is a more accurate measurement for use with children[19] in saliva and in developmental studies.[20,21] Although the majority of work in the field of epigenetic age acceleration has focused on adults,[22] children and adolescents do not just age, they mature and develop. Therefore, the use of an epigenetic clock trained specifically for evaluating the biological age of adolescent samples is integral to understanding the importance of developmental timing. In addition, although this clock was trained specifically on cheek swab samples made of predominantly buccal epithelial cells, it was tested and has been applied successfully to pediatric saliva samples, which have a different proportion but identical make-up of oral cells.[20] Thus, investigating PedBE age acceleration presents an opportunity to better understand differential associations between accelerated aging and both threat and deprivation experienced during sensitive periods.[23]

Another critical consideration when examining early life threat and deprivation are the associated risks for psychopathology. The literature thus far has demonstrated consistent associations of internalizing symptoms with accelerated epigenetic aging and higher epigenetic age, both concurrently and in later childhood and adolescence,[24,25] and 1 study has demonstrated a moderating effect of maltreatment on the association between internalizing disorders and the PedBE clock.[26] However, research connecting epigenetic age and internalizing/externalizing symptoms is new, and findings are inconsistent. Therefore, the PedBE clock may provide both the accuracy of measurement within a pediatric population and a potential biological correlate needed to connect early life threat and deprivation with later internalizing and externalizing symptoms.

Similarly lacking in the literature to date is exploration into longitudinal associations across developmental stages, both between ELA and age acceleration as well as age acceleration and clinical outcomes. Various studies have established that ELA influences accelerated aging through pubertal timing,[8,10] but none have compared these associations before and after puberty. Similarly, puberty is a highly relevant developmental stage in understanding trajectories of psychopathology development,[27] but has not been considered when examining the associations between ELA and epigenetic aging. Another serious limitation in our current understanding is that most studies examining epigenetic age acceleration and ELA use small and homogeneous samples, which limits the generalizability of findings, thus presenting a clear opportunity to examine these questions in larger and more diverse samples.

To address these limitations, the present study models the pathway of disparities that stem from early life threat and deprivation, providing even further ELA specificity by breaking down the experience of threat into threat experienced at home and in the community, and the experience of deprivation into lack of stimulation (social and cognitive deprivation) and neglect (physical and emotional deprivation).[26] Using longitudinal data from the Future of Families and Child Wellbeing Study,[28] this study assesses multiple and specific variables of early life threat and deprivation at age 3 years, the PedBE clock at ages 9 and 15 years, and adolescent internalizing and externalizing outcomes. We hypothesized that variables of both threat and deprivation at age 3 would be positively associated with later accelerated epigenetic aging as measured by the PedBE clock, which

would in turn be positively associated with both internalizing and externalizing symptoms in adolescence.

METHOD

Participants

Data from the present study come from the publicly available Future of Families and Child Wellbeing Study, an ongoing longitudinal study of 4,898 families from 20 large cities (population ≥200,000) across the United States. Families were recruited at the child's birth (1998-2000) with the goal of collecting a representative sample of married and nonmarried parents, given the heightened stress associated with having a child before marriage.[28] Given the original study's aims, nonmarital births were oversampled at a rate of 3:1, resulting in a disproportionate sample of economically disadvantaged families. The larger study has collected data at ages 3, 5, 9, 15, and 22 (age 22 data are not yet available to the public). The present study examined a subset of children (n = 2,039) from the larger sample, who were selected for having complete epigenetic data at age 9 or 15 years. Data for the present study were collected when the children were 3 (mean = 2.98, SD = 0.22), 9 (mean = 9.41, SD = 0.40), and 15 (mean = 15.55, SD = 0.65) years of age. Sex as reported by the mother at birth was 50.6% male and 49.4% female. Almost all participating girls (95.5%) reported their age of first menstruation after the age 9 wave. The sample's breakdown for child's race, as self-reported at age 15 years, was 46.7% Black or African American, 26.5% Hispanic/Latino, 5.1% multi-racial, non-Hispanic, 2.7% "other", non-Hispanic, and 19% White, non-Hispanic.

