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# Lifetime chronic stress exposures, stress hormones, and biological aging: Results from the Midlife in the United States (MIDUS) study

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ABSTRACT

Psychosocial stress and adversity have been linked to accelerated aging and increased risk for age-related diseases. Animal and *in vitro* studies have shown that exposure to stress hormones (catecholamines, glucocorticoids) can impact biological aging processes such as DNA damage and cellular senescence, suggesting they play a key role in links between stress and aging; however, these associations have not been well investigated in humans. We examined cross-sectional associations between chronic stress exposures, stress hormones, and biological aging markers in midlife adults and whether stress hormones mediated associations between stress and aging. Participants were 531 adults aged 26–78 years ($M_{age}$ = 53.9, 50.1% female) in the nationally representative Midlife in the United States Refresher cohort. They reported chronic stress exposures in childhood and adulthood (Stressful Life Event Inventory) and provided 12-hour urine samples used to assess norepinephrine, epinephrine, and cortisol. RNA sequencing of peripheral blood mononuclear cells derived aging biomarkers: the DNA damage response (DDR; 30-gene composite), cellular senescence signal $p16^{INK4a}$ (*CDKN2A*), and the pro-inflammatory senescence-associated secretory phenotype (SASP; 57-gene composite). Regression models adjusting for age, sex, race/ethnicity, BMI, smoking status, alcohol use, and medications revealed that more childhood exposures were associated with higher norepinephrine ($\beta = 0.09$, $p = 0.04$), independent from adult exposures. Higher norepinephrine was associated with elevated DDR expression ($\beta = 0.17$, $p < 0.001$). Higher norepinephrine ($\beta = 0.14$, $p = 0.003$) and epinephrine ($\beta = 0.10$, $p = 0.02$) were both associated with elevated SASP expression. Statistical mediation analyses implicated elevated norepinephrine as a plausible mediator of associations between childhood exposures and both DDR (unstandardized $b = 0.005$, 95% CI [0.0002, 0.011]) and SASP ($b = 0.002$, 95% CI [0.0001, 0.05]). Findings provide preliminary evidence in humans that stress hormones may impact key biological aging processes and may be a mechanism linking chronic stress exposures in childhood to accelerated aging later in life.

## 1. Introduction

Chronic stress has been described as exposure to a stressful life event that is prolonged or repeated over an extended period of time, such as the death of a loved one, having a parent with substance use problems, or experiencing a natural disaster. (Miller et al., 2011; Hostinar et al., 2015; Epel et al., 2018) Research suggests that exposure to chronic stressors can leave lasting imprints on physiology, particularly during developmentally sensitive periods in childhood, (Miller et al., 2011) and exposures in both childhood and adulthood have been associated with increased risk for multiple age-related diseases, including cancer, (Felitti et al., 1998; Bellis et al., 2015; Pino et al., 2022) cardiovascular disease, (Felitti et al., 1998; Epel et al., 2006; Scott et al., 2011; Pierce et al., 2020) dementia, (Conde-Sala and Garre-Olmo, 2020; Schickedanz et al., 2022) and early mortality. (Brown et al., 2009; Chen et al., 2016; Puterman et al., 2020; Rod et al., 2020) An emerging literature suggests that accelerated biological aging may be one pathway through which chronic stress contributes to poor health outcomes. For instance, studies

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have linked stressful events in childhood and adulthood to key biological aging processes such as elevated markers of inflammation (e.g., C-reactive protein [CRP], interleukin-6 [IL-6], and tumor necrosis factor [TNF]-α), (Pino et al., 2022; Kiecolt-Glaser et al., 2011; Baumeister et al., 2016) shorter telomere length, (Kiecolt-Glaser et al., 2011; Epel et al., 2004; Tyrka et al., 2010; Shalev et al., 2013; Puterman et al., 2016; Révész et al., 2016; Ridout et al., 2018; Mayer et al., 2019; Woo et al., 2022) and accelerated epigenetic aging. (Hamlat et al., 2021; Marini et al., 2020; Tang et al., 2020; Harvanek et al., 2021; Joshi et al., 2023; McCrory et al., 2022; Sumner et al., 2023) Despite this growing literature, it is unclear whether these associations extend to other hallmarks of the aging process such as cellular senescence, which is a stable state of cell cycle arrest (Campisi and D'Adda Di Fagagna, 2007) that is thought to play an important role in the pathophysiology of age-related disease.

Stressors elicit physiological responses such as sympathetic nervous system (SNS) release of catecholamines (e.g., norepinephrine, epinephrine) and hypothalamic–pituitary–adrenal (HPA) axis release of glucocorticoids (e.g., cortisol). These stress hormones bind to cellular receptors that can modulate agingrelated biological processes such as inflammatory and metabolic activities that incur oxidative stress. (Hara et al., 2011; Aschbacher et al., 2013; Flaherty et al., 2017) Prolonged or unresolved cell stress can lead to excess DNA damage that initiates cellular senescence to prevent the replication of damaged cells that could develop into cancer or other malignancies. (Campisi and D'Adda Di Fagagna, 2007; Kirkland and Tchkonia, 2017; Maggiorani et al., 2017; Rodier and Campisi, 2011) Senescent cells exhibit increased expression of the intracellular protein and cell cycle inhibitor $p16^{INK4a}$. Importantly, senescent cells resist apoptosis and are associated with a heightened release of pro-inflammatory cytokines, chemokines, and growth factors termed the senescence-associated secretory phenotype (SASP), which is thought to be a primary source of chronic inflammation observed in older age ("inflammaging") (Campisi and D'Adda Di Fagagna, 2007; Coppé et al., 2010; Effros et al., 2005; Franceschi and Campisi, 2014) and a driver of age-related disease. (Rodier and Campisi, 2011; Franceschi and Campisi, 2014) Emerging research suggests that chronic stress can impact key processes in the cellular senescence pathway; however, although several studies have linked adulthood stressors such as professional school exams, bereavement, and informal caregiving to greater DNA damage and lower DNA repair capacity, (Aschbacher et al., 2013; Cohen et al., 2000; Forlenza et al., 2000; Irie et al., 2001; Irie et al., 2004; Knickelbein et al., 2008) only one study to date has examined senescence signal $p16^{INK4a}$, finding that chronic, perceived, and accumulated daily stress were associated with elevated $p16^{INK4a}$ expression in middle-aged parents. (Rentscher et al., 2019) In addition, most of these studies have investigated stress exposures during adulthood and have not yet examined associations between chronic stress in childhood and cellular senescence.

