Routledge
Taylor & Francis Group

Aging & Mental Health

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/camh20

Multi-sample assessment of stress reactivity as a mediator between childhood adversity and mid- to late-life outcomes

Julia Sheffler, Celina Meyer & Frank Puga

To cite this article: Julia Sheffler, Celina Meyer & Frank Puga (2021): Multi-sample assessment of stress reactivity as a mediator between childhood adversity and mid- to late-life outcomes, Aging & Mental Health, DOI: 10.1080/13607863.2021.1910787

To link to this article: https://doi.org/10.1080/13607863.2021.1910787

Published online: 16 Apr 2021.

AGING & MENTAL HEALTH
https://doi.org/10.1080/13607863.2021.1910787

Routledge
Taylor & Francis Group

Multi-sample assessment of stress reactivity as a mediator between childhood adversity and mid- to late-life outcomes

Julia Sheffler[a], Celina Meyer[a] and Frank Puga[b]

[a]Behavioral Sciences and Social Medicine Department, Florida State University College of Medicine, Tallahassee, FL, USA; [b]Department of Acute, Chronic and Continuing Care, The University of Alabama at Birmingham, Birmingham, AL, USA

ABSTRACT

Objectives: We examined whether adult stress reactivity accounts for the relationship between early life adversity (ELA) and psychological, physical, and cognitive outcomes.

Methods: We examined the relationship between ELA, stress reactivity, psychological well-being, physical health, and cognitive function in two separate datasets - a cross-sectional community sample of older adults ($N = 510$) aged 60 and older, and waves I-III of the Midlife in the United States (MIDUS) dataset. Age, sex, and income served as covariates in all analyses. Bootstrapped mediation models were used to assess recent stress as a mediator between ELA and mid- to late-life outcomes.

Results: ELA was significantly associated with adult stress, anxiety, depression, health conditions, and object cognitive assessments. Adult stress partially accounted for the relationships between ELA and depression, anxiety, health conditions, and memory problems.

Conclusion: Our findings demonstrate that ELA may influence increased stress in older age, which confers additional risks for developing depression, anxiety, health problems, and cognitive decline. It is possible that intervening on adult stress may reduce risk for both psychological and physical pathology across the lifespan. Further research is needed to develop targeted interventions for mid and late-life stress to improve overall health as individuals age.

ARTICLE HISTORY
Received 11 May 2020
Accepted 25 March 2021

KEYWORDS
Depression; stress; health; anxiety

The link between early life adversity (ELA), such as childhood abuse experiences, household dysfunction, and low socioeconomic status, and increased risk for adverse emotional, cognitive, and physical health outcomes across the lifespan is well-established in the literature. For example, ELA is associated with greater vulnerability to heart disease and immune system dysregulation (Miller, Chen, & Parker, 2011; Shonkoff, Boyce, & McEwen, 2009), worse cognitive outcomes in late-life (Hostinar, Stellern, Schaefer, Carlson, & Gunnar, 2012; Short & Baram, 2019), and mood and anxiety disorders (Green et al., 2010; Rao et al., 2010). Further, ELA may disrupt biobehavioral and neurodevelopmental processes associated with healthy physiological and emotional reactivity to stress (Lovallo et al., 2013; Luby, Barch, Whalen, Tillman, & Belden, 2017). Disruptions to these early developmental processes may decrease stress vulnerability thresholds, thereby impacting stress appraisals and emotion regulation across the lifespan (Dich et al., 2015; Duffy, McLaughlin, & Green, 2018). Studies demonstrate that significant early life events and stressful experiences later in life have a cumulative impact on mid- to late-life outcomes; however, the exact mechanism by which ELA impacts mid- to late-life outcomes throughout the life course is relatively unknown (see Ferraro, Schafer, & Wilkinson, 2016; McCrory, Dooley, Layte, & Kenny, 2015; Vannorsdall & Munro, 2017).

Theories of stress and disease, such as allostatic load, highlight the interaction between individual vulnerability, environmental stressors, and repeated emotional and physiological responses to stress in the etiology of disease (McEwen, 1998, 2004, 2013; McEwen & Akil, 2020; McEwen & Wingfield, 2003). Further, chronically elevated emotional responses to stress, or emotional stress reactivity, throughout the lifespan is known to increase the risk of poor physical, psychological, and cognitive outcomes (Charles, Piazza, Mogle, Sliwinski, & Almeida, 2013; McLaughlin et al., 2010; Swartz, Knodt, Radtke, & Hariri, 2015). Thus, emotional stress reactivity may serve as a potential mechanism underlying the relationship between ELA and mid- to late-life outcomes. In the present study, we examined emotional stress reactivity in middle-aged and older adults as a potential pathway between ELA and adverse health, psychological, and cognitive outcomes.

ELA, depression, and anxiety

Exposure to ELA is associated with an increased risk of internalizing psychopathology (i.e. anxiety and depression) across the lifespan (Li, D'Arcy, & Meng, 2016; Lindert et al., 2014). Early studies using the Adverse Childhood Experiences Study demonstrated a relationship between ELAs and risk for depression, suicide attempts, and alcoholism in adults aged 18 and older (Dube et al., 2001). Individuals who experienced four or more adverse childhood experiences (e.g. poverty, sexual abuse, and emotional neglect) were over four times more likely to experience chronic depressed mood in adulthood (Felitti et al., 1998). Recent studies also highlight a graded, or cumulative effect of ELA on psychological outcomes (Tracy, Salo, Slopen, Udo, & Appleton, 2019; Van Assche, Van de Ven, Vandenbulcke, & Luyten, 2020; Wolf & Suntheimer, 2019). For example, findings from the National Comorbidity Surveys study showed a graded association between the number of ELAs and the prevalence of anxiety and mood disorders in adulthood (Sachs-Ericsson, Sheffler, Stanley, Piazza, & Preacher, 2017). Further, ELA also appears to have a long-lasting impact on late-life psychological health.

CONTACT Julia Sheffler julia.sheffler@med.fsu.edu

Older adults who experience ELA also demonstrate a higher prevalence of psychopathology in late-life than older adults who did not experience ELA. In a sample of older adults, the presence of traumatic events in childhood and the number of ELA's experienced by an individual predicted current anxiety and depression (Van Assche et al., 2020). In fact, ELA is linked to increased risk for a range of psychological disorders in late-life (Rhee, Barry, Kuchel, Steffens, & Wilkinson, 2019). Rhee et al. (2019) found that the presence of ELA in older adults was associated with higher rates of mood and anxiety disorders, substance use disorders, and a higher number of lifetime suicide attempts. Thus, the detrimental, cumulative effects of ELAs on later psychopathology highlight the need for preventative interventions to promote healthy aging.

ELA and physical health conditions

ELA significantly increases the risk for a range of physical health conditions, increased healthcare utilization, as well as increased morbidity and premature mortality (Gilbert et al., 2015; Kalmakis & Chandler, 2014). Early work in this area demonstrated a graded relationship between ELA and risk for chronic health conditions (i.e. coronary heart disease and diabetes), such that the number of adversities experienced is associated with increased risk for multi-morbidity (Felitti et al., 1998). In addition to increasing risk for multi-morbidity, recent research suggests that ELA is also associated with earlier onset of chronic health conditions, mainly when the ELA involves direct violence exposure (McLaughlin et al., 2016).