Procedure

Data for the present study were collected when the focal child was 3 (2001-2003), 5 (2003-2006), 9 (2007-2010), and 15 (2014-2017) years of age via in-home assessments. During data collection at ages 9 and 15, children's saliva samples were also collected. In all, 86% of children provided saliva samples at age 9, as did 71% of teens at age 15. Data collection and study procedures were overseen by the Princeton University Institutional Review Board. A full description of the study procedures is provided in the Methods section of Sisitsky *et al.*[29]

Measures

Home Threat. A latent variable was created to represent home threat at ages 3 and 5 via the Parent–Child Conflict Tactics Scale (CTS-PC).[30] Home threat was defined as exposure to physical and emotional abuse by a primary caregiver. Primary caregivers reported how often physical abuse (3 items: hit on the bottom with something like a belt, hairbrush, a stick, or some other hard object; spanked on the bottom with a bare hand; slapped on the hand, arm, or leg) and emotional abuse (3 items: shouted, yelled, or screamed; threatened to spank; swore or cursed) occurred in the past year using a 7-point Likert scale ranging from "never happened" to "more than 20 times." Higher scores reflect greater exposure to threat within the home environment.

Community Threat. A latent variable was created to represent community threat at ages 3 and 5 years, obtained via the National Archive of Criminal Justice Data's Uniform Crime Reports.[31] The data consisted of county-level crime rate data for the location of focal child's primary caregiver during ages 3 and 5 data collection. The measure of community threat represents exposure to violence in the child's neighborhood, calculated as the sum of violent crime instances per capita (murder, rape, robbery, and aggravated assault) and property crime instances per capita (burglary, larceny, motor vehicle theft, and arson). Crime rate data were *z* scored because of the variable's scale.

Lack of Stimulation. A latent variable was created to capture absence of cognitive and social stimulation provided by the primary caregiver at ages 3 and 5 years. Primary caregivers reported on how many days per week (from 0 to 7) they engaged in activities with their child (eg, singing songs or nursery rhymes, playing imaginary games, telling stories, playing with toys). Items were reverse scored such that higher scores indicate a greater degree of lack of stimulation.

Neglect. A latent variable was created to represent neglect by a primary caregiver, measured at age 3 and 5 years via caregiver report on the CTS-PC. Neglect was defined as the frequency of instances over the past year during which primary caregivers were unable to provide for their child physically or emotionally. Physical neglect was measured with 2 items assessing how often caregivers were unable to provide the food that their child needed and how often they were unable to take their child to a doctor or hospital when needed. Emotional neglect was measured with 1 item assessing how often caregivers were unable to show or tell their child that they loved them. Because scores above 1 on these items were rare, each item was coded into a binary (1 = occurred at least 1 time in the past year, and 0 = did not occur at all in the past year). Tables S1 and S2, available online, provide full descriptions of how these categories were created.

Internalizing Symptoms. Internalizing symptoms were measured via parent report on the Child Behavior Checklist

at ages 3, 9, and 15 years.[32] Primary caregivers answered items about their child using the response options never/not true, sometimes/somewhat true, and often/very true. At age 3 years, the mean score of items from the anxious/depressed subscale (8 items) and the withdrawn subscale (8 items) were used. At age 9, the mean score of items from the anxious/depressed subscale (13 items) and the withdrawn/depressed subscale (8 items) were used. At age 15, the mean score of items from the anxious/depressed subscale (6 items) and the withdrawn/depressed subscale (2 items). To remain consistent across timepoints and with prior work,[33] only the anxious/depressed and withdrawn/depressed subscales, not somatic symptoms, were used.

Externalizing Symptoms. Externalizing symptoms were also measured via parent report on the CBCL at ages 3, 9, and 15 years, using the same response options as above. At age 3, the mean score of items from the aggressive subscale (19 items) was used. At age 9, the mean score of items from the aggressive subscale (18 items) and the rule breaking behavior subscale (17 items) were used. At age 15, the mean score of items from the aggressive subscale (11 items) and the rule breaking behavior subscale (9 items) were used.

Covariates. Sex was included as a covariate in the primary model as well as in follow-up analyses. Sex of the child was reported by the mother at birth, with options "male" and "female." Race and ethnicity were used as covariates in follow-up analyses, aligned with previous research suggesting these constructs influence epigenetic age acceleration.[34,35] Race and ethnicity were self-reported at age 15 years, with options as follows: Black or African American, non-Hispanic or Latino; Hispanic or Latino; Multi-racial, non-Hispanic; Other only, non-Hispanic; White, non-Hispanic. Finally, 8 profiles of threat and deprivation developed by Sisitsky *et al.*[29] were examined. Profiles captured experiences that were characterized mainly by low risk (1), average risk (2), home adversity (3), high stimulation (4), safe community (5), low home threat (6), community threat (7), and home neglect (8).