Animal and *in vitro* studies have shown that exposure to stress hormones (catechoamines, glucocorticoids) can also impact biological aging process such as DNA damage and cellular senescence, suggesting that they may mediate links between stress and aging. Specifically, mice that received a synthetic catecholamine, isoproterenol, had increased DNA damage in the thymus (Hara et al., 2011) and upregulated p21 expression, another marker of cellular senescence. (Katsuumi et al., 2018) In addition, *in vitro* studies with a variety of cell types have shown that exposure to catecholamines and cortisol increased DNA damage and decreased DNA damage repair activity in the cells. (O'Brien et al., 1993; Flint et al., 2007; Flint et al., 2013; Patel et al., 2015; Lamboy-Caraballo et al., 2020) Interestingly, one study found that exposure to cortisol suppressed the SASP in senescent cells, which the authors explained may have been due to the anti-inflammatory effects of cortisol. (Laberge et al., 2012) To date, there have been a few studies of stress hormones and biological aging in humans. For instance, elevated norepinephrine, epinephrine, and cortisol were associated with shorter telomeres in medically healthy women. (Epel et al., 2006) Other research has suggested that a lower cortisol/ACTH ratio was related to greater epigenetic aging in a large community-based sample. (Harvanek et al., 2021) In addition, a previous study that used data from the Midlife in the United States (MIDUS) II study (which did not include participants in the present study) found that elevated urinary norepinephrine and *lower* urinary cortisol mediated associations between childhood chronic stress exposures and peripheral markers of inflammation (a composite that included CRP, IL-6, fibrinogen, E-Selectin, and Intercellular Adhesion Molecule [ICAM]-1). (Hostinar et al., 2015) To our knowledge, however, research has not yet examined associations between stress hormones and cellular senescence.

The present study extends the literature on psychosocial stress and biological aging by investigating associations between lifetime chronic stress exposures, stress hormones, and cellular senescence—a hallmark of biological aging—in a large, nationally representative sample of middle-aged adults in the MIDUS Refresher 1 cohort. Whereas the majority of previous studies have focused on links between a stressor during childhood or adulthood and a single marker of biological aging, we aimed to examine associations between chronic stress exposures in both childhood and adulthood and several key molecular processes in the cellular senescence pathway, including gene expression of the DNA damage response (DDR), senescence signal $p16^{INK4a}$, and the pro-inflammatory SASP. We also aimed to investigate cross-sectional associations between urinary levels of stress hormones (norepinephrine, epinephrine, and cortisol) assessed over a 12-hour period—which are thought to reflect steady-state operating levels of sympathetic nervous system and HPA axis activity (Seeman et al., 1997; Stress and McEwen, 1998)—and markers of biological aging. Finally, as an exploratory aim of the study, we examined stress hormones as potential statistical mediators of associations between stress exposures and biological aging to inform future research involving longitudinal assessments of stress exposures, hormones, and biological aging. Based on previous human, animal, and *in vitro* research that has linked stress exposures and hormones to markers of biological aging, we hypothesized that participants who had experienced a higher number of chronic stressors in childhood and adulthood would show elevated basal levels of urinary stress hormones and gene expression profiles indicative of a greater senescent cell burden during midlife. We also hypothesized that higher urinary stress hormone levels would be associated with elevated expression of cellular senescence markers and may serve as statistical mediators of associations between chronic stress and biological aging.

## 2. Methods

### 2.1. Participants

The present study used data from the Midlife in the United States (MIDUS) study, a longitudinal, nationally representative study of over 7,000 U.S. adults that was developed to examine the role of behavioral, psychological, and social factors in age-related variations in health and well-being. From 2011 to 2014, the MIDUS Refresher 1 study recruited a national sample of 3,577 adults aged 25–74 years to replenish the original MIDUS baseline cohort, which included an oversampling of 508 African American adults from Milwaukee, Wisconsin to increase the racial diversity of the study. A subsample of these respondents ($n = 863$) also participated in the MIDUS Refresher Biomarker Project, which involved a comprehensive biomarker assessment. Of the 543 participants that had gene expression data available as part of the Biomarker Project, 11 were excluded from this analysis because they had an incomplete urine sample to assess stress hormones. One additional participant was excluded because they had a high BMI value and large discrepancy in their recorded height between study enrollment and the Biomarker Project assessment. Therefore, the final sample size for this study included 531 adults with complete questionnaire, gene expression, and norepinephrine data. Participants who were missing data for epinephrine ($n = 19$) or cortisol ($n = 9$) were excluded from those specific analyses only.

### 2.2. Procedure

Participants in the MIDUS Refresher 1 study completed a 30-minute phone interview followed by a set of self-administered questionnaires to assess demographic, psychosocial, and physical and mental health information. As part of the MIDUS Refresher Biomarker Project, participants stayed for 24 h at a regional Clinical Research Unit at either the University of California, Los Angeles, Georgetown University, or University of Wisconsin-Madison. To assess stress hormones, participants provided a urine sample over a 12-hour collection period from 7:00 p.m. to 7:00 a.m. On the morning of the second day, participants also provided a fasting blood sample between 6:30 and 7:00 a.m. that was used to assess markers of biological aging. Blood samples were collected in a BD Vacutainer CPT tube, from which peripheral blood mononuclear cells (PBMCs) were isolated and stored in a −60°C to −80°C freezer until shipped on dry ice to the MIDUS Biocore Lab. Samples were subsequently stored in a −65°C freezer until assayed, as described in the MIDUS Documentation for Blood, Urine, and Saliva Data for the MIDUS Refresher Biomarker Project, which is available at ICPSR (https://www.icpsr.umich.edu/icpsrweb/ICPSR/studies/36901) or via the MIDUS Colectica Portal (https://midus.colectica.org/). (Midlife in the United States Study, 2018) The average length of time between completion of the self-administered questionnaires and the biomarker collection was 1.85 years (SD = 0.75 years).

### 2.3. Measures

#### 2.3.1. Chronic stress exposures

As part of the self-administered questionnaire, participants completed the MIDUS Stressful Life Event Inventory, which was developed based on previously validated lifetime stress measures (Turner and Wheaton, 1995) to assess the frequency and age(s) at which they had experienced a checklist of stressful life events. We categorized the events into childhood chronic stress exposures (17 events; e.g., repeating a school year, parent divorce) that occurred when participants were less than 18 years of age, and adulthood chronic stress exposures (20 events; e.g., the death of a parent, being fired from a job) that occurred when participants were 18 years of age or older (see Supplemental Table S1 for complete list of exposures). (Chen et al., 2022) Based on this categorization and the age range of the present sample (i.e., 26–78 years), the childhood stressors occurred decades (i.e., 8–60 years) prior to the chronic stress and biomarker assessments for the study. The frequency of each type of stress exposure was summed to create a total score for childhood and adulthood exposures. If a participant reported that an exposure had occurred but could not recall the age at which it had occurred, the exposure was not included in the total score (20 instances total). Given the lower frequencies of scores greater than 4, we created a single category to represent 4 or more exposures so that the total scores for childhood and adulthood chronic stress exposures ranged from 0 to 4, consistent with previous research. (Hostinar et al., 2015).