A growing body of literature also suggests that ELA can impact healthy biological and cognitive aging (Höltge, Mc Gee, & Thoma, 2019; Short & Baram, 2019); however, the mechanisms by which ELA impacts late-life outcomes are still relatively unknown. Recent findings suggest a dose-response relationship between an increasing number of ELAs and a higher likelihood of poor general health, activity limitation, and chronic disease morbidity in older adults (Chanlongbutra, Singh, & Mueller, 2018). Further, the economic burden of long-term physical care increases significantly for adults exposed to ELA (Heckman, 2006). Thus, understanding modifiable factors that reduce the risk of disease and lessen disease severity may be especially critical in middle and older-aged adults.

ELA and cognitive outcomes

Relatively little is known about the association between ELA and cognitive functioning in adulthood. There is some evidence that suggests possible executive function impairment in adolescence attributable to specific ELAs, including physical abuse and neglect (Hostinar et al., 2012; Sheridan, Peverill, Finn, & McLaughlin, 2017). Additionally, abuse and neglect may contribute to verbal learning deficits, poor working memory, and poor episodic memory in young and older adults (Berthelot et al., 2015; Danese et al., 2017; Dannehl, Rief, & Euteneuer, 2017). Thus, the presence of ELA may initiate a life-course cascade of damaging cognitive consequences, which ultimately have broader impacts on multiple areas, such as episodic memory and executive function (Nurius, Green, Logan-Greene, & Borja, 2015; Su, D'Arcy, Yuan, & Meng, 2019). Few studies to date have looked at the long-lasting impact of cumulative ELA on cognitive function, and the underlying mechanisms are not well established.

One possible explanation is that early life experiences can impact cognitive and brain resiliency, such that individuals with a history of ELA may then be more susceptible to developing neurodegenerative processes in older ages. Results from recent studies suggest that early major traumas, chronic stress, and other major stressful life events may result in hippocampal dysfunction, impaired working and episodic memory, and poor executive function in middle-aged and older adults (Barch, Harms, Tillman, Hawkey, & Luby, 2019; Bremner, 1999; Lajud & Torner, 2015; Stawski, Sliwinski, & Smyth, 2006). Further, in specific populations, ELA has specifically been associated with the onset of Alzheimer's disease and age-related cognitive decline (Lesuis et al., 2018; Seifan, Schelke, Obeng-Aduasare, & Isaacson, 2015). While there is support for the negative impact of ELA on cognitive domains, physical health, and psychological well-being, the mechanism by which this occurs is not known. In the present study, we aim to address this gap by examining mid- and late-life emotional stress reactivity as a pathway between ELA and later pathology.

Mechanisms of action

Given the range of outcomes associated with ELA, there are multiple theories that help explain why ELA leads to such diverse and detrimental outcomes across the lifespan. Established theories identify 'toxic stress', or chronic overexposure to stressors that increase emotional stress reactivity. Emotional responses to stress result in a cascade of physiological processes that help the body adapt to challenging situations (McEwen, 1998, 2007). Over time, repeated emotional stress reactivity can increase multi-systemic physiological strain, or allostatic load, that disrupts cellular and system level functioning (Juster, McEwen, & Lupien, 2010; McEwen, 1998). Thus, ELA may result in a chronic imbalance in the emotional stress response resulting in biological changes (e.g. biological embedding) that have reaching impacts on physical and mental health across the life-course (Danese & McEwen, 2012).

Contemporary theories also highlight functional neural pathways impacted by ELA that can potentially account for the deleterious effects of chronic emotional stress reactivity throughout the life course. For example, the neuroimmune network hypothesis suggests that both physiological and emotional sensitization of the cortico-amygdala regions due to ELA promote increased threat sensitivity and emotional stress reactivity across adulthood (Nusslock & Miller, 2016). Thus, both allostatic load and the neuroimmune network hypothesis suggest that ELA may increase emotional stress reactivity across the lifespan that is subsequently associated with a wide range of negative physical, psychological, and cognitive outcomes. If a primary pathway through which ELA acts on later outcomes is through increased emotional stress reactivity across adulthood, then this pathway may act as a modifiable target for potential interventions to reduce the risk for psychopathology, health problems, and cognitive impairments in middle-aged and older adults. In the present study, we examined whether emotional stress reactivity in middle and older-aged individuals may account for the relationship between ELA and later outcomes in two distinct samples of middle-aged and older adults.

Hypotheses

Based on our theoretical frameworks, we hypothesized that ELA is associated with more depression and anxiety symptoms,

adverse health outcomes, and cognitive problems mid- to late-life. We also hypothesized that ELA is associated with greater emotional stress reactivity. Finally, we hypothesized that emotional stress reactivity in middle and older age mediates the association between ELA and each of the outcomes we assessed. We first established these relationships in a cross-sectional sample of older adults. We then investigated these relationships in a longitudinal sample of middle-aged and older adults to assess the generalizability of our cross-sectional analysis.

Methods

Participants

We used a multi-sample method to examine our hypotheses, 1) a cross-sectional sample of older adults and 2) a secondary analysis of the Midlife in the United States (MIDUS) dataset. These samples are described separately below. Of note, both samples include individuals under the age of 65, but older than 45 (middle-aged), as well as individuals over the age of 65 (older adults).

Cross-sectional sample

Data are drawn from a community-based sample of older adults. Participants were recruited through a participant registry for older adults who are interested in research, developed and managed by [blinded for review]. Participants are recruited for the registry at community events, through mailed flyers, and through automated voter registry calls. For the current study, registry participants ($N = 1,500$) were sent an email describing the study with a link to complete the on-line survey. Participants were also recruited through flyers posted in the community. Potential participants for the current study were invited via email to participate in our survey, which was administered using Qualtrics. Participants were aged 54–93 years old ($M = 70$, $SD = 5.5$). There was a total of 510 survey responses after eliminating responses with missing data. Only participants with complete data on all study variables were included in our analysis.

National sample

Data were drawn from a sub-sample of the participants who completed three waves of the Midlife Development in the United States surveys (MIDUS I, MIDUS II, and MIDUS III). The MIDUS study is one of the largest, longitudinal investigations of aging and health in the United Sates and, thus, an appropriate sample for our analysis. The full sample is described below.

Midus I

The first wave of MIDUS was collected between 1995 and 1996. The primary goal was to examine how social, psychological, and behavioral factors influence physical and mental health in mid to late life. The full sample comprised four subsamples: (1) a national random digit dialing (RDD) sample ($n = 3,487$); (2) oversamples from five metropolitan areas in the U.S. ($n = 757$); (3) siblings of individuals from the RDD sample ($n = 950$); and (4) a national RDD sample of twin pairs ($n = 1,914$). MIDUS I included 7,108 non-institutionalized, English-speaking adults in the contiguous United States, aged 25 to 74 years. Participants completed a telephone interview (30 min in length) and a mail survey that included two self-administered questionnaires, each approximately 45 pages in length. For the current study, ELAs and demographic covariates (e.g. age, gender, and income) were obtained from the first MIDUS wave.