Epigenetic Age Acceleration. Epigenetic age was estimated from pediatric salivary DNA methylation at ages 9 and 15 years using the Oragene DNA Self-Collection Kit (DNA Genotek Inc., Ottawa, ON, Canada). Further details about the collection and processing of these saliva samples are available on the Future of Families and Child Wellbeing Study portal (https://ffcws.princeton.edu) and detailed in a previous publication.[34] Samples were characterized on either the Illumina HumanMethylation450k or EPIC BeadChip arrays (Illumina, San Diego, CA). In total, 3,945 samples from 2,039 individuals with DNA methylation at age 9 and/or age 15 were estimated for epigenetic age using the pediatric buccal epigenetic (PedBE) clock.[20] The PedBE clock was trained in oral tissue to estimate biological age in children within an error of less than 4 months using 95 sites across the epigenome; it is currently the most accurate pediatric epigenetic clock and performs similarly across racial groups.[19] Predicted epigenetic age was correlated $r(2037) = 0.66$ with reported chronological age in this sample, as expected in a pediatric saliva sample cohort with the PedBE clock.[20] Although DNA methylation was assessed on 2 array types, given the identical technology between them, PedBE was trained and tested on both arrays, allowing these data to be combined, as is recommended.[20,36] To maximize the robustness of the epigenetic age acceleration calculation across ages similar to previous work on repeated samples in epigenetic age,[37] this was measured by the residuals of a linear mixed effect model with maximum likelihood estimation of predicted PedBE age on reported chronological age, accounting for predicted buccal epithelial cell proportion (as recommended by the authors of the tool[20]) and a random effect of individual (as most individuals had samples at both age 9 and age 15 years). This was completed in *R* (4.3.1) with the *nlme* package. Buccal epithelial cell proportion was estimated using the *EpiDISH* package and accounted for during epigenetic age acceleration calculation because of the association of this cell type and age.[38] PedBE epigenetic age acceleration across all samples and at each timepoint was normally distributed and centered around zero, as expected, and not associated with buccal epithelial cell proportions.[7]

Data Analysis

Based on theory and available measures, an initial *a priori* pool of items that could fit either threat or deprivation constructs was selected. From this initial set of items, we examined the item-level correlations and tested several models consistent with a dimensional approach to adversity using confirmatory factor analysis (CFA) and following standard structural equation modeling (SEM) procedures.[38] Sisitsky *et al.*[29] and Tables S1 and S2, available online, provide further detail regarding these steps.

A path analysis model was conducted using Mplus, applying full information maximum likelihood (FIML) for any missing data. Age 3 threat and deprivation were the primary predictors in the model of epigenetic age acceleration at age 9 and 15 years as well as youth internalizing and externalizing symptoms at age 15. Use of the term "longitudinal" reflects the examination of associations across childhood, rather than an examination of change in trajectory over time. Stability of youth outcomes was accounted for by the inclusion of the same outcomes at ages 3 and 9 years in

the model. Finally, concurrent and longitudinal associations between epigenetic age acceleration at ages 9 and 15 were examined for youth outcomes at age 15. Youth sex was included as a covariate for all outcomes given past work showing an association with epigenetic age acceleration.[39]

The same analyses with relevant covariates were also conducted to assess how variables known to be associated with these constructs may change the findings in the proposed models. Four additional analyses were explored. First, we conducted a multiple test correction using the Benjamini–Hochberg method. Next, to test for differential sensitivity of the associations when adding relevant variables to the model and allowing them to covary, 3 follow-up regressions were run examining child race and ethnicity (Table S3, available online), threat and deprivation levels at age 5 instead of age 3 (Table S4, available online), and family poverty status and maternal education (Table S5, available online).

Finally, we explored profiles of threat and deprivation as a categorical predictor of epigenetic age acceleration (Table S6, available online). Finally, descriptive statistics were calculated for sociodemographic (Table 1) and study variables (Table 2) from participants who reported these data.