#### 2.3.2. Stress hormones

High-performance liquid chromatography was used to fractionate the catecholamines (norepinephrine and epinephrine) and cortisol from the 12-hour urine samples. The catecholamines were quantified using electrochemical detection and cortisol was quantified using mass spectrometry. (Midlife in the United States Study, 2018) Levels of each stress hormone were adjusted for urinary creatinine, which was measured from the same urine sample using an enzymatic colorimetric assay. The inter-assay coefficient of variation (CV) for norepinephrine and epinephrine ranged from 10.4 to 16.8% and 12.6 to 18.6%, respectively. The inter-assay CV for cortisol ranged from 8.1 to 15.5%. Stress hormone values that exceeded three standard deviations from the mean were winsorized (norepinephrine: $n = 6$; epinephrine: $n = 5$; cortisol: $n = 5$) and a natural logarithmic transformation was applied to each variable to normalize the skewed distribution (all had a positive skew prior to transformation).

#### 2.3.3. Biological aging

To assess biological aging, specimens were assayed in 96-sample batches, with RNA extracted (Qiagen RNeasy) from the stored PBMCs, tested for suitable RNA yield (Nanodrop ND1000) and integrity (Agilent Bioanalyzer), and subjected to transcriptome profiling by RNA sequencing. (Midlife in the United States Study, 2021) To maximize measurement precision and accommodate as many samples as possible, the RNA sequencing used a highly efficient mRNA-targeted approach, with cDNA library preparation by Lexogen QuantSeq FWD 5′ gene counting assay and sequencing on an Illumina HiSeq 4000 instrument targeting >10 million single-strand 65-nucleotide reads per sample. Sequence reads were mapped to the consensus human transcriptome and quantified on a per-gene basis using the STAR aligner. (Dobin et al., 2013) Raw read counts for each gene were normalized to transcript rates per million total mapped reads (transcripts per million; TPM), log2 transformed, and screened by standard endpoint quality control metrics to exclude aberrant data ($r < 0.85$ of sample-specific transcriptome profile with other profiles). Data represent log2-transformed TPM values for all samples that passed endpoint quality screening. (Midlife in the United States Study, 2021).

The present analysis examined key molecular processes in the cellular senescence pathway, including the DNA damage response (DDR), senescence signal $p16^{INK4a}$, and the pro-inflammatory SASP. Senescence signal $p16^{INK4a}$ was assessed using transcript abundance of the $p16^{INK4a}$-encoding gene *CDKN2A*. (Rentscher et al., 2019; Liu et al., 2009; Rentscher et al., 2022) We also assessed *a priori*-defined sets of genes that previous research has shown are up-regulated during the DNA damage response (DDR; 30 genes; e.g., *BRCA1, RAD51, TP53, TERT, SIRT1*; full gene list appears in Supplemental Table S2) (Jackson and Bartek, 2009) and the senescence-associated secretory phenotype (SASP), which is comprised of pro-inflammatory cytokines, chemokines, growth factors, and proteases (57 genes; e.g., *IL6, CSF2, CCL8, IL8, CCL13*; full gene list appears in Supplemental Table S3). (Coppé et al., 2010) The MIDUS Refresher Biomarker Project includes DDR and SASP composite scores that were calculated by mean-centering and averaging gene expression values for the respective component genes (i.e., individual genes are not yet publicly available). (Midlife in the United States Study, 2021) This approach is consistent with previous research (Carroll et al., 2016) and higher scores indicate greater biological aging.

#### 2.3.4. Covariates

Several variables that might affect biological aging estimates were evaluated as covariates in the main analyses based on previous research, (Rentscher et al., 2019; Cole et al., 2015) including chronological age, biological sex, self-identified Black or African American race and Hispanic ethnicity, body mass index (BMI; $kg/m^2$), smoking status (never, previous, current), alcohol use in the past month (none, light/moderate, heavy; based on current NIAAA guidelines, heavy alcohol use was defined as consuming more than 4 drinks on any day or more than 14 drinks per week for men and consuming more than 3 drinks on any day or more than 7 drinks per week for women; any other alcohol use that did not meet these criteria was defined as light/moderate use) (National Institute on Alcohol Abuse and Alcoholism, 2023) and number of self-reported prescription medications at the time of the Biomarker Project assessment.[1] Sensitivity analyses also considered as covariates 8 mRNA transcripts indicating the relative prevalence of major leukocyte subsets within the circulating blood cell pool: *CD14* for monocytes, *CD3D*, *CD3E*, *CD4*, and *CD8A* for T lymphocyte subsets, *CD19* for B lymphocytes, and

[1] As part of the MIDUS Refresher Biomarker Project, participants also reported their history of chronic conditions and illnesses. Post-hoc sensitivity analyses that included the number of self-reported symptoms and conditions as an additional covariate yielded the same pattern of findings.

*NCAM1* and *FCGR3A* for natural killer cells.

### 2.4. Data analysis plan

To examine whether chronic stress exposures in childhood and adulthood were associated with stress hormones and biological aging, we conducted separate multiple linear regression models for each predictor and outcome measure. The chronic stress exposure variables were coded continuously, and models adjusted for age, biological sex, self-identified race and ethnicity, BMI, smoking status, alcohol use, and number of prescription medications. Childhood stress exposure models also adjusted for stress exposures during adulthood. The regression model was as follows:

$Y = b_0 + b$(Chronic stress exposure) $+ b$(Age) $+ \ldots + b$(Number of prescription medications)

To examine whether stress hormones were associated with biological aging, we conducted a second set of multiple regression models for each outcome measure, adjusting for the same set of covariates. We then applied a 5% false discovery rate (FDR) correction for multiple testing across the set of chronic stress exposure models and the set of stress hormone models. (Benjamini and Hochberg, 1995) Finally, to explore stress hormones as potential mechanisms linking chronic stress exposures and biological aging, we performed a set of exploratory cross-sectional mediation models using the PROCESS macro for SPSS with 10,000 bootstrap samples to generate 95% confidence intervals for the indirect effects, (Hayes, 2022) adjusting for the same set of covariates. The childhood stress exposure mediation models also adjusted for stress exposures during adulthood. We performed sensitivity analyses for each set of models that further adjusted for leukocyte subsets. All analyses were conducted using SPSS Statistics software.