Midus II

The second wave of MIDUS consisted of a follow-up survey ten years after the initial wave ($N = 4,693$). MIDUS II consisted of several parallel projects, including daily diary, biomarker, cognitive, and neuroscience studies. The MIDUS II survey and cognitive datasets were used to establish our emotional stress reactivity mediator variable and was the source for outcome variables used as covariates in the mediation models (i.e. depression, anxiety, health conditions, and the Brief Test of Adult Cognition by Telephone [BTACT] total composite score).

Midus III

The third wave of MIDUS ($N = 3,294$) consisted of follow up surveys with baseline and MIDUS II participants between 2013 and 2016. The MIDUS III response rate was 77% of living participants (46.3% of *all* MIDUS I participants). Specifically, of the original sample, 4% were deceased, 1.4%, were physically or mentally unable to complete the survey, 5.4% refused, 5.2% were unable to be interviewed, 3.5% no longer had a working number, and 34.2% were not interviewed at MIDUS III due to incomplete MIDUS II survey. MIDUS III largely repeated baseline measures and included a phone interview and an extensive self-administered questionnaire. For the current study, health conditions, depressive symptoms, anxiety symptoms, and BTACT total composite score obtained at Wave III were used as outcome variables in order to examine the development of new health conditions over time. The age range at MIDUS 3 was 46–100 ($M = 71.08$, SD = 11.38).

Measures

Covariates

We included the participants' age, self-reported sex (1 = male, 2 = female), and total household income (self-reported numerical value) for the previous year as covariates in all analyses.

Early life adversity (ELA)

In the *cross-sectional sample*, ELAs were summed to create a total ELA score (range 0–10), using an Adverse Childhood Experience questionnaire based on Felitti et al. (1998). For example, participants were asked, 'While you were growing up, during your first 18 years of life: Did a parent or other adult in the household often… swear at you, insult you, put you down, or humiliate you?' These items assessed different aspects of childhood physical, sexual, and emotional abuse, neglect, parental psychopathology, divorce, imprisonment, substance use, and violence in the home. 'Yes' responses were summed to create a continuous variable. This variable was winsorized at 6 to reduce skewness.

For the *MIDUS data*, based on the methodology of well-noted studies of ELAs (Friedman, Karlamangla, Gruenewald, Koretz, & Seeman, 2015; Schafer, Ferraro, & Mustillo, 2011; Slopen, Fitzmaurice, Williams, & Gilman, 2010), a total ELAs score was created by summing seven items obtained from the MIDUS I survey. Items representing ELAs were coded or recoded, such that 1 indicated the presence of ELA, whereas 0 represented the absence of the specific ELAs. Items included: 1) retrospective

report of family financial status in childhood, 2) measures of mother and father education levels, 3) parental separation/divorce, 4) death of a parent, and whether the participant experienced 5) emotional, 6) physical or 7) severe physical abuse. Coding for each of these items is explained in more detail below.

Retrospective report of family financial status in childhood included whether the participants' family was on welfare (1 = yes, 0 = no) and whether they viewed their family as financially worse off than others (recoded so that 'a little worse off' to 'a lot worse off' were counted as 1 and 'same as average family' to 'a lot better off' were coded as 0). These items were combined to create a single measure indicating the participants' relative socioeconomic status in childhood, where a score of 0 indicates scores of 0 on both items, and a score of 1 represents a score of 1 on either (or both) items. Measures of mother and father education levels (coded 1 if both parents received less than a high school education and coded 0 if either had a high school diploma or higher) were combined to create a single indicator of combined parental education to reduce redundancy in the ELA score. Finally, parental separation/divorce (coded 1 if yes before age of 18, 0 if no), death of parent (coded 1 if parent died before the age of 18, and 0 if there was no death), and whether the participant experienced emotional, physical or severe physical abuse (each coded '1' if the participant reported experiencing any amount of abuse, 'rarely' to 'often' and 0 if there was 'No Abuse') were included in the ELA count. Each of these items was recoded as 0 (absent) or 1 (present) and summed to create an ELA score with a possible range of 0–7.

Emotional stress reactivity

For the *cross-sectional sample*, participants were asked to self-report their emotional reactions to recent stress within the previous six months using four items (e.g. 'how often has stress been a problem for you in handling…Your family or social relationships?'). Responses were rated on a 0 (never or rarely) to 3 (always) and summed; the total was winsorized at 7 to reduce skewness.

In the *MIDUS* dataset, emotional stress reactivity was assessed at wave 2 using the stress reactivity subscale (alpha = .74) of the Multidimensional Personality questionnaire (Tellegen, 1982). It included three items, scored 1 (True of you) to 4 (False). Items were reverse coded as appropriate such that higher scores indicate higher emotional stress reactivity. Questions included, 'My mood often goes up and down', and 'minor setbacks sometimes irritate me too much'.

Outcome variables

Depression

In the *cross-sectional sample* of older adults, we administered the Patient Health Questionnaire (PHQ-9; Spitzer, Williams, Kroenke, Hornyak, & McMurray, 2000). This measure uses a 4-point scale, rated 1 (not at all) to 4 (nearly every day), to assess symptoms of depression during the past two weeks, such as having 'little interest or pleasure in doing things'. Note, one-item related to suicide was removed due to institutional IRB restrictions. The total score was winsorized at 20 to reduce skewness.

In the *MIDUS* sample, depression was assessed using the DSM III-R criteria for major depression and included seven items assessing depressed affect and anhedonia (e.g. 'lose interest in most things' and 'feel more tired or low on energy than is usual'). 'Yes' responses were summed to create a continuous variable for depressed affect and anhedonia symptoms, ranging from 0 to 7.

Anxiety

In the *cross-sectional sample*, anxiety symptoms were assessed using a 5-item version of the Beck Anxiety Inventory at MIDUS I and MIDUS III (Beck, Epstein, Brown, & Steer, 1988). Participants were asked to rate how often in the past week they felt the following on a scale of 1 (never) to 4 (most of the time). For example, items included, 'I was nervous', 'I had fear of the worst happening', and 'I felt my hands trembling'. The total score was winsorized at 13 to reduce skewness.

In the *MIDUS data*, anxiety was assessed using a 10-item scale based on the DSM-III criteria for generalized anxiety disorder at MIDUS I and MIDUS III. Participants were asked to rate how often in the past 12-months they 'were restless because of your worry' and 'were keyed up, on edge, or had a lot of nervous energy', on a scale of 1 (most days) to 4 (Never). Responses of 'most days' were summed to create a continuous variable (range = 0–10).

Cognitive functioning

In the *cross-sectional sample*, self-reported memory complaints were assessed using a 24-item memory complaints questionnaire (McDougall et al., 2016). Items were rated on a 1 (disagree strongly) to 5 (agree strongly) Likert scale and included items such as, 'the older I get, the harder it is to remember clearly' and 'I have no trouble keeping track of my appointments'. Items were reverse coded as appropriate so that higher scores indicated more memory complaints.

In the *MIDUS data*, cognitive functioning was assessed at waves II and III using the brief test of adult cognition by telephone (BTACT; Tun & Lachman, 2006). This measure was designed to assess multiple areas of cognitive functioning that are sensitive to the effects of aging. We examined the composite score at wave III across these domains as our outcome, while controlling for the BTACT composite score at wave II. The composite measure was calculated as the mean of z-scores for the five subtests (i.e. word list immediate, digits backward, category fluency, number series, backward counting, and word list delayed). These were calculated only for individuals with scores on all tests. The composite measure has shown good internal consistency (alpha = .712).

