



Risky family climates presage increased cellular aging in young adulthood

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ABSTRACT

A scientific consensus is emerging that children reared in risky family climates are prone to chronic diseases and premature death later in life. Few prospective data, however, are available to inform the mechanisms of these relationships. In a prospective study involving 323 Black families, we sought to determine whether, and how, childhood risky family climates are linked to a potential risk factor for later-life disease: increases in cellular aging (indexed by epigenetic aging). As hypothesized, risky family climates were associated with greater outflows of the stress hormones epinephrine and norepinephrine at ages 19 and 20 years; this, in turn, led to increases in cellular aging across ages 20–27 years. If sustained, these tendencies may place children from risky family climates on a trajectory toward the chronic diseases of aging.

1. Introduction

Growing up in an unsupportive, emotionally cold, and harsh family climate is a topic of increasing concern to scientists and physicians because this experience is linked to elevated blood pressure, poor metabolic profiles, cardiovascular disease, and psychiatric problems later in life (Chen et al., 2017). The risky family model gives a psychosocial account of the impact that stress during childhood exerts on health (Repetti et al., 2002). It posits that some families confer risk for later health problems by creating emotionally nonsupportive rearing climates. Such climates are hypothesized to influence the development of the body's stress response systems, calibrating the way in which individuals respond to threats throughout the life course (Repetti et al., 2011). Most of the research to date on risky family climates has focused on the hypothalamic-pituitary-adrenal axis, but studies in animal models demonstrate the importance of the sympathetic nervous system (SNS) as a mediator that connects exposure to risky family climates to long-term physical health outcomes (Manuck et al., 1995; Schloss et al., 2020; Sloan et al., 2008).

The SNS supports biobehavioral responses, such as fight or flight, that mobilize the body's resources to cope with threats. Everyday SNS

activity is typically indexed by measuring overnight urinary concentrations of the system's endproducts, the catecholamines epinephrine and norepinephrine (Evans and English, 2002). Although an immediate, short-term catecholamine burst is an adaptive response to environmental demands, studies in animal models indicate that excessive or prolonged sympathetic activation may contribute to health problems including heart disease, some cancers, and worsening of HIV/AIDS (Juster et al., 2010; Schloss et al., 2020).

The suggestion that risky family climates have a durable influence on the SNS that contributes to subsequent health outcomes has received little empirical attention (Matthews and Gallo, 2011). The available research has shown that overnight concentrations of catecholamines have been linked to living in poverty during childhood (Brody et al., 2013; Evans and English, 2002), being exposed to violence during adolescence (Wilson et al., 2002), and experiencing economic hardship and negative life events during adulthood (Cohen et al., 2012; Janicki-Deverts et al., 2007). Other relevant evidence comes from studies that construe SNS endproducts as biomarkers of stress exposure and relate them to health outcomes. This small body of work has described associations of SNS endproducts with shortened telomere lengths (Fair et al., 2017), mortality risk, and functional decline in old

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age (Reuben et al., 2000). Clearly, these literatures are still developing and findings are preliminary. However, on the basis of the available evidence, we reasoned that risky family climates would be associated with higher levels of the SNS endproducts epinephrine and norepinephrine, which, in turn, would forecast accelerated aging and declining health. Because this study focused on young adults, who seldom develop serious diseases, we considered an “intermediate” marker of health, increases in cellular aging.

To measure cellular aging, we used a recently developed biomarker derived from the DNA methylation of cells. This marker has been validated in cells from more than a dozen tissues and reflects the disparity between an individual’s biological and chronological ages (Horvath and Raj, 2018). Using this metric, faster cellular aging rates forecast heightened rates of cardiovascular disease, cancer, obesity, and all-cause mortality (Horvath and Raj, 2018). As a starting point in understanding variation in the development of cellular aging, recent research has shown that exposure to psychosocial adversity is associated with accelerated cellular aging during childhood and adolescence, and that children’s family environments may play a role in contributing to these effects (Brody et al., 2016a; Gettler et al., 2019; Javed et al., 2016; Jovanovic et al., 2017; Lawn et al., 2018; Sumner et al., 2019; Wolf et al., 2018). To date, this literature has focused primarily on concurrent associations between a family risky factor (e.g., harsh treatment) and cellular aging. The present study is the first of which we are aware to examine the mechanisms through which exposure to risky family climates during childhood is indirectly associated with increases in cellular aging during adulthood.

The study predictions were tested with a longitudinal cohort of rural Black youth from the southern United States who have a distinctive profile of characteristics. Risk factors include the economic hardships and limited opportunities endemic to many rural areas, isolation imposed by geographic distances, and limited access to physical and mental health services. For young Black adults living in the rural South, the transition to a productive career poses a transitional challenge. The transition routes to steady employment are unstructured and are left largely to individual initiative, in jobs that offer little training and few opportunities to advance on a stable career path (Silva, 2012). Previous research with this sample has shown that growing up in disadvantaged rural circumstances (Chen et al., 2016; Miller et al., 2015) and exposure to frequent encounters with racial discrimination in rural communities (Brody et al., 2016b) were associated prospectively with accelerated cellular aging at age 20. To test the hypotheses for the present study, the following data were collected. When youth were age 11 years, youth and caregivers provided data on risky family climates. At ages 19 and 20 years, youth collected overnight urine output from which epinephrine and norepinephrine outflows were assayed. When youth were 20 and 27 years of age, peripheral blood was collected to quantify increases in cellular aging.