RESULTS

Primary results of the model are depicted in Figure 1 and Table 3 (full results in Table S7, available online). Standardized results are depicted and interpreted below. Model fit was excellent (χ^2 [14] = 63.75, root mean square error of approximation [RMSEA] = 0.042, 95% CI = 0.032, 0.052, CFA = 0.983, and standardized root mean squared residual [SRMR] = 0.025). Age 3 and 9 levels of internalizing and externalizing problems were included in the model, and stability paths were significant across waves. Child sex was included as a covariate for all outcomes and was associated with epigenetic age acceleration at age 9 ($\beta = 0.08$, SE = 0.02, $p = .002$) and age 15 ($\beta = 0.05$, SE = 0.02, $p = .013$), as well as with age 15 youth internalizing problems ($\beta = 0.08$, SE = 0.02, $p \leq .001$), such that natal female individuals demonstrated higher levels of acceleration and internalizing than did natal male individuals. Regarding primary model results, home threat was a significant predictor of PedBE aging at ages 9 ($\beta = 0.06$, SE = 0.03, $p = .034$) and 15 ($\beta = 0.05$, SE = 0.02, $p = .023$), such that higher levels of home threat longitudinally predicted higher epigenetic age acceleration across peripubertal development. Furthermore, higher levels of community threat predicted increased epigenetic age acceleration at age 15 ($\beta = 0.10$, SE = 0.02, $p \leq .001$) but not at age 9. None of the deprivation variables (lack of stimulation and neglect) were significant predictors of accelerated aging. Regarding youth psychopathology outcomes, higher levels of age 9 epigenetic age acceleration predicted higher levels of youth externalizing symptoms at 15 ($\beta = 0.05$, SE = 0.02, $p = .028$), but not internalizing symptoms. Moreover, higher levels of community threat had a direct effect on youth externalizing problems at 15

TABLE 1 Sociodemographic Variables of Study Participants Who Reported

Variable		n	%
Child sex			
Male		875	50.6
Female		855	49.4
Child race and Ethnicity			
Black/African American, non-Hispanic or Latino		901	46.7
Hispanic/Latino		511	26.5
Multi-racial, non-Hispanic		99	5.1
Other only, non-Hispanic		52	2.7
White, non-Hispanic		366	19.0
Mother education at child's birth			
No high school diploma		536	31.0
High school or equivalent		548	31.7
Some college		452	26.2
College or graduate degree		192	11.1
	Mean	SD	Range
Household income	$33,35.16	$32,323.13	$0-$133,750.00
Chronological age (year 9)	9.41	0.40	8.76-12.25
Chronological age (year 15)	15.55	0.65	14.43-18.52

TABLE 2 Means, Standard Deviations, and Correlations for All Study Variables

Variable	Mean	SD	1	2	3	4	5	6	7	8	9	10	11	12	13
1. PedBE age acceleration at 9	0.001	0.65	1												
2. PedBE age acceleration at 15	−0.003	0.85	−0.536	1											
3. Ext. at 15	0.225	0.25	0.048	−0.001	1										
4. Ext. at 9	0.180	0.19	−0.007	0.031	0.493	1									
5. Int. at 15	0.269	0.31	0.013	−0.019	0.525	0.271	1								
6. Int. at 9	0.184	0.19	−0.031	0.039	0.233	0.64	0.314	1							
7. Lack of stimulation at 3	0.016	0.54	−0.005	0.012	0.06	0.026	0.040	0.052	1						
8. Neglect at 3	0.087	0.4	−0.001	0.034	0.074	0.097	0.048	0.093	0.318	1					
9. Home threat at 3	0.021	0.57	0.052	0.049	0.145	0.17	0.027	0.057	0.174	0.391	1				
10. Community threat at 3	−0.009	0.59	0.047	0.085	0.087	0.047	−0.037	−0.011	0.049	−0.099	0.207	1			
11. Sex	1.495	0.50	0.071	0.008	−0.048	−0.11	0.072	−0.022	−0.041	−0.052	−0.107	0.02	1		
12. Int. at 3	9.719	6.04	0.024	0.021	0.214	0.279	0.182	0.273	0.117	0.189	0.198	0.073	−0.048	1	
13. Ext. at 3	13.168	7.55	0.03	0.017	0.300	0.394	0.189	0.24	0.095	0.215	0.374	0.108	−0.077	0.69	1

Note: Ext. = externalizing; Int. = internalizing; PedBE = Pediatric Buccal Epigenetic Clock.