## 3. Results

### 3.1. Preliminary analyses

Sample characteristics appear in Table 1, with post-hoc comparisons based on chronic stress exposures in childhood or adulthood shown in Supplemental Table S4. Participants had a mean age of 53.9 years ($SD$ = 13.3) and approximately half the sample was female (50.1%). The majority self-identified as white (72.1%), followed by Black or African American (16.9%), Native American or Alaska Native Aleutian Islanders/Eskimo (1.7%), Asian (1.5%), and other (7.3%), as well as non-Hispanic (96.4%). Age was significantly associated with the biological aging variables, such that older age correlated with elevated expression of the DDR ($r = 0.34$, $p < 0.001$), senescence signal $p16^{INK4a}$ ($r = 0.11$, $p$=.01), and the SASP ($r = 0.38$, $p < 0.001$; Supplemental Figures S1a–c). Age was also positively associated with stress hormone variables norepinephrine ($r = 0.45$, $p < 0.001$), epinephrine ($r = 0.18$, $p < 0.001$), and cortisol ($r = 0.14$, $p = 0.002$; Supplemental Figures S1d–f).

Descriptive statistics and correlations between the main study variables—chronic stress exposures, stress hormones, and biological aging—are shown in Table 2. Chronic stress exposures in childhood and adulthood were weakly but significantly correlated ($r = 0.18$, $p < 0.001$). The stress hormone variables were moderately intercorrelated ($r$=.29–.36, $p < 0.001$). DDR and SASP were weakly but significantly associated with $p16^{INK4a}$ ($r = 0.15$, $p < 0.001$ and $r = 0.12$, $p = 0.008$, respectively) and were highly correlated with each other ($r = 0.78$, $p < 0.001$). Childhood stress exposures were inversely correlated with cortisol ($r$ = -0.09, $p = 0.03$) and showed a trend with $p16^{INK4a}$ ($r = 0.07$, $p = 0.09$) but were not associated with the other stress hormone or biological aging variables. Adulthood stress exposures were correlated with the DDR ($r = 0.16$, $p < 0.001$) and SASP ($r = 0.12$, $p = 0.005$) and showed a trend for norepinephrine ($r = 0.08$, $p = 0.05$) but were not associated with $p16^{INK4a}$ or the other stress hormone variables.

**Table 1**
Sample characteristics for participants in the Midlife in the United States study with complete gene expression and norepinephrine data ($N = 531$).

| Characteristic | Mean (SD) / n (%) |
|---|---|
| Age, years | 53.85 (13.25) |
| Biological sex | |
| Female | 266 (50.1%) |
| Male | 265 (49.%) |
| Self-identified race | |
| White | 383 (72.1%) |
| Black or African American | 90 (16.9%) |
| Native American or Alaska Native Aleutian Islanders/Eskimo | 9 (1.7%) |
| Asian | 8 (1.5%) |
| Other | 39 (7.3%) |
| Missing | 2 (0.4%) |
| Ethnicity | |
| Hispanic | 17 (3.2%) |
| Non-Hispanic | 512 (96.4%) |
| Marital status | |
| Married or living as married | 336 (63.3%) |
| Separated | 11 (2.1%) |
| Divorced | 77 (14.4%) |
| Widowed | 20 (3.8%) |
| Never married | 87 (16.4%) |
| Employment status | |
| Employed | 280 (52.7%) |
| Self-employed | 50 (9.4%) |
| Unemployed / Looking for work | 20 (3.8%) |
| Temporarily laid off | 1 (0.2%) |
| Retired | 101 (19.0%) |
| Homemaker | 18 (3.4%) |
| Full-time student | 4 (0.8%) |
| Permanently disabled | 8 (1.7%) |
| Other | 8 (1.5%) |
| Missing | 40 (7.5%) |
| Educational attainment | |
| Less than high school diploma | 20 (3.8%) |
| High school diploma / GED | 72 (13.6%) |
| Some college / Associate's degree | 157 (29.6%) |
| Bachelor's degree | 136 (25.6%) |
| Graduate school or Professional degree | 145 (27.3%) |
| Missing | 1 (0.2%) |
| Income | |
| Less than $10,000 | 43 (8.1%) |
| $10,001–$25,000 | 44 (8.3%) |
| $25,001–$40,000 | 54 (10.2%) |
| $40,001–$55,000 | 50 (9.4%) |
| $55,001–$70,000 | 48 (9.0%) |
| $70,001–$85,000 | 48 (9.0%) |
| $85,001–$100,000 | 53 (10.0%) |
| More than $100,000 | 191 (36.0%) |
| Body mass index (kg/m2) | 30.16 (7.07) |
| Smoking status | |
| Never | 337 (63.5%) |
| Past | 137 (25.8%) |
| Current | 56 (10.5%) |
| Missing | 1 (0.2%) |
| Alcohol use | |
| None | 149 (28.1%) |
| Light / moderate | 271 (51.0%) |
| Heavy | 109 (20.5%) |
| Missing | 2 (0.4%) |
| Number of prescription medications | 3.08 (3.33) |

### 3.2. Chronic stress exposures

For all models, full model results appear in the supplementary materials. Consistent with hypotheses, covariate-adjusted analyses showed greater chronic stress exposures in childhood to be significantly associated with higher levels of urinary norepinephrine ($\beta = 0.09$, $p = 0.04$, 95% CI [.004, 0.14]) and a trend for higher levels of epinephrine ($\beta = 0.09$, $p = 0.07$, 95% CI [-0.01, 0.19]; Table 3, full model results appear in Supplemental Table S5) in midlife. The association between norepinephrine and childhood stress exposures remained statistically

**Table 2**
Descriptive statistics and correlations between chronic stress exposure, stress hormone, and biological aging variables ($N = 531$).

| Variable | Mean (*SD*) | Range | Adulthood stress exposures | Norepinephrine | Epinephrine | Cortisol | DDR | $p16^{INK4a}$ | SASP |
|---|---|---|---|---|---|---|---|---|---|
| Childhood stress exposures | 0.92 (1.17) | 0–4+ | **0.18***** | 0.002 | 0.03 | **−0.09*** | −0.04 | 0.07$^{\dagger}$ | −0.06 |
| Adulthood stress exposures | 2.27 (1.38) | 0–4+ | – | 0.08$^{\dagger}$ | −0.02 | −0.05 | **0.16***** | 0.07 | **0.12**** |
| Norepinephrine (Ln) | 5.32 (0.98) | 1.75–7.89 | | – | **0.36***** | **0.30***** | **0.28***** | 0.05 | **0.27***** |
| Epinephrine (Ln) | 3.57 (1.22) | −0.55–6.76 | | | – | **0.29***** | **0.11*** | 0.06 | **0.15***** |
| Cortisol (Ln) | 3.09 (0.60) | 0.83–4.69 | | | | – | 0.03 | −0.07 | 0.05 |
| DDR | 0.003 (0.39) | −1.17–0.95 | | | | | – | **0.15***** | **0.78***** |
| $p16^{INK4a}$ | 0.007 (0.71) | −0.52–3.25 | | | | | | – | **0.12**** |
| SASP | 0.001 (0.21) | −0.54–0.54 | | | | | | | – |

Note. DDR = DNA damage response; SASP = Senescence-associated secretory phenotype. Bold font denotes statistically significant associations. The sample size for correlations with epinephrine is $n = 512$ and cortisol is $n = 522$. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$, $^{\dagger}p < 0.10$.