Health conditions

In the *cross-sectional sample*, participants were asked to check any conditions diagnosed by a physician, including high blood pressure, cancer, and arthritis. A total of 13 conditions were included and summed. This variable was positively skewed (1.21), which we addressed by winsorizing the variable at 5 (skew = .37).

In the *MIDUS data*, a total of 39 different chronic health problems were assessed at MIDUS II and MIDUS III. Participants were asked, 'In the past twelve months, have you experienced or been treated for any of the following?' A list of conditions was then presented to the participants, which included: autoimmune disorders, bone-related conditions (arthritis, rheumatism or other bone/joint diseases; sciatica, lumbago or recurring backache), cancer, chronic sleeping problems, diabetes/high blood sugar, digestive conditions (recurring stomach trouble, indigestion, or diarrhea; constipated all/most of time; ulcer; piles/hemorrhoids), food problems, gallbladder problems, hay fever, heart trouble (suspected or confirmed by doctor), high blood pressure/hypertension, lung conditions (asthma, bronchitis, emphysema; other lung problems; tuberculosis), migraine headaches, neurological conditions, skin trouble, stroke, thyroid disease, trouble with gums, mouth, or teeth, and urinary/bladder

problems. Physical conditions were reduced to 21 chronic condition categories to prevent similar conditions from causing redundancy in the count variable. For example, arthritis, rheumatism, other bone/joint diseases, sciatica, lumbago, and recurring backache were grouped together as 'bone-related conditions.' Two variables assessing psychological problems were removed from the summed chronic condition variable (i.e. anxiety/depression and alcohol/drug problem). The remaining 'Yes' responses for chronic conditions were summed for each wave of data collection. Health conditions from MIDUS II were used as a covariate in all relevant analyses. Health conditions at MIDUS III were used as a dependent variable in analyses. Both variables were winsorized at 8 to reduce skewness.

Analyses

To test our first and second hypotheses, we examined the direct effects of ELA on each outcome and mid- to late-life stress using linear regression modeling, as all predictors and outcomes were continuous. We used the PROCESS macro in SPSS (IBM Corp, 2016; model 4) to test direct associations of ELA using ordinary least squares path analysis. Specifically, mediation models were used to assess our outcome variables, testing for emotional stress reactivity as an indirect pathway between ELA and outcomes. The model controlled for possible confounders such as age, sex, and income. In the MIDUS models, covariates included MIDUS I levels of depression and anxiety symptoms, and MIDUS II health conditions and the cognitive total score based on the outcome assessed. Indirect effects of emotional stress reactivity were tested using bootstrapping methods.

Results

We included age, sex, and total household income as covariates in all analyses (see Table 1 for descriptives). All covariates were significantly associated with recent emotional stress reactivity (*ps* < .05); older age was significantly associated with more health conditions, and lower income was associated with more memory complaints and depressive symptoms (*ps* < .05). We have separated the results based on the sample and outcomes analyzed – model paths reported from the cross-sectional sample correspond with Figure 1, while the MIDUS model paths correspond with Figure 2.

Cross-sectional survey sample

Depression (N = 430)

ELAs were associated with higher emotional stress reactivity (a path: β = 0.20, $p < 0.001$) and with higher levels of depressive symptoms (c' path: β = 0.13, $p = <0.003$). Emotional stress reactivity was associated with higher depression (b path: β = 0.39, $p < 0.001$). ELAs indirectly increased depressive symptoms through increased emotional stress reactivity (*IE* = .08, 95%CI = 0.042–0.123).

Anxiety (N = 434)

ELAs were associated with higher levels of emotional stress reactivity (a path: β = 0.20, $p = <0.001$) and with higher anxiety (c' path: β = 0.10, $p = 0.017$). Emotional stress reactivity was significantly associated with higher levels of anxiety (b path: β = 0.45, $p < 0.001$). ELAs indirectly increased anxiety symptoms through increased emotional stress reactivity (*IE* = 0.09, 95%CI = 0.045–0.142).

Health conditions (N = 436)

ELAs were associated with higher reported levels of emotional stress reactivity (a path: β = 0.20, $p < 0.001$) and with an increased number of health conditions (c' path: β = 0.12, $p < .015$). Recent emotional stress reactivity was also associated with a higher number of reported health conditions (b path: β = 0.16, $p < 0.001$). ELAs indirectly increased health problems through increased emotional stress reactivity (*IE* = 0.03, 95%CI = 0.009–0.065).

Memory complaints (N = 409)

ELAs were associated with higher levels of emotional stress reactivity (a path: β = 0.20, $p < 0.001$), and emotional stress reactivity was significantly associated with memory complaints (b path: β = .18, $p < 0.001$). Although ELAs were not directly associated with memory (c' path: β = .03, $p = .524$), mediation analyses demonstrated that ELAs significantly influenced memory complaints indirectly through emotional stress reactivity (*IE* = 0.04, 95%CI = 0.012–0.067).

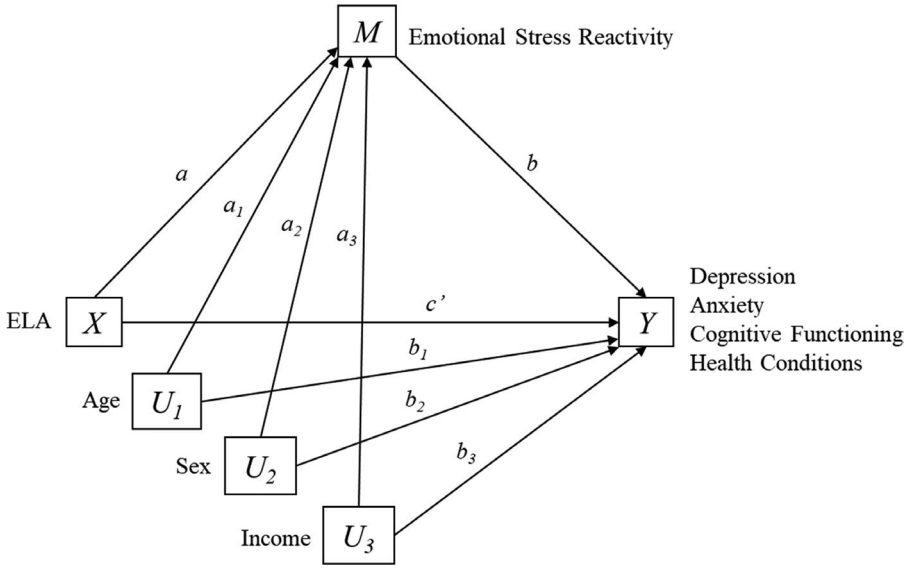

Figure 1. Cross-sectional sample mediation model.

Note. ELA = Early life adversity.

Table 1. Demographics.