($\beta = 0.05$, SE = 0.02, $p = .027$). No association emerged with youth internalizing problems, other than a main effect of youth sex.

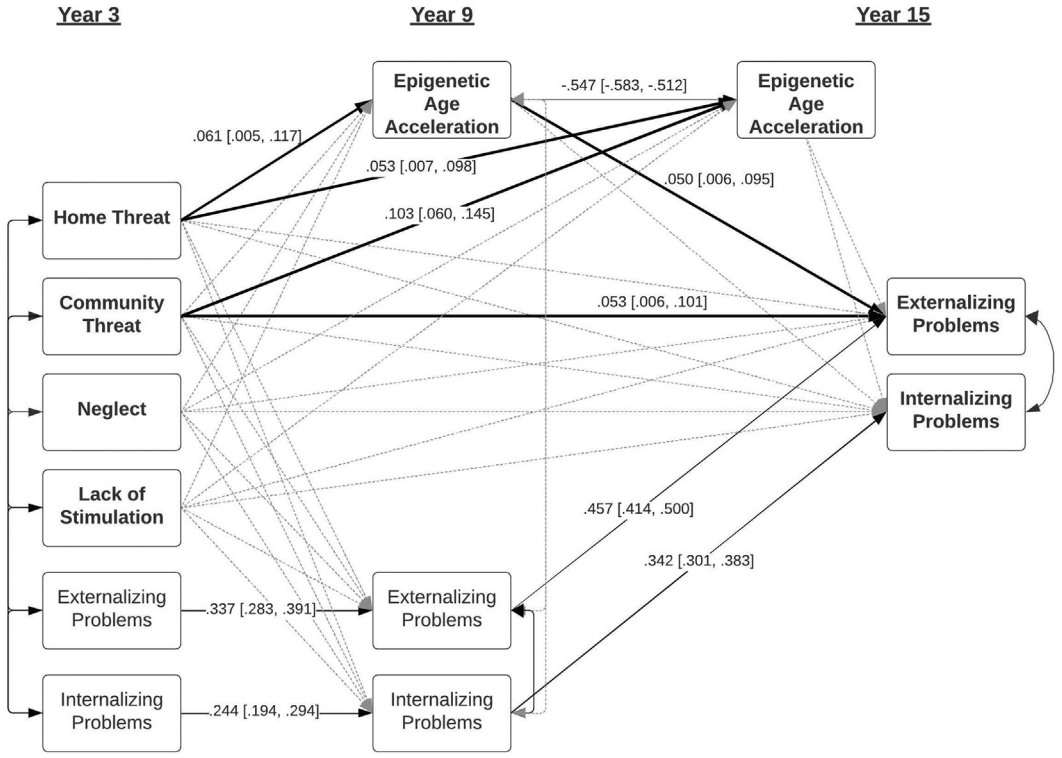
Follow-Up Analyses

Five follow-up analyses were explored. First, all p values below .02 met a false discovery rate (FDR) threshold of 0.05 using the Benjamini–Hochberg method to account for multiple test correction (all tests in the model). Both the impact of home threat on increased epigenetic age acceleration at age 9 years and community threat on increased epigenetic age acceleration at age 15 passed FDR<0.05 and had the highest confidence in their statistical significance. Second, child race and ethnicity were added as predictors of all outcomes and were allowed to covary with threat and deprivation at age 3. Latinx youth exhibited higher levels of epigenetic age acceleration at age 15, and Black youth reported higher levels of internalizing problems at age 15. No other race or ethnicity associations emerged, and all primary associations in the model above remained unchanged with the inclusion of youth race and ethnicity (Table S3, available online). Third, we explored threat and deprivation measured at age 5 years. Results were consistent with age 3 adversity, and suggest early childhood as a consistent sensitive period for adversity (Table S4, available online). Next, we explored family poverty status and maternal education (Table S5, available online), and found no changes to the statistical significance, direction, or strength of associations between primary variables. Finally, we explored profiles of threat and deprivation as a categorical predictor of epigenetic age acceleration (Tables S6 and S8, available online). Significant differences between profiles emerged for acceleration at age 15 years but were largely nonsignificant at age 9 (consistent with prior telomere length findings by Sisitsky *et al.*[29]). The profile characterized by high community threat demonstrated the highest levels of age acceleration. Furthermore, profiles characterized by low adversity, safe communities, or low home threat showed age deceleration at age 15. Divergent from primary dimensional results, the profile characterized by high home neglect (with average levels of the other domains) also demonstrated epigenetic age acceleration and was not significantly different from the community threat profile.