2. Methods

2.1. Sample

Data for this study were drawn from the Strong African American Families Healthy Adults Project (SHAPE; Brody et al., 2013). Starting in 2001, SHAPE enrolled 667 Black children in fifth grade (mean age = 11.2 years, $SD = 0.3$) and each child’s primary caregiver. The families resided in nine rural counties in Georgia, where poverty rates are among the highest in the nation. Of the youth in the sample, 53% were female. At Wave 1, 80% of the caregivers had completed high school or earned a GED. Economically, these households can be characterized as working poor. The primary caregivers worked an average of 30.6 h per week and had a median household income of \$1612 per month; 42.3% of the families were living below federal poverty standards. In 2009–2010, when the youth had reached ages 19–20 years, a subgroup of 500 was randomly selected for a substudy of stress hormones and DNA

methylation. The selection of a random subsample was necessary because of financial constraints associated with the costs of assaying these biomarkers. Of these 500 participants, 399 (79.8%) provided an overnight urine sample and a blood sample. In 2017, when the participants’ mean age was 27 years, we re-assessed the cohort and obtained blood draws from 388 participants from which DNA methylation was assayed. The sample for the present study was composed of 323 participants (125 men and 198 women) from whom blood was drawn at both ages 20 and 27 years, and for whom data were available on the other study measures from ages 11–18. Compared with the original study cohort, the analytic sample had a higher percentage of female participants (61.3% vs. 52.8%); otherwise, the samples were similar on the other study variables. The University of Georgia’s Institutional Review Board approved the protocol, and written informed consent was obtained from participants and their caregivers at all assessments.

2.2. Data collection procedures

A Black field researcher who was also a certified phlebotomist went to each participant’s home to draw blood samples when participants were 20 and 27 years of age, from which cellular aging was assessed. Each parent was paid \$100 after the assessment, and each youth was paid \$160 after the assessment and blood draw. Informed consent forms were completed at all data collection points. The University of Georgia’s Institutional Review Board reviewed and approved all study procedures.

2.3. Measures

2.3.1. Risky family climates

When participants were 11 years of age, risky family climates were assessed using indicators of parental depression, harsh-inconsistent parenting, and low parental warmth, support, and involvement. Parents reported their depressive symptoms using the Center for Epidemiologic Studies–Depression scale (CES–D; Radloff, 1977), which is widely used with community samples. Cronbach’s alpha was .83. Harsh-inconsistent parenting was measured using youth reports on a scale that assessed parents’ use of slapping, hitting, and shouting to discipline the youth (Brody et al., 2001). Cronbach’s alpha was .55. Low internal consistency is common in the literature for measures of harsh parenting because these disciplinary practices have low base rates (Brody et al., 2001; Lorber and Slep, 2018). Parental warmth, support, and involvement were measured using youth reports on three indicators. First, the 20-item Interaction Behavior Questionnaire (Prinz et al., 1979) assessed the level of encouragement and communication in the parent-child relationship. Cronbach’s alpha was .78. The second and third indicators were developed by the authors. The second assessed the frequency and quality of communication in parent-child interactions (Brody et al., 2001). Cronbach’s alpha was .76, whereas the third assessed structure and rules in the household (Brody et al., 2006). Cronbach’s alpha was .66. To form a risky family climate composite, we reverse coded these three parenting indicators and then standardized and summed them with the parental depression and harsh-inconsistent items. Together, these indicators form the risky family climate indicator, which is characterized by elevated levels of parent depression, harsh parenting, and low levels of warmth, communication, involvement, and routines. This characterization of risky family climates is consistent with those found in the literature (Repetti et al., 2002; Repetti et al., 2011). As a check on the nonclinical status of the sample, we obtained retrospective reports of adverse childhood experiences of maltreatment and neglect using the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994). The study sample’s scores represented the following percentages of the moderate to severe to extreme levels for each category: emotional abuse, 6.5%; physical abuse, 5.3%; sexual abuse, 5.9%; emotional neglect, 6.2%, and physical neglect, 7.1%. These data suggested that maltreatment was low in this sample.