	MIDUS sample				Cross-sectional sample			
	N[a]	*M* (*SD*)	Percent (%)	Range	N	*M* (*SD*)	Percent (%)	Range
Covariates & independent variables[b]								
MIDUS I age	2958	45.77 (11.26)	–	24–74	510	69.6 (5.51)	–	54–93
Sex (male)	2944	–	44.8	–	192	–	35.2	–
Race (Caucasian)	2655	–	93.9	–	475	–	87.2	–
12-month household income								
Less than $10,000	118	–	4.2	–	3	–	.6	–
$10,000–$19,999	164	–	5.9	–	32	–	5.9	–
$20,000–$29,999	248	–	8.8	–	29	–	5.3	–
$30,000–$49,000	552	–	19.7	–	95	–	17.4	–
$50,000–$74,999	565	–	20.8	–	122	–	22.4	–
$75,000–$99,999	300	–	12.6	–	82	–	15	–
More than $100,000	855	–	27.8	–	130	–	23.9	–
Education								
Did not completehigh school	139	–	4.7	–	–	–	–	–
High school diploma (or equivalent)	748	–	25.3	–	15	–	2.8	–
Some college	657	–	22.3	–	68	–	12.5	–
Associate's degree	226	–	7.7	–	38	–	7	–
Bachelor's degree	759	–	25.7	–	145	–	26.6	–
Master's degree	287	–	9.7	–	170	–	31.2	–
Doctoral degree	138	–	4.7	–	65	–	11.9	–
ELA	2368	1.31 (1.25)	–	0–6	481	1.63 (1.81)	–	0–6
Emotional stress reactivity	2643	6.11 (2.24)	–	3–12	467	1.83 (1.79)	–	0–7
MIDUS II health[c]	2656	2.17 (1.90)	–	0–8	–	–	–	–
MIDUS I depression	2958	0.59 (1.72)	–	0–7	–	–	–	–
MIDUS I anxiety	2958	0.12 (0.81)	–	0–10	–	–	–	–
MIDUS II cognition[d]	2630	0.21 (0.95)	–	−2.47–3.63	–	–	–	–
Outcomes[e]								
Depression	2958	0.58 (1.67)	–	0–7	481	10.87 (2.94)	–	8–20
Anxiety	2958	0.11 (0.82)	–	0–10	486	7.13 (2.22)	–	5–13
Cognition	2733	0.02 (0.69)	–	−2.59–2.03	456	67.26 (14.58)	–	31–106
Health conditions	2514	3.01 (2.19)	–	0–8	545	2.08 (1.60)	–	0–5

Note. ELA = Early life adversity.
[a]MIDUS N includes all participants with complete data on at least one of the MIDUS outcome variables.
[b]In the MIDUS sample, ACEs, health, recent emotional stress reactivity, depression and anxiety were used as independent variables assessed during Wave 2 of MIDUS data collection.
[c]Health conditions were winsorized at 8 to reduce skewness.
[d]All Wave 2 cognition composite variables were z-scored.
[e]In the MIDUS sample, these outcome variables were assessed during Wave 3 of MIDUS data collection.

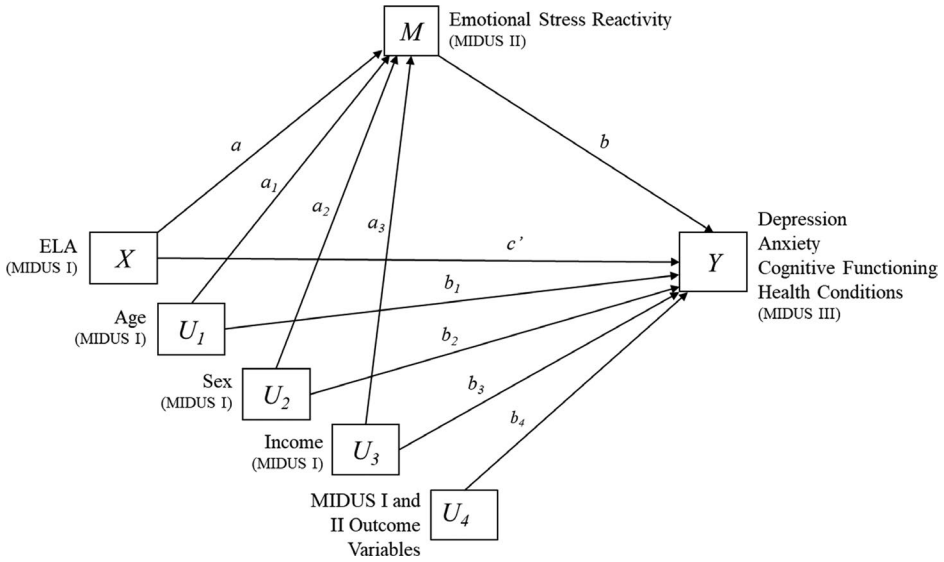

Figure 2. MIDUS national sample mediation model.

Note. ELA = Early life adversity. MIDUS I and II Outcome Variables were used as covariates in the mediation models (i.e. MIDUS I depression, MIDUS I anxiety, MIDUS II health conditions, and the MIDUS II Brief Test of Adult Cognition by Telephone [BTACT] total composite score).

MIDUS longitudinal sample

Depression (N = 2,514)

ELAs were associated with new-onset of depressive symptoms at MIDUS III (c' path: β = 0.12, $p < 0.001$) and with higher levels of emotional stress reactivity at MIDUS II (a path: β = 0.10, $p < 0.001$). Emotional stress reactivity was associated with higher levels of depression (b path: β = 0.13, $p < 0.001$), and the indirect effect of ELA (MIDUS I) on MIDUS III depression through emotional stress reactivity was significant (*IE* = 0.01, 95%CI = 0.007–0.020).

Anxiety (N = 2,514)

ELAs were associated with increased levels of anxiety at MIDUS III, (c' path: β = 0.05, $p < 0.003$), and with higher levels of emotional stress reactivity in middle age (a path: β = 0.11, $p < 0.001$). Emotional stress reactivity was associated with higher levels of anxiety (b path: β = 0.06, $p < 0.001$). ELAs indirectly increased anxiety symptoms through increased emotional stress reactivity (*IE* = 0.01, 95%CI = 0.001–0.013).

Health conditions (N = 2,202)

Consistent with previous literature, ELAs were significantly associated with new-onset of health conditions at MIDUS III (c' path: β = 0.06, $p < 0.001$). ELAs were also associated with higher emotional stress reactivity in middle age (a path: β = 0.07, $p < 0.001$). Emotional stress reactivity in middle age was associated with the onset of later health conditions (b path: β = 0.06, $p < 0.001$), and emotional stress reactivity in middle age mediated the relationship between ELAs and later health conditions (*IE* = 0.005, 95%CI = 0.002–0.009).

Cognitive functioning (N = 1,991)

ELAs were significantly associated with higher levels of emotional stress reactivity in adulthood (a path: β = 0.09, $p < 0.001$) and with lower composite scores on the MIDUS III BTACT (c' path: β = –0.05, $p < 0.001$). Emotional stress reactivity was also significantly associated with lower BTACT composite scores (b path: β = –0.01, $p < 0.003$). Emotional stress reactivity in adulthood mediated the relationship between ELAs and later BTACT composite scores (*IE* = –0.004, CI = –0.007 to –0.001), even controlling for MIDUS II BTACT composite score. Table 2 demonstrates the examined main effects of ELA and emotional stress reactivity on all outcome variables.

Table 2. Direct and indirect effects of key variables.