DISCUSSION

This study sought to examine the predictive influence of early life threat and deprivation on later epigenetic age acceleration, and, in turn, later and concurrent youth internalizing and externalizing symptoms. The results showed that threat measures (home and community), rather than

FIGURE 1 Primary Model Results



Note: *Youth sex was a covariate for all outcomes but is not depicted. Statistically significant standardized β coefficients and confidence intervals are depicted. Gray dotted lines are statistically nonsignificant. Covariances in boldface type are statistically significant, but the estimates are not depicted, for clarity of the figure. Complete results are available in Table 3 and the Supplemental Material.*

assessments of deprivation (neglect and lack of stimulation), most consistently predicted epigenetic age acceleration. Although hypotheses predicted that each of the ELA variables would significantly predict aging because of the improved accuracy of the PedBE clock, results are instead consistent with other measures of epigenetic age that have shown that threat, not deprivation, is associated with accelerated aging in children and adolescents.[17,18]

Overall, the findings provide support that early childhood, measured at both 3 and 5 years of age, may be a sensitive period for adversity, given the longitudinal impact demonstrated. Aligned with the Dimensional Model of Adversity tenet that heterogeneity in ELA is essential to understanding negative outcomes,[14] our results also demonstrate unique patterns of predictive associations from home threat vs community threat; violence and abuse experienced in the home were predictive of accelerated epigenetic age at 9 and 15 years of age, whereas violence witnessed or experienced in the community was predictive of accelerated epigenetic age only at 15 years. These findings may reflect a shift in the impact of the 2 forms of threat over time, such that early in development the home is the primary context for adversity, and over time this context becomes less salient as the child spends more time outside of the house in the community. Interestingly, the community threat variables were also measured at 3 years of age, yet still had predictive ability at 15 years of age. Explanation for this difference may come from the nature of these variables; community threat may have been assessed with less bias and could therefore show its lasting impact on age acceleration. Alternatively, these findings may be understood using an evolutionary lens, such that early maturation, and therefore reproduction, could provide an advantage to children in a threatening environment. This hypothesis has some support in research explicitly examining pubertal timing, although more research is needed to understand the mechanisms at play.[10,18]

Results were somewhat contrary to hypotheses that accelerated epigenetic aging would be associated with both internalizing and externalizing symptoms (results showed associations only with externalizing symptoms). Importantly, new work examining externalizing symptoms has shown associations between externalizing and epigenetic age acceleration.[40] These authors suggest that those who experience these symptoms may also be more at risk for drug/alcohol use and aggression, factors that could cause faster

TABLE 3 Results of Primary Model, in Which Threat and Deprivation Variables at Age 3 Years Predict Pediatric Buccal Epigenetic Clock (PedBE) Age Acceleration at Ages 9 and 15

	Estimate	SE	*p* Value	95% CI
Outcome: PedBE age acceleration at 15 y on				
PedBE age acceleration at 9	−0.55	0.02	≤.001[a]	−0.58, −0.52
Lack of stimulation at 3	−0.01	0.02	.580	−0.05, 0.02
Neglect at 3	0.03	0.02	.204	−0.01, 0.07
Home threat at 3	0.05	0.02	.023	0.01, 0.09
Community threat at 3	0.10	0.02	≤.001[a]	0.07, 0.14
Child sex	0.05	0.02	.013[a]	0.02, 0.09
Outcome: PedBE age acceleration at 9 y on				
Lack of stimulation at 3	−0.01	0.03	.730	−0.05, 0.04
Neglect at 3	−0.02	0.03	.592	−0.06, 0.03
Home threat at 3	0.06	0.03	.034	0.01, 0.11
Community threat at 3	0.03	0.03	.230	−0.01, 0.08
Child sex	0.08	0.02	.002[a]	0.04, 0.12
Outcome: Externalizing at 15 y on				
Externalizing at 9	0.46	0.02	≤.001[a]	0.42, 0.49
PedBE age acceleration at 9	0.05	0.02	.028	0.01, 0.09
PedBE age acceleration at 15	0.01	0.03	.821	−0.04, 0.05
Lack of stimulation at 3	0.04	0.02	.130	0.00, 0.08
Neglect at 3	0.01	0.03	.834	−0.04, 0.05
Home threat at 3	0.05	0.03	.062	0.01, 0.09
Community threat at 3	0.05	0.02	.027	0.01, 0.09
Child sex at 3	0.00	0.02	.843	−0.03, 0.04