**Table 3**
Multiple regression models with chronic stress exposures predicting stress hormones and biological aging.

| | Stress hormones | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Norepinephrine | | | Epinephrine | | | Cortisol | | |
| Model | $\beta$ | *b* [95% CI] | *p* | $\beta$ | *b* [95% CI] | *p* | $\beta$ | *b* [95% CI] | *p* |
| 1. Childhood stress exposures | **0.09** | **0.07 [0.004, 0.14]** | **0.04*** | 0.09 | 0.09 [−0.01, 0.19] | 0.07 | −0.02 | −0.01 [−0.06, 0.04] | 0.69 |
| 2. Adulthood stress exposures | −0.03 | −0.02 [−0.08, 0.04] | 0.43 | −0.06 | −0.06 [−0.14, 0.03] | 0.18 | −0.04 | −0.02 [−0.06, 0.02] | 0.38 |
| | | | | Biological aging | | | | | |
| | DDR | | | $p16^{INK4a}$ | | | SASP | | |
| Model | $\beta$ | *b* [95% CI] | *p* | $\beta$ | *b* [95% CI] | *p* | $\beta$ | *b* [95% CI] | *p* |
| 1. Childhood stress exposures | −0.004 | −0.001 [−0.03, 0.03] | 0.93 | 0.06 | 0.03 [−0.02, 0.09] | 0.23 | −0.02 | −0.003 [−0.02, 0.01] | 0.69 |
| 2. Adulthood stress exposures | 0.06 | 0.02 [−0.01, 0.04] | 0.16 | 0.04 | 0.02 [−0.03, 0.07] | 0.44 | 0.02 | 0.003 [−0.01, 0.02] | 0.66 |

Note. CI = confidence interval; DDR = DNA damage response; SASP = Senescence-associated secretory phenotype. Bold font denotes statistically significant associations. Asterisks indicate statistically significant associations following false discovery rate correction. Models adjust for age, biological sex, self-identified Black or African American race and Hispanic ethnicity, body mass index, smoking status, alcohol use, and the number of prescription medications at the time of the Biomarker Project assessment. Childhood stress exposure models also adjust for adulthood chronic stress exposures. Due to missing data for self-identified race ($n = 2$), ethnicity ($n = 1$), smoking status ($n = 1$), and alcohol use ($n = 2$), the sample size for models with norepinephrine is $n = 525$, epinephrine is $n = 506$, and cortisol is $n = 516$.

significant following FDR correction. However, chronic stress exposures in childhood were not significantly related to the other stress hormones or biological aging markers (Table 3; full model results appear in Supplemental Table S6). Similarly, chronic stress exposures in adulthood were not significantly associated with the stress hormones or biological aging markers after accounting for covariates. Further adjustment for mRNA markers of leukocyte subsets revealed a similar pattern of findings (Supplemental Table S7). Given the distribution of the $p16^{INK4a}$ variable, which had a skewness of 1.41 following normalization and log2 transformation, in which 49.2% of participants had a value that fell below the limit of assay detection (i.e., there was not enough mRNA present in the blood sample for the assay to detect it), we also dichotomized the variable and conducted a sensitivity analysis using logistic regression models that revealed the same pattern of results (Supplemental Table S8).

### 3.3. Stress hormones

Also as expected, higher levels of urinary norepinephrine were significantly associated with elevated expression of the DDR ($\beta = 0.17$, $p < 0.001$, 95% CI [.03, 0.10]) and pro-inflammatory SASP ($\beta = 0.14$, $p = 0.003$, 95% CI [0.01, 0.05]) but not senescence signal $p16^{INK4a}$ ($p = 0.74$; Table 4, full model results appear in Supplemental Table S9). Higher levels of urinary epinephrine were also associated with enhanced expression of the SASP ($\beta = 0.10$, $p = 0.02$, 95% CI [0.002, 0.03]) but not with the other biological aging markers (*p*s > 0.20). Counter to hypotheses, higher cortisol was associated with lower $p16^{INK4a}$ ($\beta = -0.10$, $p = 0.03$, 95% CI [−0.22, −0.01]) but not with the DDR or SASP (*p*s > 0.60). With the exception of the association between cortisol and $p16^{INK4a}$, these findings remained statistically significant following FDR correction. Further adjustment of mRNA markers of leukocyte subsets revealed a similar pattern of findings for epinephrine and cortisol but suggested that monocyte, T cell, and natural killer cell prevalence may mediate associations between norepinephrine and the DDR and SASP (Supplemental Table S10).

### 3.4. Mediation models with stress hormones linking chronic stress exposures and biological aging

Consistent with expectations, exploratory mediation models

**Table 4**
Multiple regression models with stress hormones predicting biological aging.

| | | | | | Biological aging | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | DDR | | | $p16^{INK4a}$ | | | SASP | |
| Model | $\beta$ | *b* [95% CI] | *p* | $\beta$ | *b* [95% CI] | *p* | $\beta$ | *b* [95% CI] | *p* |
| 1. Norepinephrine | **0.17** | **0.07 [0.03, 0.10]** | **<0.001*** | −0.02 | −0.01 [−0.08, 0.06] | 0.74 | **0.14** | **0.03 [0.01, 0.05]** | **0.003*** |
| 2. Epinephrine | 0.06 | 0.02 [-0.01, 0.05] | 0.20 | 0.03 | 0.02 [−0.03, 0.07] | 0.46 | **0.10** | **0.02 [0.002, 0.03]** | **0.02*** |
| 3. Cortisol | −0.02 | −0.02 [−0.07, 0.04] | 0.60 | **−0.10** | **−0.11 [−0.22, −0.01]** | **0.03** | 0.01 | 0.002 [−0.03, 0.03] | 0.88 |

Note. CI = confidence interval; DDR = DNA damage response; SASP = Senescence-associated secretory phenotype. Bold font denotes statistically significant associations. Asterisks indicate statistically significant associations following false discovery rate correction. Models adjust for age, biological sex, self-identified Black or African American race and Hispanic ethnicity, body mass index, smoking status, alcohol use, and the number of prescription medications at the time of the Biomarker Project assessment. Due to missing data for self-identified race ($n = 2$), ethnicity ($n = 1$), smoking status ($n = 1$), and alcohol use ($n = 2$), the sample size for models with norepinephrine is $n = 525$, epinephrine is $n = 506$, and cortisol is $n = 516$.