	Depression		Anxiety		Health conditions		Cognition	
	β/IE	*SE*	β/IE	*SE*	β/IE	*SE*	β/IE	*SE*
Cross-sectional sample								
ELA (c prime path)	0.13	0.07	0.10	0.05	0.12	0.04	0.03	0.39
Emotional stress reactivity (b path)	0.39	0.07	0.45	0.06	0.16	0.04	0.18	0.40
Indirect effects	0.08	0.02	0.09	0.02	0.03	0.01	0.04	0.01
MIDUS longitudinal sample								
ELA (c prime path)	0.12	0.03	0.05	0.01	0.06	0.03	–0.05	0.01
Emotional stress reactivity (b path)	0.13	0.01	0.06	0.01	0.06	0.02	–0.04	0.00
Indirect effects	0.01	0.00	0.01	0.00	0.01	0.00	–0.01	0.00

Note. ELA = Early life adversity; SE = Standard Error; IE = Indirect Effect.

Discussion

ELA is known to impact psychopathology, physical health conditions, and cognitive function throughout the life course. The mechanisms through which ELA impacts mid- to late-life outcomes are relatively unknown. Current theories and models of stress and aging, such as allostatic load and the neuroimmune network hypothesis, posit that ELA can result in a cascade of physiological and emotional changes that disrupt stress responses and increase vulnerability to age-related disease. Examining mid- and late-life emotional stress reactivity as a mediator between ELA and later outcomes expands on current theories by identifying a potential point for intervention across the lifespan for individuals exposed to ELA. Thus, as a transdiagnostic risk factor, ELA can potentially inform the development of interventions to improve physical health and cognitive resiliency in addition to psychological well-being.

In this study, we used both cross-sectional and longitudinal data to analyze the relationship between ELA and health outcomes, anxiety, depression, and cognitive functioning in middle-aged and older adults. Through a combination of linear regression modeling and bootstrapping methods for mediation analysis, we determined that ELA was associated with an increase in negative, subjective experiences of stress in late-life, as well as increased self-reported emotional stress reactivity in mid- to late-life. Further, the observed subjective experiences of stress-mediated the deleterious effect of ELA on all outcomes examined – a finding we replicated across two distinct datasets.

The results from this study are consistent with the allostatic load theory of disease, which suggests that early environmental stressors, life events, trauma, and abuse impact stress appraisals and physiological responses to stressful events. Over-activation of physiological stress-responses potentially increases oxidative stress, inflammation, and disruptions in normal cellular signaling (Picard, Juster, & McEwen, 2014; Picard & McEwen, 2018). Specifically, neuroendocrine (e.g. cortisol) and metabolic (e.g. blood glucose) stress mediators are associated with an increase in interleukin-6 (IL-6) proinflammatory cytokines and mitochondrial function impairment (Picard et al., 2015). Findings from recent studies demonstrate a relationship between psychological stress, allostatic load, aging, and increased levels of circulating mtDNA, a known driver of inflammation and risk factor for mid to late-life health conditions, including cardiovascular disease and dementia (Pinti et al., 2014; Trumpff et al., 2019). Thus, disruptions in adult emotional responses to stress may result in physiological and psychological strain across the lifespan, increasing the risk of disease, psychopathology, and cognitive impairment with age (McEwen, 1998; Picard, 2011). Consistent with previous research, our study supports that ELA is a pivotal environmental stressor that may set these deleterious stress processes into motion and set the trajectory for the development of age-related diseases.

In addition to physiological changes, the effects of ELA on mid-and late-life emotional stress reactivity and subsequent outcomes may also be related to social and emotional dysregulation. The neuro-immune network hypothesis suggests that adverse outcomes related to the bidirectional relationship between

behaviors, emotional processes, and physiological changes are linked early in life (Hostinar, Nusslock, & Miller, 2018). Specifically, early stress exposure may lead to alterations in threat sensitivity in the amygdala, which combine with maladaptive coping and emotion regulation strategies to maintain a cycle of chronic activation of stress systems. For example, early abuse experiences may lead to more negative cognitive styles and more avoidant coping mechanisms, leading to greater social conflict as an adult (Kuyken & Brewin, 1999). Further, ELA may also increase the likelihood of poor health behaviors, such as substance use, unhealthy nutrition, and reduced exercise (Windle et al., 2018), which may further exacerbate chronic inflammation through biological pathways. Thus, the behavioral and emotional consequences of ELA likely play an integral role in promoting higher levels of stress across the lifespan, indirectly influencing a range of health and psychological outcomes later in life.

Our data provide evidence to support the potential long-term impact of ELA on psychological well-being, physical health, and cognitive functioning. Specifically, emotional stress reactivity may play a role as a transdiagnostic risk factor that persists across the lifespan. The potential implications of this finding are significant for intervention development and testing in older adults. For example, existing behavioral interventions using emotion regulation strategies to reduce emotional stress reactivity in specific psychiatric populations (e.g. Borderline Personality Disorder, Depression, and Anxiety) and are effective across age groups (Gratz & Gunderson, 2006; Prakash, Hussain, & Schirda, 2015). Based on our results, emotion regulation strategies may serve as an effective intervention to improve physical health and cognitive function throughout the life course in addition to current psychological applications. Future studies are needed to test the effectiveness of such interventions on late-life physiological and cognitive outcomes.

Limitations

Several limitations associated with our study warrant mention. First, the population of both samples examined is mostly White and consists of individuals with higher than average levels of education. Thus, our findings may not fully generalize to minority and disadvantaged populations at higher risk for specific health conditions. Additionally, our analysis of outcomes specific to ELA and emotional stress reactivity in the current study depended on available measures from secondary data. Although associated with expected correlates, these measures were brief, subjective, and did not provide the sensitivity and specificity needed for intervention development. For ELA, we chose to examine a traditional, retrospective and cumulative indicator.

Regarding retrospective self-reports, previous studies have noted that retrospective reporting of ELA may lead to underreporting (Femina, Yeager, & Lewis, 1990; Williams, 1995), although adult reports are generally reliable (Dube, Williamson, Thompson, Felitti, & Anda, 2004) and strongly correlate with prospective reports (Reuben et al., 2016). Concerning the adversities included in our count variable of ELAs, some researchers have pointed out that the conventional childhood adversity counts may exclude important adverse experiences of various minority groups, such as discrimination or environmental factors, such as neighborhood safety (see Cronholm et al., 2015). Further, we acknowledge that our outcome measures of depression, anxiety, and cognition were not designed to provide clinical cutoffs, but rather capture symptom experience. Thus, it is difficult to determine to fully extend our findings to individuals with diagnosable psychopathology and neurocognitive disorders.

Conclusions and future directions

In sum, our multi-sample study found that the relationship between ELA and age-related psychological well-being, physical health, and cognitive functioning is mediated by emotional stress reactivity in middle age and older adulthood. Our findings indicated that emotional stress reactivity might provide a point for intervention across the lifespan for individuals exposed to ELA.