2.3.2. Catecholamines

At ages 19 and 20 years, participants' overnight urinary catecholamine levels were assayed. Beginning on the evening of data collection, all urine that the young adult voided from 8 p.m. to 8 a.m. was stored on ice in a container with metabisulfite as a preservative. Urine was delivered to the Emory University Hospital medical laboratory in Atlanta, Georgia, for assaying. Epinephrine and norepinephrine were assayed with high-pressure liquid chromatography with electrochemical detection (Riggin and Kissinger, 1977). For epinephrine, mean intra-assay coefficients of variation (CV) for nonsequential duplicates are 27.1% (< 40 pg/ml), 13.5% (40–80 pg/ml), and 9.6% (> 80 pg/ml); pooled samples mean inter-assay CV for 60–140 pg/ml is 16.3%; and blanks read 7.0 ± 14.5 (SD) pg/ml. For norepinephrine, mean intra-assay CVs for nonsequential duplicates are 6.6% (< 400 pg/ml), 6.5% (400–800 pg/ml), and 7.1% (> 800 pg/ml); pooled mean inter-assay CV for 300–500 pg/ml is 10.3%; and blanks read 6.0 ± 10.3 (SD) pg/ml. Creatinine was assayed to control for differences in body size and incomplete urine voiding (Tietz, 1976). The epinephrine and norepinephrine values were first averaged across ages 19 and 20 years and then were standardized and summed to form a catecholamine composite.

2.3.3. Accelerated cellular aging

When participants were ages 20 and 27 years, a certified phlebotomist went to each of their homes in the morning to draw a fasting blood sample. Participants were requested not to eat or drink after midnight prior to the blood draw. Peripheral blood mononuclear cells (PBMC) were isolated through density-gradient centrifugation, and DNA methylation was subsequently assessed with the Illumina Infinium (Sequenom, Inc., San Diego, CA, USA) HumanMethylation450 Beadchip at age 20 and HumanMethylationEPIC850 Beadchip at age 27. Recent research indicated that DNAm age correlations with chronological age are similar across the EPIC and 450K chips (Logue et al., 2017). The beta value at each CpG locus was calculated as the ratio of the intensity of the methylated probe to the sum of intensities of the methylated and unmethylated probes. Quantile normalization methods were used, with separate normalization of Type I and Type II assays, because this approach has been found to produce marked improvement for the Illumina array in detection of relationships by correcting distributional problems inherent in the manufacturer's default method for calculating the beta value. We then assessed cellular aging using Horvath and colleagues' (2018) skin and blood clock. This estimates an individual's biological age based on DNA methylation assessments at 391 CpGs scattered across the human genome; it was analyzed using the online "New Methylation Age Calculator" (<https://dnamage.genetics.ucla.edu/>) with the Advanced Analysis and the Normalize Data options. To transform the skin and blood clock into a measure of accelerated cellular aging, we regressed the clock on chronological age, resulting in a measure of accelerated cellular aging that is adjusted to correlate with chronological age at 0. A positive value on this variable indicates accelerated cellular aging in years, whereas a negative value indicates decelerated aging in years. Because the PBMC pool contains multiple types of cells, whose distribution varies across people, we included estimates of cell type as covariates in regression models. These estimates were bioinformatically derived from DNA methylation profiles by the cellular age calculator (Horvath and Levine, 2015). Blood cell types (CD4T, CD8T, Monocytes, Granulocytes, B cells and natural killer cells) were imputed using the reference-based method described by Houseman et al. (2012). For naive and exhausted T cells, and plasma blasts, the estimations were based on the Horvath method (2015). The associations between cell types and the Horvath skin and blood clock were as follows: at ages 20 and 27 separately: CD8.naive, $\beta = -0.26$ and -0.19 ; CD8pCD28nCD45RA.n, $\beta = 0.37$ and 0.33 ; PlasmaBlast, $\beta = -0.47$ and -0.06 ; CD4T, $\beta = 0.37$ and 0.13 ; NK, $\beta = 0.21$ and 0.26 ; Mono, $\beta = 0.22$ and 0.07 ; Gran, $\beta = 0.57$ and -0.03 .

2.3.4. C-reactive protein (CRP)

At age 20, serum levels of CRP were determined using a Duo Set Kit (DY1707; R&D Systems, Minneapolis, MN, USA) according to the manufacturer's directions. A normal concentration of CRP in healthy human serum is usually lower than 10 mg/L. No participants had CRP levels outside the normal range. Because CRP is characterized by a skewed distribution (skewness = 1.90, kurtosis = 2.94), we applied a log transformation to normalize the readings (skewness = 0.91, kurtosis = -0.31 after the transformation).

2.3.5. Covariates

Sex was dummy coded; male participants were coded 1 and female participants were coded 0. Family SES-related risk at age 11 was measured as the sum of six indicators (0 if absent, 1 if present; see Brody et al., 2013): current family poverty, primary caregiver's noncompletion of high school or an equivalent, primary caregiver current unemployment, single-parent family structure, current receipt of Temporary Assistance for Needy Families, and income rated by the caregiver as inadequate to meet all needs. The SHAPE cohort was initially recruited for a randomized controlled trial of a family-oriented intervention to prevent youth behavior problems and substance abuse. Participation in the intervention was not associated with any of the outcomes. To minimize any residual confounding, however, we included a dichotomous covariate reflecting intervention condition (treatment versus control) in all models. At ages 20 and 27, body mass index (BMI) and smoking were assessed because both variables contribute to cellular aging. Trained research staff measured weight using a standard home scale and height using a tape measure in a standardized way. BMI was calculated as weight in kilograms divided by the square of height in meters. Youths reported their past-month cigarette use on a rating scale ranging from 0 = none at all to 7 = more than 2 packs a day. Past-month cigarette use was log-transformed because its distribution was skewed.