revealed significant indirect effects, suggesting that greater chronic stress exposures in childhood were associated with elevated expression of the DDR (unstandardized $b = 0.005$, $SE = 0.003$, 95% CI [0.0002, 0.011]) and the SASP ($b = 0.002$, $SE = 0.001$, 95% CI [0.0001, 0.005]) via higher levels of urinary norepinephrine (Table 5; Fig. 1). Similarly, sensitivity analyses that adjusted for leukocyte subsets suggested that increased monocyte, T cell, and natural killer cell prevalence may mediate associations between norepinephrine and the DDR and SASP (Supplemental Table S11). The residual direct effects for both models were not significant. The other mediation models that included adulthood stress exposure, epinephrine, cortisol, and cellular senescence signal $p16^{INK4a}$ did not yield statistically significant direct or indirect effects.

**Table 5**
Mediation models with stress hormones mediating associations between childhood and adulthood chronic stress exposures and biological aging.

| Model | Direct effect *b* [95% CI] | Indirect effect *b* [95% CI] | Total effect *b* [95% CI] |
|---|---|---|---|
| Childhood stress exposures → NE → DDR | −0.006 [−0.036, 0.023] | **0.005 [0.0002, 0.011]** | −0.001 [−0.031, 0.028] |
| Childhood stress exposures → E → DDR | −0.005 [−0.034, 0.025] | 0.002 [−0.001, 0.005] | −0.003 [−0.033, 0.027] |
| Childhood stress exposures → Cortisol → DDR | −0.002 [−0.031, 0.028] | 0.0001 [−0.001, 0.002] | −0.002 [−0.031, 0.028] |
| Childhood stress exposures → NE → $p16^{INK4a}$ | 0.035 [−0.021, 0.090] | −0.001 [−0.007, 0.005] | 0.033 [−0.022, 0.089] |
| Childhood stress exposures → E → $p16^{INK4a}$ | 0.029 [−0.027, 0.085] | 0.002 [−0.003, 0.008] | 0.031 [-0.025, 0.086] |
| Childhood stress exposures → Cortisol → $p16^{INK4a}$ | 0.027 [−0.028, 0.082] | 0.001 [−0.005, 0.008] | 0.028 [−0.028, 0.083] |
| Childhood stress exposures → NE → SASP | −0.005 [−0.021, 0.010] | **0.002 [0.0001, 0.005]** | −0.003 [−0.019, 0.012] |
| Childhood stress exposures → E → SASP | −0.005 [−0.021, 0.010] | 0.002 [−0.0002, 0.004] | −0.004 [−0.019, 0.012] |
| Childhood stress exposures → Cortisol → SASP | −0.003 [−0.018, 0.013] | 0.000 [−0.001, 0.001] | −0.003 [−0.018, 0.013] |
| Adulthood stress exposures → NE → DDR | 0.020 [−0.005, 0.045] | −0.002 [−0.006, 0.002] | 0.018 [−0.007, 0.043] |
| Adulthood stress exposures → E → DDR | 0.016 [−0.01, 0.042] | −0.001 [−0.004, 0.001] | 0.015 [−0.010, 0.041] |
| Adulthood stress exposures → Cortisol → DDR | 0.016 [−0.010, 0.041] | 0.0002 [−0.001, 0.002] | 0.016 [−0.009, 0.042] |
| Adulthood stress exposures → NE → $p16^{INK4a}$ | 0.018 [−0.029, 0.065] | 0.0003 [−0.002, 0.004] | 0.018 [−0.029, 0.066] |
| Adulthood stress exposures → E → $p16^{INK4a}$ | 0.020 [−0.028, 0.068] | −0.001 [−0.006, 0.002] | 0.019 [−0.029, 0.067] |
| Adulthood stress exposures → Cortisol → $p16^{INK4a}$ | 0.008 [−0.039, 0.056] | 0.002 [−0.003, 0.008] | 0.010 [−0.037, 0.058] |
| Adulthood stress exposures → NE → SASP | 0.004 [−0.009, 0.017] | −0.001 [−0.003, 0.001] | 0.003 [−0.010, 0.016] |
| Adulthood stress exposures → E → SASP | 0.002 [−0.011, 0.016] | −0.001 [−0.003, 0.0004] | 0.001 [−0.012, 0.015] |
| Adulthood stress exposures → Cortisol → SASP | 0.004 [−0.010, 0.017] | 0.000 [−0.001, 0.001] | 0.003 [−0.010, 0.017] |

Note. CI = Confidence interval; NE = Norepinephrine; E = Epinephrine; DDR = DNA damage response; SASP = Senescence-associated secretory phenotype. Bold font denotes statistically significant effects. Models adjust for age, biological sex, self-identified Black or African American race and Hispanic ethnicity, body mass index, smoking status, alcohol use, and the number of self-reported prescription medications at the time of the Biomarker Project assessment. Childhood stress exposure models also adjust for adulthood chronic stress exposures. Due to missing data for self-identified race ($n = 2$), ethnicity ($n = 1$), smoking status ($n = 1$), and alcohol use ($n = 2$), the sample size for models with norepinephrine is $n = 525$, epinephrine is $n = 506$, and cortisol is $n = 516$.

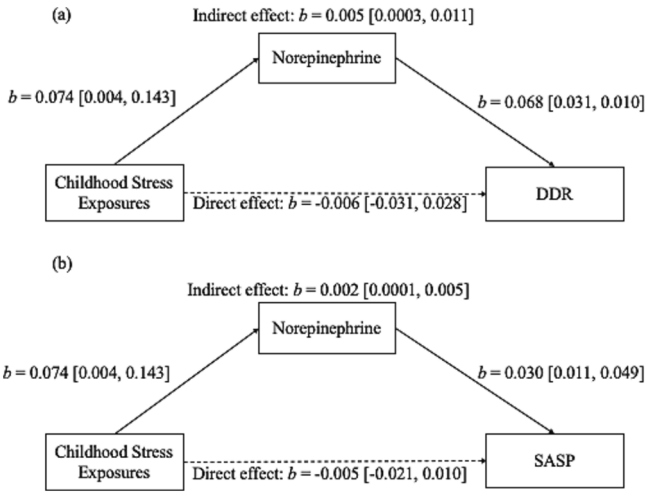


**Fig. 1. Mediation models with norepinephrine levels linking childhood stress exposures to biological aging.** Exploratory statistical mediation models with unstandardized coefficients showing elevated urinary norepinephrine levels in midlife as a mediator of associations between childhood stress exposures and greater expression of (a) the DNA damage response (DDR) and (b) the pro-inflammatory senescence-associated secretory phenotype (SASP). Models adjusted for age, biological sex, self-reported Black or African American race and Hispanic ethnicity, body mass index, smoking status, alcohol use, number of prescription medications at the time of the Biomarker Project assessment, and adulthood chronic stress exposures. Model results also appear in Table 5.