Note: [a]*Denotes associations that passed the false discovery rate threshold (p<.020).*

aging. Similarly, externalizing symptoms may present an "unpredictable" environment, also associated with faster life history.[41] Alternatively, the lack of association with internalizing symptoms may also be explained by the well-known difficulty of accurately assessing these symptoms,[42] although other work continues to reflect contradictory findings,[24,43] highlighting the opportunity for future work to consider the symptoms within these categories for greater specificity.

The current study had important limitations that could have had an impact on the findings or their application. First, the present study assessed aging up only to 15 years of age because of the availability of these data. It is possible that these effects compound as a person continues aging, and thus highlight the need for continued longitudinal work on equally large and diverse populations. Indeed, some research has begun to indicate that ELA continues to have an impact on accelerated aging into adulthood.[9,44] Similarly, the current study used a longitudinal lagged panel modeling approach, and future research should consider alternative longitudinal modeling methods, such as latent change scores or latent cure models. Furthermore, longitudinal pathways had small effect sizes. As such, interpretation of these findings may be limited in terms of clinical applicability on an individual basis. However, even a small effect size is highly relevant when considering the potential for cascading and cumulative effects over the lifespan and the association between epigenetic age acceleration and early mortality.[45] In addition, although the PedBE clock is the most appropriate epigenetic clock to evaluate an adolescent epigenetic age acceleration,[20] it was trained on cheek swabs, which are predominantly composed of buccal epithelial cells with a smaller proportion of oral immune cells such as neutrophils. Cell type differentiation is a major biological function of DNA methylation[6] from which the epigenetic age acceleration measure is derived, and so, although saliva is composed of the same cells (ie, buccal epithelial cells and oral immune cells), the proportion of those cells are different and may have affected the accuracy of the clock.[46] To combat this potential influence, we corrected for estimated buccal epithelial cell proportion in the calculation of epigenetic age acceleration in this sample. Finally, because of the high levels of adversity experienced by the participants in the dataset, findings may not be applicable to cohorts with fewer experiences with ELA. Similarly, more research is needed to understand the role of socioeconomic position in epigenetic aging, as there are mixed findings for its associations,[47,48] despite well-established associations between socioeconomic position and adversity or psychopathology.

A particular strength of the present study's findings is their applicability to diverse and minoritized populations because of the sample characteristics. All children in the sample were from families living in large cities in the United States, and the sample's mean household income was significantly lower than the national average household income. The sample was also large and racially diverse, allowing for greater generalizability to minoritized populations than currently exists in the literature. Additional strengths of the current study were the use of multiple methods (ie, parent-report, geocoded neighborhood level data, biomarkers) and the 12-year, 3-wave longitudinal design.

Collectively, results from the current study highlight the need for future research to investigate possible intervention points in these demonstrated pathways. In addition to understanding possible accumulating effects, researchers could

explore how family-focused interventions such as family therapy, community supports, and psychoeducation may alter this connection between ELA and accelerated aging. Furthermore, continued longitudinal work may explore whether accelerated aging could be malleable, and what types of interventions show the most impact at differing stages of development. For example, emerging results suggest that intervention or prevention programs that increase positive parenting and support family well-being may buffer the impact of ELA on accelerated epigenetic aging.[39] Overall, the current findings demonstrate that threat variables experienced early in life are more predictive of accelerated aging compared to deprivation, and highlight the critical impact of early life violence exposure and abuse on children's psychopathology outcomes in adolescence.

CRediT authorship contribution statement

Christina M. Hogan: Writing – review & editing, Writing – original draft, Project administration, Formal analysis, Data curation, Conceptualization. **Sarah M. Merrill:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Evelyn Hernandez Valencia:** Writing – review & editing. **Allison A. McHayle:** Writing – review & editing. **Michaela D. Sisitsky:** Writing – review & editing, Writing – original draft, Methodology. **Jennifer M. McDermott:** Writing – review & editing. **Justin Parent:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Data Sharing: Deidentified patient data and data dictionary will be made available at https://ffcws.princeton.edu.

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