2.3.6. Plan of analysis

Linear regression models were executed to test the study hypotheses. An initial, preliminary model was designed to examine the possibility that risky family climates at age 11 were indirectly linked to cellular aging at age 20 through catecholamine levels at ages 19 and 20 years. The second model tests the study hypothesis that residing in a risky family climate at age 11 years would forecast higher catecholamine levels at ages 19–20 years. Catecholamines, in turn, would be associated with participants' cellular aging at age 27 years, with youth cellular aging at age 20 years controlled. The hypotheses were tested using regression-based indirect effect analysis procedures (Hayes, 2013). To do this, the regression coefficients were calculated for the association between risky family climates and catecholamines (path a). Second, a regression coefficient for the association of catecholamines with cellular aging was calculated (path b). Finally, the indirect effect in which catecholamines serve as a link to connect risky family climates to cellular aging was quantified as the product of the two regression coefficients ($a \times b$). In addition, nonparametric bootstrapping was used to obtain the bias-corrected and accelerated (BCA) confidence intervals of parameter estimates for significance testing (Preacher et al., 2007). The parameter estimate was calculated 1000 times using random sampling with replacement to build a sampling distribution. In all models, sex, family SES-related risk, and intervention status were included as covariates. The model examining the association between catecholamines and cellular aging also included BMI and smoking at ages 20 and 27 years as additional covariates. We used GPower to obtain power estimates for the hypothesized models described above. For the study sample of 323, power estimates exceeded 0.80 for detecting effect sizes as small as 0.024. Thus, the study had sufficient power to test the planned hypotheses. All analyses were conducted using Mplus (Muthén and Muthén, 1998–2012).

Table 1
Correlations and descriptive statistics among study variables.

Variable	Mean (SD)	n (%)	Correlations											
			1	2	3	4	5	6	7	8	9			
1. Sex, male		125 (38.7%)	—											
2. Assignment, intervention		202 (62.5%)	.011	—										
3. Risky family climates (age 11)	0 (2.715)		.004	.107	—									
4. Family SES-related risk (age 11)	2.443 (1.434)		-0.018	.074	.161**	—								
5. Catecholamines (ages 19 & 20)	0 (1.788)		.163**	-.042	.142*	-.027	—							
6. Smoking (age 20)	0.096 (0.202)		.341***	.005	.053	.082	.076	—						
7. BMI (age 20)	29.164 (8.718)		-0.149**	.020	.046	.143*	.014	-0.060	—					
8. CRP (age 20)	0.745 (0.704)		-0.271***	.045	.111*	.053	-0.032	.019	.583***	—				
8. Cellular aging (age 20)	-0.099 (3.182)		.122*	-.006	.027	.006	.064	.004	.008	.042	—			
9. Cellular aging (age 27)	0.056 (2.373)		.018	-0.034	-0.034	.051	.148**	-0.024	.041	.083	.459***	—		

N = 323. Pearson correlations are presented for continuous variables; Spearman’s correlations are presented for dichotomous variables. SD = standard deviation. SES = socioeconomic status. BMI = body mass index. CRP = C-reactive protein.

* $p < .05$.
 ** $p < .01$.
 *** $p < .001$.

Table 2
Indirect effects of risky family climates at age 11 on cellular aging at age 27 (controlling for age 20) through catecholamine levels at ages 19 and 20.

Predictors	Catecholamines (ages 19 & 20)		Cellular Aging (age 27)	
	b	[95% CI]	b	[95% CI]
1. Sex, male	.565**	[.187, 1.019]	-0.161	[-0.622, .359]
2. Assignment, intervention	-0.260	[-0.741, .124]	-0.207	[-0.698, .292]
3. Family SES-related risk (age 11)	-0.054	[-0.203, .081]	.106	[-0.055, .273]
4. Risky family climates (age 11)	.104*	[.030, .191]	-0.062	[-0.151, .027]
5. BMI (age 20)	—	—	.006	[-0.020, .030]
6. Smoking (age 20)	—	—	-0.296	[-1.574, .857]
7. Cellular aging (age 20)	—	—	.340***	[.213, .483]
8. Catecholamines (ages 19&20)	—	—	.179**	[.052, .306]

N = 323; b = unstandardized regression coefficient; CI = confidence interval. SES = socioeconomic status. BMI = body mass index.

* $p < .05$.
 ** $p < .01$.
 *** $p < .001$.