## 4. Discussion

The present study examined whether chronic stress exposures during childhood or adulthood were associated with elevated levels of urinary stress hormones (norepinephrine, epinephrine, cortisol) and molecular processes in the cellular senescence pathway, including expression of the DDR, senescence signal $p16^{INK4a}$, and the pro-inflammatory SASP. As hypothesized, greater chronic stress exposures in childhood were associated with greater SNS activity in midlife—indexed by higher urinary norepinephrine and a trend for higher epinephrine output over a 12-hour period—after accounting for stressful life experiences in adulthood. Also as expected, norepinephrine was associated with greater expression of the DDR, and both norepinephrine and epinephrine were associated with greater expression of the SASP, suggesting that basal levels of circulating stress hormones may be related to a higher senescent cell burden in middle-aged adults. Furthermore, exploratory mediation analyses provided preliminary evidence to suggest that exposure to chronic stressors in childhood may be associated with greater biological aging (i.e., elevated DDR and SASP) decades later via higher norepinephrine output in adulthood. Interestingly, sensitivity analyses that adjusted for mRNA estimates of leukocyte subsets suggested that the observed associations between norepinephrine (but not epinephrine or cortisol) and biological aging may be mediated by individual variations in blood cell composition (particularly monocyte, T cell, and NK cell prevalence). Given that leukocyte subsets can fluctuate in response to biological and psychosocial conditions and the aging process itself (Dhabhar, 2014; Hawkley and Cacioppo, 2010; Herbert and Cohen, 1993; Schedlowski et al., 1993) and variations in their prevalence can influence the estimation of biological aging, this warrants additional investigation in future research.

Our findings that exposure to chronic stressors during childhood was associated with higher urinary norepinephrine and a trend for higher

epinephrine output, accounting for exposures that occurred during adulthood, are consistent with and extend previous research that has linked childhood stress exposures to elevated norepinephrine levels in adulthood. (Hostinar et al., 2015) Specifically, Hostinar and colleagues (2015) found that childhood (but not adulthood) chronic stress exposures were associated with peripheral markers of inflammation (a composite that included CRP, IL-6, fibrinogen, E-Selectin, and ICAM-1) via elevated norepinephrine levels in the MIDUS II cohort (which did not include MIDUS Refresher participants examined here). (Hostinar et al., 2015) Our results build on these findings by suggesting that the observed associations extend to markers of biological aging beyond systemic inflammation. However, our findings that childhood exposures were not associated with cortisol levels and that adulthood exposures did not relate to any stress hormones are somewhat surprising given that some prior studies have linked chronic stressors across the lifespan to epinephrine and cortisol output in adulthood. (Hostinar et al., 2015; Pruessner et al., 2003; Schlotz et al., 2004; Cohen et al., 2006; Janicki-Deverts et al., 2007; Miller et al., 2007; Gustafsson et al., 2010; Miller et al., 2009; Huggenberger et al., 2013; Stalder et al., 2017; Sullivan et al., 2019; Torrecilla and Barrantes-Vidal, 2023) The literature is mixed, however, with other studies finding no association between chronic stressors in adulthood and these stress hormones. (Dowd and Goldman, 2006; Lutgendorf et al., 2023; Oresta et al., 2021; Schulz et al., 2023).

Although adulthood stress exposures were correlated with expression of the DDR and SASP and there was a trending correlation between childhood stress exposures and $p16^{INK4a}$, it was surprising that we did not observe direct associations between chronic stress exposures and biological aging following adjustment for covariates. It is important to note that the correlations did not account for the age of the participants, which was associated with both the stress hormones and biological aging measures in this study. However, these results are in contrast with previous research that identified direct associations between stressful life experiences in childhood and adulthood and other hallmarks of biological aging such as shorter telomere length (Epel et al., 2004; Shalev et al., 2013; Puterman et al., 2016; Révész et al., 2016; Mayer et al., 2019) and epigenetic aging. (Harvanek et al., 2021; Joshi et al., 2023; Sumner et al., 2023) It is possible that associations between chronic stressors and cellular senescence are not as consistent or robust as other hallmarks of aging or that the findings reported in previous research are specific to the populations studied (i.e., children, older adults) and don't as readily generalize to a midlife sample with a broader age range. However, these findings are also inconsistent with results from a study of midlife parents in which chronic stress exposures (as well as perceived and accumulated daily stress) were associated with elevated gene expression of cellular senescence signal $p16^{INK4a}$. (Rentscher et al., 2019) The discrepancy in findings between the two studies may be attributable in part to the measurement of $p16^{INK4a}$ mRNA in this study, which employed RNA sequencing (compared to microarray gene expression profiling used by Rentscher et al. [2019]), and the skewed distribution of $p16^{INK4a}$ may have constrained the ability to detect significant associations with chronic stressors. It may also be attributable to the measures of chronic stress that were used: Although the present study assessed the frequency of a relatively large number of stressors, it relied on a checklist approach that did not take into account the perceived severity or duration of the stressors (Epel et al., 2018) and retrospective reporting which can introduce error due to memory difficulties or other response biases, whereas Rentscher and colleagues (2019) employed a semi-structured interview that assessed the presence and severity of stressors across several domains over the previous 6 months. (Rentscher et al., 2019) (However, it is important to note that childhood stress exposures were assessed using the same method in this study and significant indirect associations were observed between childhood stress exposures and biological aging.) It is possible that stressful events experienced in adulthood may be more nuanced than stressful events in childhood and require a more detailed measurement approach of the stressor itself (i.e., frequency, duration, and severity). In addition, individual differences in protective factors such as available coping resources (e.g., social relationships, sense of purpose and meaning) (Asok et al., 2013; Carroll et al., 2013; Chen et al., 2011; Skinner et al., 2024; Uchino et al., 2018) that may moderate associations between chronic stress exposures and biological aging were not examined in this study but are important directions for future research. Regardless, research that takes a lifespan approach is valuable for improving our understanding of the exposures that are most likely to contribute to accelerated aging.