Future studies will build on our current results to identify measures of stress that increase specificity and objectivity. For example, which types of stress best predict cellular damage in older adults, as well as subjective and objective measures of depression and memory, are relatively unknown. As our findings corroborate relationships proposed in the allostatic load theory of stress and disease, targeted biomarkers such as cortisol and mitochondrial DNA can be further investigated within the context of ELA and emotional stress reactivity. Specific studies on ethnically and racially underrepresented populations can expand on these results to identify culturally specific risk and protective factors of stress and age-related disease and cognitive function. Results from this and future studies can build toward the development of targeted interventions to improve emotional regulation throughout the lifespan in order to reduce the risk for pathology in mid- to late-life. Overall, the present study adds to our understanding of the long-term impact of ELA and advances our understanding of the mechanisms underlying age-related disease and cognitive function.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

Barch, D. M., Harms, M. P., Tillman, R., Hawkey, E., & Luby, J. L. (2019). Early childhood depression, emotion regulation, episodic memory, and hippocampal development. *Journal of Abnormal Psychology*, *128*(1), 81–95. doi:10.1037/abn0000392

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology*, *56*(6), 893–897. doi:10.1037//0022-006X.56.6.893

Berthelot, N., Paccalet, T., Gilbert, E., Moreau, I., Mérette, C., Gingras, N., … Maziade, M. (2015). Childhood abuse and neglect may induce deficits in cognitive precursors of psychosis in high-risk children. *Journal of Psychiatry & Neuroscience: JPN*, *40*(5), 336–343. doi:10.1503/jpn.140211

Bremner, J. D. (1999). Does stress damage the brain?*Biological Psychiatry*, *45*(7), 797–805. doi:10.1016/S0006-3223(99)00009-8

Chanlongbutra, A., Singh, G. K., & Mueller, C. D. (2018). Adverse childhood experiences, health-related quality of life, and chronic disease risks in rural areas of the United States. *Journal of Environmental and Public Health*, *2018*, 7151297. doi:10.1155/2018/7151297

Charles, S. T., Piazza, J. R., Mogle, J., Sliwinski, M. J., & Almeida, D. M. (2013). The wear and tear of daily stressors on mental health. *Psychological Science*, *24*(5), 733–741. doi:10.1177/0956797612462222

Cronholm, P. F., Forke, C. M., Wade, R., Bair-Merritt, M. H., Davis, M., Harkins-Schwarz, M., … Fein, J. A. (2015). Adverse childhood experiences: Expanding the concept of adversity. *American Journal of Preventive Medicine*, *49*(3), 354–361. doi:10.1016/j.amepre.2015.02.001

Danese, A., & McEwen, B. S. (2012). Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiology & Behavior*, *106*(1), 29–39. doi:10.1016/j.physbeh.2011.08.019

Danese, A., Moffitt, T. E., Arseneault, L., Bleiberg, B. A., Dinardo, P. B., Gandelman, S. B., … Caspi, A. (2017). The origins of cognitive deficits in victimized children: Implications for neuroscientists and clinicians. *The American Journal of Psychiatry*, *174*(4), 349–361. doi:10.1176/appi.ajp.2016.16030333

Dannehl, K., Rief, W., & Euteneuer, F. (2017). Childhood adversity and cognitive functioning in patients with major depression. *Child Abuse & Neglect*, *70*, 247–254. doi:10.1016/j.chiabu.2017.06.013

Dich, N., Hansen, A. M., Avlund, K., Lund, R., Mortensen, E. L., Bruunsgaard, H., & Rod, N. H. (2015). Early life adversity potentiates the effects of later life stress on cumulative physiological dysregulation. *Anxiety, Stress, and Coping*, *28*(4), 372–390. doi:10.1080/10615806.2014.969720

Dube, S. R., Anda, R. F., Felitti, V. J., Chapman, D. P., Williamson, D. F., & Giles, W. H. (2001). Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: Findings from the adverse childhood experiences study. *JAMA*, *286*(24), 3089–3096. doi:10.1001/jama.286.24.3089

Dube, S. R., Williamson, D. F., Thompson, T., Felitti, V. J., & Anda, R. F. (2004). Assessing the reliability of retrospective reports of adverse childhood experiences among adult HMO members attending a primary care clinic. *Child Abuse & Neglect*, *28*(7), 729–737. doi:10.1016/j.chiabu.2003.08.009

Duffy, K. A., McLaughlin, K. A., & Green, P. A. (2018). Early life adversity and health-risk behaviors: Proposed psychological and neural mechanisms. *Annals of the New York Academy of Sciences*, *1428*(1), 151–169. doi:10.1111/nyas.13928

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., … Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *American Journal of Preventive Medicine*, *14*(4), 245–258. doi:10.1016/S0749-3797(98)00017-8

Femina, D. D., Yeager, C. A., & Lewis, D. O. (1990). Child abuse: Adolescent records vs. adult recall. *Child Abuse & Neglect*, *14*(2), 227–231. doi:10.1016/0145-2134(90)90033-P

Ferraro, K. F., Schafer, M. H., & Wilkinson, L. R. (2016). childhood disadvantage and health problems in middle and later life: Early imprints on physical health?*American Sociological Review*, *81*(1), 107–133. doi:10.1177/0003122415619617

Friedman, E. M., Karlamangla, A. S., Gruenewald, T. L., Koretz, B., & Seeman, T. E. (2015). Early life adversity and adult biological risk profiles. *Psychosomatic Medicine*, *77*(2), 176–185. doi:10.1097/PSY.0000000000000147

Gilbert, L. K., Breiding, M. J., Merrick, M. T., Thompson, W. W., Ford, D. C., Dhingra, S. S., & Parks, S. E. (2015). Childhood adversity and adult chronic disease: An update from ten states and the District of Columbia, 2010. *American Journal of Preventive Medicine*, *48*(3), 345–349. doi:10.1016/j.amepre.2014.09.006

Gratz, K. L., & Gunderson, J. G. (2006). Preliminary data on an acceptance-based emotion regulation group intervention for deliberate self-harm among women with borderline personality disorder. *Behavior Therapy*, *37*(1), 25–35. doi:10.1016/j.beth.2005.03.002

Green, J. G., McLaughlin, K. A., Berglund, P. A., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2010). Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I: Associations with first onset of DSM-IV disorders. *Archives of General Psychiatry*, *67*(2), 113–123. doi:10.1001/archgenpsychiatry.2009.186

Heckman, J. J. (2006). Skill formation and the economics of investing in disadvantaged children. *Science (New York, N.Y.)*, *312*(5782), 1900–1902. doi:10.1126/science.1128898

Höltge, J., Mc Gee, S. L., & Thoma, M. V. (2019). The curvilinear relationship of early-life adversity and successful aging: The mediating role of mental health. *Aging & Mental Health*, *23*(5), 608–617. doi:10.1080/13607863.2018.1433635

Hostinar, C. E., Nusslock, R., & Miller, G. E. (2018). Future directions in the study of early-life stress and physical and emotional health: Implications of the neuroimmune network hypothesis. *Journal of Clinical Child and Adolescent Psychology: The Official Journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53*, *47*(1), 142–156. doi:10.1080/15374416.2016.1266647

Hostinar, C. E., Stellern, S. A., Schaefer, C., Carlson, S. M., & Gunnar, M. R. (2012). Associations between early life adversity and executive function in children adopted internationally from orphanages. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(Suppl 2), 17208–17212. doi:10.1073/pnas.1121246109

IBM Corp. (2016). IBM SPSS Statistics for Windows (Version 24.0). Armonk, NY: IBM Corp.