3. Results

Bivariate correlations (Pearson correlations for continuous variables and Spearman correlations for dichotomous variables) and descriptive statistics for the study variables are presented in Table 1. Preliminary analyses showed that childhood risky family climates (at age 11) were associated with higher catecholamine outflows (at ages 19–20). However, the contemporaneous association of catecholamine outflows with cellular aging was not significant. A different pattern of results was found when the regression models were applied to changes in cellular aging across ages 20–27. The results of these regression models (Table 2) revealed that risky family climates (at age 11) were associated with higher catecholamine levels (at ages 19–20; $b = 0.104$, 95% CI [.030, .191], $p = .014$). These catecholamine levels, in turn, were positively associated with cellular aging (at age 27, with age 20 cellular aging controlled): $b = 0.179$, 95% CI [.052, .306], $p = .004$. The indirect effect of risky family climates (at age 11) on changes in cellular aging (from ages 20–27) via catecholamine levels (at ages 19–20) was significant: Indirect effect = 0.019, 95% CI [.004, .043] (see Fig. 1). These results did not change when the covariates, BMI and smoking, assessed at age 27 were included in the analyses in place of the same covariates assessed at age 20.

Finally, to clarify further the study findings, we also considered the possibility that catecholamine levels were associated with low-grade inflammation, which, in turn, contributed to cellular aging (Jones et al., 2015). In a separate model, we included low-grade inflammation (CRP) at age 20 as a mediator linking catecholamine levels with changes in cellular aging. However, catecholamine levels were not associated with CRP levels ($b = -.001$, 95% CI [-.062, .047], $p = .975$), and CRP

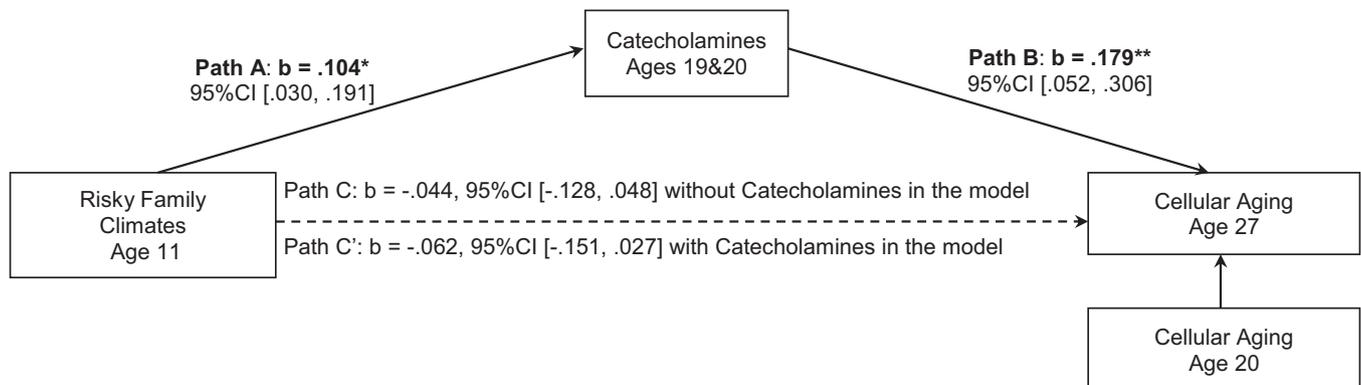


Fig. 1. The indirect effect of risky family climates at age 11 on youths’ cellular aging at age 27 (controlling for age 20) through catecholamine levels at ages 19 and 20. Statistically significant pathways indicated by boldface type. b = unstandardized regression coefficient; CI = confidence interval. * $p < .05$. ** $p < .01$.

levels were not associated with changes in cellular aging ($b = .292$, 95% CI $[-.110, .744]$, $p = .181$). The indirect/mediating pathways did not reach statistical significance: indirect effect = 0, 95% CI $[-.023, .019]$. Thus, we found no evidence, in the analyses conducted in this study, to support a scenario in which low-grade inflammation at age 20 serves as a mediator linking catecholamine levels at ages 19 and 20 with increases in cellular aging.

4. Discussion

A growing body of evidence indicates that children reared in risky family climates are vulnerable to chronic disease when they reach the later decades of life. Although the mechanisms underlying these observations are not well understood, one prominent hypothesis states that risky family climates contribute to persistent and excessive activity of the SNS, the hormonal products of which affect tissue and organ functions in a manner that contributes to worsening health (McEwen, 1998; Repetti et al., 2011). Our data support this notion by showing that, at ages 19 and 20, youth who were reared in risky families displayed elevated tonic output of epinephrine and norepinephrine; this output, in turn, was associated with increases in cellular aging, as measured using DNA methylation across ages 20–27 years. Moreover, these findings retained their significance when covariates that are associated with cellular aging—smoking, BMI, and socioeconomic risk—were included in the data analyses. The study's prospective design also avoided a common limitation in this literature, reliance on retrospective assessments of childhood family experiences. Recall bias, inaccurate descriptions of family climates, and lack of information regarding age of exposure can undermine strong inferences (Reuben et al., 2016).