Although direct associations between stress exposures and biological aging were not observed in this study after accounting for demographic and lifestyle factors, exploratory mediation analyses suggested that chronic stress exposures in childhood were associated with greater expression of the DDR and SASP via elevated norepinephrine output in adulthood, accounting for adulthood stress exposures. These findings are in line with the notion that early life adversity can become biologically embedded during sensitive periods of development and heightened plasticity to influence the programming of the stress response system and alter brain and immune function into adulthood. (Miller et al., 2011) Our results are also consistent with prior work in which stress exposures during childhood were stronger predictors of telomere length (Puterman et al., 2016) and attrition (Mayer et al., 2019) in midlife than exposures during adulthood. Together, these findings support the hypothesis that adverse experiences early in life may have long-lasting consequences for the stress response system and health, whereby individuals exposed to chronic stress as children may exhibit elevated SNS activity in midlife that is associated with a pattern of accelerated biological aging.

Findings from this study build upon previous experimental animal (Hara et al., 2011; Katsuumi et al., 2018) and *in vitro* (O'Brien et al., 1993; Flint et al., 2007; Flint et al., 2013; Patel et al., 2015; Lamboy-Caraballo et al., 2020; Laberge et al., 2012) studies on the impact of stress hormones on key molecular processes in the cellular senescence pathway by beginning to test these associations in humans. Our findings that elevated catecholamine levels were associated with greater expression of the DDR and SASP also extend previous research in humans that has linked higher catecholamines to other markers of biological aging such as shorter telomere length, (Epel et al., 2006) and elevated circulating markers of inflammation. (Hostinar et al., 2015) Although our finding that *lower* urinary cortisol output was associated with enhanced expression of senescent signal $p16^{INK4a}$ did not survive correction for multiple testing, it is consistent with prior research which found that lower urinary cortisol mediated associations between chronic stress exposures and elevated peripheral inflammation (Hostinar et al., 2015) and a lower cortisol/ACTH ratio related to greater epigenetic aging in adulthood. (Harvanek et al., 2021) This pattern of findings is consistent with the idea that the anti-inflammatory properties of cortisol may act to reduce inflammation-related damage to cells and tissues that contributes to accelerated biological aging (Laberge et al., 2012); however, future research is recommended that examines the time course of stress exposures, cortisol production, and cellular senescence. Another interesting future direction is to examine the potential moderating role that psychiatric disorders such as posttraumatic stress disorder and major depression may have on these associations, given that both disorders have been associated with accelerated biological aging and may show different patterns of cortisol production and glucocorticoid receptor sensitivity in the context of chronic stress. (Lorenzo et al., 2023; Miller et al., 2007; Pan et al., 2018; Rohleder et al., 2010; Wolf et al.; Wolf and Morrison, 2017; Zorn et al., 2017).

Our results should be considered in light of study limitations, which suggest avenues for future research. First, the Midlife in the United States (MIDUS) Refresher study currently includes a comprehensive biomarker assessment at only a single timepoint, which limited the present analyses to concurrent associations. Thus, although the exploratory mediation analyses provide preliminary evidence in support of the

hypothesis that norepinephrine is a plausible biological mechanism through which experiences of chronic stress may be associated with biological aging, additional research is needed to examine longitudinal associations between chronic stress, stress hormones, and biological aging and test causal pathways. In addition, given that this study focused on potential biological mediators of associations between chronic stress exposures and biological aging, it did not examine lifestyle covariates as potential behavioral mediators of the associations and findings should therefore be interpreted accordingly. Future research may also benefit from investigating more complex mediation models that account for potential interactions between the predictor and mediator variables as well as multiple mediators. (Hayes, 2022; VanderWeele, 2016) Second, although the MIDUS study included an oversampling of African American participants, the present sample was largely comprised of self-identified white and non-Hispanic participants, which limits the generalizability of the findings. In addition, as mentioned previously, this investigation used a checklist approach to measure stressful life events during childhood and adulthood and did not assess the severity or duration of the stress exposures. It will be important for future research to examine how these features, as well as other forms of chronic stress such as racial discrimination and socioeconomic status, might impact stress hormone mediators and cellular senescence burden. Although it is possible that the 24-hour stay at the Clinical Research Unit may have been a source of stress for participants and their urinary stress hormone levels may have been elevated from their resting levels, all participants in this study followed the same procedures. However, on account of this, stress hormone levels from this study may not be directly comparable to those observed in a natural environment and there is a need for more ecologically valid assessments in future research. Finally, although MIDUS Refresher 1 included previously validated aging-related gene expression profiles—DDR, senescence signal $p16^{INK4a}$, and SASP—whole-genome transcriptional profiling data are not currently available and future research may benefit from the investigation of additional cellular senescence markers (e.g., p21) beyond $p16^{INK4a}$.

Despite these limitations, the present study extends the literature on psychosocial stress and biological aging by examining associations between both childhood and adulthood chronic stress exposures, stress hormones, and key processes in the cellular senescence pathway in a large, nationally representative sample of middle-aged adults. Findings suggested that childhood stress exposures were associated with elevated SNS activity (indexed by higher urinary catecholamine levels over a 12-hour period) and may be associated with elevated DDR and SASP expression via higher norepinephrine output in midlife, after accounting for adulthood stressors. These results provide preliminary evidence in humans that stress hormones are associated with key molecular processes in the cellular senescence pathway and that norepinephrine may be a plausible mechanism through which chronic stress exposures in childhood contribute to accelerated biological aging later in life. This study also identified that older age was associated with elevated basal levels of norepinephrine as well as gene expression of the DDR, senescent signal $p16^{INK4a}$, and the pro-inflammatory SASP. These findings extend prior research that has linked older age to greater expression of senescent signal $p16^{INK4a}$ (Liu et al., 2009) and, importantly, suggest that older individuals may be more vulnerable to the deleterious health effects of stress hormones in addition to greater biological aging. Together, these findings suggest that stress hormone levels may serve as potential targets for pharmacological (e.g., beta-blockers such as propranolol) (Flint et al., 2013) or behavioral (e.g., cognitive behavioral therapy [CBT] or mindfulness-based stress reduction [MBSR]) (Gaab et al., 2006; Khoury et al., 2015; Paudel et al., 2022; Zisopoulou and Varvogli, 2023) interventions in midlife adults with a history of early life adversity and elevated catecholamine levels to slow the aging process and delay the onset of age-related diseases such as cancer, cardiovascular disease, diabetes, and dementia.

## CRediT authorship contribution statement

**Jenna L. Hansen:** Writing – original draft, Formal analysis, Conceptualization. **Judith E. Carroll:** Writing – review & editing, Conceptualization. **Teresa E. Seeman:** Writing – review & editing, Conceptualization. **Steve W. Cole:** Conceptualization, Writing – review & editing. **Kelly E. Rentscher:** Writing – original draft, Supervision, Formal analysis, Conceptualization.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2024.10.022.

## Data availability

Data are publicly available from the Midlife in the United States study at https://midus.wisc.edu/ and https://www.icpsr.umich.edu/web/ICPSR/series/203.

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