The mechanisms underlying the links among risky family climates, catecholamine levels, and increases in cellular aging are undefined. Mechanistically oriented research could advance understanding of the ways in which elevated catecholamine levels, presaged by risky family climates, contribute to increases in cellular aging. For example, scientists performing basic research have described the capacity of catecholamines and other end products of stress-response systems to modify the chromatin architecture of leukocytes by altering the enzymatic activity of DNA methyltransferases, histone deacetylases, and acetyltransferases. SNS endproducts could also affect cellular aging by changing patterns of inflammatory activity or oxidative stress (Barnes and Adcock, 2009). We explored the possibility that CRP, a marker of systemic inflammation, might serve as a mediator connecting catecholamine levels with increases in cellular aging. Although our findings did not support CRP mediation, it will be important in follow-up studies to evaluate more thoroughly ways in which exposures to sympathetic activation over time contribute to accelerated cellular aging through alterations of DNA architecture and through changes in inflammatory activity and oxidative stress.

Additional research is also needed to explore the contributions of psychological vulnerabilities that risky family climates foster—including variations in social competence, emotion regulation, and attribution biases—to the maintenance of high levels of sympathetic activation and to increases in cellular aging over time. When established, we expect these vulnerabilities to contribute to persistent catecholamine outflows and, in turn, to increases in cellular aging across time. We were unable to test this hypothesis in this study because we did not assess the psychological vulnerabilities associated with growing up in a risky family climate. A follow-up study with multiple waves of psychological, neuroendocrine, and cellular aging data would be ideally suited to test these pathways.

Finally, education and support for parents in risky family climates to learn and practice important parenting skills have the potential to promote supportive behaviors, parenting confidence, and children's well-being. Programs that promote strong skills for parents, such as the Family Check-Up program, Triple-P (Positive Parenting Program), Incredible Years, and the Strong African American Families Program,

have been shown to improve parenting skills, improve family emotional climates, and enhance children's ability to cope with adversity (Van Ryzin et al., 2016). The findings of the current study highlight the importance of access to these and other prevention programs in primary care contexts, schools, and community settings. This is particularly important because emerging research demonstrates the potential of family-centered programs to influence a range of outcomes, including inflammation (Miller et al., 2014), the structure of limbic regions (Hanson et al., 2019), and cardiometabolic health (Chen et al., 2018).

The study's results should be interpreted in the context of its limitations. First, it is not known whether the results generalize to other racial and ethnic groups living in rural or urban areas. Second, risky family climates could act as a proxy for other experiences (e.g., early caregiving) or allelic variations that are involved in adaptation. Testing an array of variables that were not included in this study should be a priority in future research. Finally, it is unclear why catecholamine levels at age 20 were not associated concurrently with cellular aging. Perhaps a lengthier exposure to elevated catecholamines is necessary for an association to emerge. These limitations notwithstanding, the results provide some clues about the ways in which risky family climates during childhood carry forward to increase the chances of later health problems.

CRedit authorship contribution statement

Gene Brody took part in the study's conceptualization, project administration, and in writing the original draft. Tianyi Yu conducted formal statistical analysis. Edith Chen took part in reviewing and editing the manuscript. Michael Kobor contributed to the development of the methodology and took part in reviewing and editing the manuscript. Steven Beach, Man-Kit Lei, Ashley Barr, David Lin, and Gregory Miller took part in reviewing and editing the manuscript. Gregory Miller also took part in the study's conceptualization.

Declaration of Competing Interest

None.

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References

- Barnes, P.J., Adcock, I.M., 2009. Glucocorticoid resistance in inflammatory diseases. *Lancet* 373, 1905–1917.
- Bernstein, D.P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., Saperito, E., Ruggiero, J., 1994. Initial reliability and validity of a new retrospective measure of child abuse and neglect. *Am. J. Psychiatry* 151, 1132–1136.
- Brody, G.H., Chen, Y.-f., Murry, V.M., Ge, X., Simons, R.L., Gibbons, F.X., Gerrard, M., Cutrona, C.E., 2006. Perceived discrimination and the adjustment of African American youths: A five-year longitudinal analysis with contextual moderation effects. *Child Dev.* 77, 1170–1189.
- Brody, G.H., Ge, X., Conger, R.D., Gibbons, F.X., Murry, V.M., Gerrard, M., Simons, R.L., 2001. The influence of neighborhood disadvantage, collective socialization, and parenting on African American children's affiliation with deviant peers. *Child Dev.* 72, 1231–1246.
- Brody, G.H., Miller, G.E., Yu, T., Beach, S.R.H., Chen, E., 2016a. Supportive family environments ameliorate the link between racial discrimination and epigenetic aging: a replication across two longitudinal cohorts. *Psychol. Sci.* 27, 530–541.
- Brody, G.H., Yu, T., Chen, E., Miller, G.E., Kogan, S.M., Beach, S.R.H., 2013. Is resilience only skin deep? Rural African Americans' socioeconomic status-related risk and competence in preadolescence and psychological adjustment and allostatic load at age 19. *Psychol. Sci.* 24, 1285–1293.
- Brody, G.H., Yu, T., Miller, G.E., Chen, E., 2016b. Resilience in adolescence, health, and psychosocial outcomes. *Pediatrics* 138. Article e20161042.
- Chen, E., Brody, G.H., Miller, G.E., 2017. Childhood close family relationships and health. *Am. Psychol.* 72, 555–556.
- Chen, E., Miller, G.E., Yu, T., Brody, G.H., 2016. The Great Recession and health risks in African American youth. *Brain Behav. Immun.* 53, 234–241.

- Chen, E., Miller, G.E., Yu, T., Brody, G.H., 2018. Unsupportive parenting moderates the effects of family psychosocial intervention on metabolic syndrome in African American youth. *Int. J. Obes.* 42, 634–640.
- Cohen, S., Janicki-Deverts, D., Doyle, W.J., Miller, G.E., Frank, E., Rabin, B.S., 2012. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *PNAS* 109, 5995–5999.
- Evans, G.W., English, K., 2002. The environment of poverty: multiple stressor exposure, psychophysiological stress, and socioemotional adjustment. *Child Dev.* 73, 1238–1248.
- Fair, B., Mellon, S.H., Epel, E.S., Lin, J., Révész, D., Verhoeven, J.E., Penninx, B.W.J.H., Reus, V.I., Rosser, R., Hough, C.M., Mahan, L., Burke, H.M., Blackburn, E.H., Wolkowitz, O.M., 2017. Telomere length is inversely correlated with urinary stress hormone levels in healthy controls but not in un-medicated depressed individuals: preliminary findings. *J. Psychosom. Res.* 99, 177–180.
- Gettler, L.T., Sarma, M.S., Lew-Levy, S., Bond, A., Trumble, B.C., Boyette, A.H., 2019. Mothers' and fathers' joint profiles for testosterone and oxytocin in a small-scale fishing-farming community: Variation based on marital conflict and paternal contributions. *Brain Behav.* 9. Article e01367.
- Hanson, J.L., Gilmore, A.D., Yu, T., Holmes, C.J., Hollowell, E.S., Barton, A.W., Beach, S. R.H., Galván, A., MacKillop, J., Windle, M., Chen, E., Miller, G.E., Sweet, L.H., Brody, G.H., 2019. A family focused intervention influences hippocampal-prefrontal connectivity through gains in self-regulation. *Child Dev.* 90, 1389–1401.
- Hayes, A.F., 2013. *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-based Approach*. Guilford Press, New York.
- Horvath, S., Levine, A.J., 2015. HIV-1 infection accelerates age according to the epigenetic clock. *J. Infect. Dis.* 212 (10), 1563–1573.
- Horvath, S., Raj, K., 2018. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. *Nat. Rev. Genet.* 19, 371–384.
- Houseman, E.A., Accomando, W.P., Koestler, D.C., Christensen, B.C., Marsit, C.J., Nelson, H.H., Wiencke, J.K., Kelsey, K.T., 2012. DNA methylation arrays as surrogate measures of cell mixture distribution. *BMC Bioinforma.* 13. Article 86.
- Janicki-Deverts, D., Cohen, S., Adler, N.E., Schwartz, J.E., Matthews, K.A., Seeman, T.E., 2007. Socioeconomic status is related to urinary catecholamines in the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Psychosom. Med.* 6, 514–520.
- Javed, R., Chen, W., Lin, F., Liang, H., 2016. Infant's DNA methylation age at birth and epigenetic aging accelerators. *Biomed. Res. Int.* 2016. Article 4515928.
- Jones, M.J., Goodman, S.J., Kobor, M.S., 2015. DNA methylation and healthy human aging. *Aging Cell* 14, 924–932.
- Jovanovic, T., Vance, L.A., Cross, D., Knight, A.K., Kilaru, V., Michopoulos, V., Klengel, T., Smith, A.K., 2017. Exposure to violence accelerates epigenetic aging in children. *Sci. Rep.* 7. Article 8962.
- Juster, R.-P., McEwen, B.S., Lupien, S.J., 2010. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci. Biobehav. Rev.* 35, 2–16.
- Lawn, R.B., Anderson, E.L., Suderman, M., Simpkin, A.J., Gaunt, T.R., Teschendorff, A.E., Widschwendter, M., Hardy, R., Kuh, D., Relton, C.L., Howe, L.D., 2018. Psychosocial adversity and socioeconomic position during childhood and epigenetic age: analysis of two prospective cohort studies. *Hum. Mol. Genet.* 27, 1301–1308.
- Logue, M.W., Smith, A.K., Wolf, E.J., Maniates, H., Stone, A., Schichman, S.A., McGlinchey, R.E., Milberg, W., Miller, M.W., 2017. The correlation of methylation levels measured using Illumina 450K and EPIC BeadChips in blood samples. *Epigenomics* 9, 1363–1371.
- Lorber, M.F., Slep, A.M.S., 2018. The reliability paradox of the Parent-Child Conflict Tactics corporal punishment subscale. *J. Fam. Psychol.* 32, 145–150.
- Manuck, S.B., Marsland, A.L., Kaplan, J.R., Williams, J.K., 1995. The pathogenicity of behavior and its neuroendocrine mediation: an example from coronary artery disease. *Psychosom. Med.* 57, 275–283.
- Matthews, K.A., Gallo, L.C., 2011. Psychological perspectives on pathways linking socioeconomic status and physical health. *Annu. Rev. Psychol.* 62, 501–530.
- McEwen, B.S., 1998. Protective and damaging effects of stress mediators. *NEJM* 338, 171–179.
- Miller, G.E., Murphy, M.L.M., Cashman, R., Ma, R., Ma, J., Arevalo, J.M.G., Kobor, M.S., Cole, S.W., 2014. Greater inflammatory activity and blunted glucocorticoid signaling in monocytes of chronically stressed caregivers. *Brain Behav. Immun.* 14, 191–199.
- Miller, G.E., Yu, T., Chen, E., Brody, G.H., 2015. Self-control forecasts better psychosocial outcomes but faster epigenetic aging in low-SES youth. *PNAS* 112, 10325–10330.
- Muthén, B.O., Muthén, L.K., 1998-2012. *Mplus users' guide, version 7*. Muthén & Muthén, Los Angeles, CA.
- Preacher, K.J., Rucker, D.D., Hayes, A.F., 2007. Addressing moderated mediation hypotheses: theory, methods, and prescriptions. *Multivar. Behav. Res.* 42, 185–227.
- Prinz, R.J., Foster, S.L., Kent, R.N., O'Leary, K.D., 1979. Multivariate assessment of conflict in distressed and nondistressed mother-adolescent dyads. *J. Appl. Behav. Anal.* 12, 691–700.
- Radloff, L.S., 1977. The CES-D scale: a self-report depression scale for research in the general population. *Appl. Psychol. Meas.* 1, 385–401.
- Repetti, R.L., Robles, T.F., Reynolds, B., 2011. Allostatic processes in the family. *Dev. Psychopathol.* 23, 921–938.
- Repetti, R.L., Taylor, S.E., Seeman, T.E., 2002. Risky families: family social environments and the mental and physical health of offspring. *Psychol. Bull.* 128, 330–336.
- Reuben, A., Moffitt, T.E., Caspi, A., Belsky, D.W., Harrington, H., Schroeder, F., Hogan, S., Ramrakha, S., Poulton, R., Danese, A., 2016. Lest we forget: comparing retrospective and prospective assessments of adverse childhood experiences in the prediction of adult health. *J. Child Psychol. Psychiatry* 57, 1103–1112.
- Reuben, D.B., Talvi, S.L.A., Rowe, J.W., Seeman, T.E., 2000. High urinary catecholamine excretion predicts mortality and functional decline in high-functioning, community-dwelling older persons: MacArthur Studies of Successful Aging. *J. Gerontol. A Biol. Sci. Med. Sci.* 55, M618–M624.
- Riggin, R.M., Kissinger, P.T., 1977. Determination of catecholamines in urine by reverse-phase liquid chromatography with electrochemical detection. *Anal. Chem.* 49, 2109–2111.
- Schloss, M.J., Swirski, F.K., Nahrendorf, M., 2020. Modifiable cardiovascular risk, hematopoiesis, and innate immunity. *Circ. Res.* 126, 1242–1259.
- Silva, J.M., 2012. Constructing adulthood in an age of uncertainty. *Am. Sociol. Rev.* 77, 505–522.
- Sloan, E.K., Capitanio, J.P., Cole, S.W., 2008. Stress-induced remodeling of lymphoid innervation. *Brain Behav. Immun.* 22, 15–21.
- Sumner, J.A., Colich, N.L., Uddin, M., Armstrong, D., McLaughlin, K.A., 2019. Early experiences of threat, but not deprivation, are associated with accelerated biological aging in children and adolescents. *Biol. Psychiatry* 85, 268–278.
- Tietz, N.W., 1976. *Fundamentals of Clinical Chemistry*, second ed. Saunders,, Philadelphia, PA.
- Van Ryzin, M.J., Kumpfer, K.L., Fosco, G.M., Greenberg, M.T. (Eds.), 2016. *Family-Based Prevention Programs for Children and Adolescents: Theory, Research, and Large-scale Dissemination*. Psychology Press.
- Wilson, D.K., Klierer, W., Teasley, N., Plybon, L., Sica, D.A., 2002. Violence exposure, catecholamine excretion, and blood pressure nondipping status in African American male versus female adolescents. *Psychosom. Med.* 64, 906–915.
- Wolf, E.J., Maniates, H., Nugent, N., Maihofer, A.X., Armstrong, D., Ratanatharathorn, A., Ashley-Koch, A.E., Garrett, M., Kimbrel, N.A., Lori, A., VA Mid-Atlantic MIRECC Workgroup, Aiello, A.E., Baker, D.G., Beckham, J.C., Boks, M. P., Galea, S., Geuze, E., Hauser, M.A., Kessler, R.C., Koenen, K.C., Miller, M.W., Ressler, K.J., Risbrough, V., Rutten, B.P.F., Stein, M.B., Ursano, R.J., Vermetten, E., Vinkers, C.H., Uddin, M., Smith, A.K., Nievergelt, C.M., Logue, M.W., 2018. Traumatic stress and accelerated DNA methylation age: a meta-analysis. *Psychoneuroendocrinology* 92, 123–134.