Juster, R. P., McEwen, B. S., & Lupien, S. J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience and Biobehavioral Reviews*, *35*(1), 2–16. doi:10.1016/j.neubiorev.2009.10.002

Kalmakis, K. A., & Chandler, G. E. (2014). Adverse childhood experiences: Towards a clear conceptual meaning. *Journal of Advanced Nursing*, *70*(7), 1489–1501. doi:10.1111/jan.12329

Kuyken, W., & Brewin, C. R. (1999). The relation of early abuse to cognition and coping in depression. *Cognitive Therapy and Research*, *23*(6), 665–677. doi:10.1023/A:1018793026132

Lajud, N., & Torner, L. (2015). Early life stress and hippocampal neurogenesis in the neonate: Sexual dimorphism, long term consequences and possible mediators. *Frontiers in Molecular Neuroscience*, *8*, 3. doi:10.3389/fnmol.2015.00003

Lesuis, S. L., Hoeijmakers, L., Korosi, A., de Rooij, S. R., Swaab, D. F., Kessels, H. W., … Krugers, H. J. (2018). Vulnerability and resilience to Alzheimer's disease: Early life conditions modulate neuropathology and determine cognitive reserve. *Alzheimer's Research & Therapy*, *10*(1), 95. doi:10.1186/s13195-018-0422-7

Li, M., D'Arcy, C., & Meng, X. (2016). Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: Systematic review, meta-analysis, and proportional attributable fractions. *Psychological Medicine*, *46*(4), 717–730. doi:10.1017/s0033291715002743

Lindert, J., von Ehrenstein, O. S., Grashow, R., Gal, G., Braehler, E., & Weisskopf, M. G. (2014). Sexual and physical abuse in childhood is associated with depression and anxiety over the life course: Systematic review and d meta-analysis. *International Journal of Public Health*, *59*(2), 359–372. doi:10.1007/s00038-013-0519-5

Lovallo, W. R., Farag, N. H., Sorocco, K. H., Acheson, A., Cohoon, A. J., & Vincent, A. S. (2013). Early life adversity contributes to impaired cognition and impulsive behavior: Studies from the Oklahoma Family Health Patterns Project. *Alcoholism, Clinical and Experimental Research*, *37*(4), 616–623. doi:10.1111/acer.12016

Luby, J. L., Barch, D., Whalen, D., Tillman, R., & Belden, A. (2017). Association between early life adversity and risk for poor emotional and physical health in adolescence: A putative mechanistic neurodevelopmental pathway. *JAMA Pediatrics*, *171*(12), 1168–1175. doi:10.1001/jamapediatrics.2017.3009

McCrory, C., Dooley, C., Layte, R., & Kenny, R. A. (2015). The lasting legacy of childhood adversity for disease risk in later life. *Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association*, *34*(7), 687–696. doi:10.1037/hea0000147

McDougall, G. J., George, S. D., Mcdonough, I. M., Lyon, L., LaRocca, M. & Arheart, K. (2016). O3-10-03: Development and validation of the memory complaints questionnaire. *Alzheimer's & Dementia*, *12*, P311–P311. doi:10.1016/j.jalz.2016.06.563

McEwen, B. S. (1998). Stress, adaptation, and disease. Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, *840*, 33–44. doi:10.1111/j.1749-6632.1998.tb09546.x

McEwen, B. S. (2004). Protection and damage from acute and chronic stress: Allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Annals of the New York Academy of Sciences*, *1032*(1), 1–7. doi:10.1196/annals.1314.001

McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiological Reviews*, *87*(3), 873–904. doi:10.1152/physrev.00041.2006

McEwen, B. S. (2013). The brain on stress: Toward an integrative approach to brain, body, and behavior. *Perspectives on Psychological Science: A Journal of the Association for Psychological Science*, *8*(6), 673–675. doi:10.1177/1745691613506907

McEwen, B. S., & Akil, H. (2020). Revisiting the stress concept: Implications for affective disorders. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *40*(1), 12–21. doi:10.1523/JNEUROSCI.0733-19.2019

McEwen, B. S., & Wingfield, J. C. (2003). The concept of allostasis in biology and biomedicine. *Hormones and Behavior*, *43*(1), 2–15. doi:10.1016/s0018-506x(02)00024-7

McLaughlin, K. A., Basu, A., Walsh, K., Slopen, N., Sumner, J. A., Koenen, K. C., & Keyes, K. M. (2016). Childhood exposure to violence and chronic physical conditions in a national sample of US adolescents. *Psychosomatic Medicine*, *78*(9), 1072–1083. doi:10.1097/PSY.0000000000000366

McLaughlin, K. A., Kubzansky, L. D., Dunn, E. C., Waldinger, R., Vaillant, G., & Koenen, K. C. (2010). Childhood social environment, emotional reactivity to stress, and mood and anxiety disorders across the life course. *Depression and Anxiety*, *27*(12), 1087–1094. doi:10.1002/da.20762

Miller, G. E., Chen, E., & Parker, K. J. (2011). Psychological stress in childhood and susceptibility to the chronic diseases of aging: Moving toward a model of behavioral and biological mechanisms. *Psychological Bulletin*, *137*(6), 959–997. doi:10.1037/a0024768

Nurius, P. S., Green, S., Logan-Greene, P., & Borja, S. (2015). Life course pathways of adverse childhood experiences toward adult psychological well-being: A stress process analysis. *Child Abuse & Neglect*, *45*, 143–153. doi:10.1016/j.chiabu.2015.03.008

Nusslock, R., & Miller, G. E. (2016). Early-life adversity and physical and emotional health across the lifespan: A neuroimmune network hypothesis. *Biological Psychiatry*, *80*(1), 23–32. doi:10.1016/j.biopsych.2015.05.017

Picard, M. (2011). Pathways to aging: The mitochondrion at the intersection of biological and psychosocial sciences. *Journal of Aging Research*, *2011*, 814096. doi:10.4061/2011/814096

Picard, M., Juster, R. P., & McEwen, B. S. (2014). Mitochondrial allostatic load puts the 'gluc' back in glucocorticoids. *Nature Reviews Endocrinology*, *10*(5), 303–310. doi:10.1038/nrendo.2014.22

Picard, M., & McEwen, B. S. (2018). Psychological stress and mitochondria: A systematic review. *Psychosomatic Medicine*, *80*(2), 141–153. doi:10.1097/PSY.0000000000000545

Picard, M., McManus, M. J., Gray, J. D., Nasca, C., Moffat, C., Kopinski, P. K., … Wallace, D. C. (2015). Mitochondrial functions modulate neuroendocrine, metabolic, inflammatory, and transcriptional responses to acute psychological stress. *Proceedings of the National Academy of Sciences of the United States of America*, *112*(48), E6614–E6623. doi:10.1073/pnas.1515733112

Pinti, M., Cevenini, E., Nasi, M., De Biasi, S., Salvioli, S., Monti, D., … Cossarizza, A. (2014). Circulating mitochondrial DNA increases with age and is a familiar trait: Implications for "inflamm-aging". *European Journal of Immunology*, *44*(5), 1552–1562. doi:10.1002/eji.201343921

Prakash, R. S., Hussain, M. A., & Schirda, B. (2015). The role of emotion regulation and cognitive control in the association between mindfulness disposition and stress. *Psychology and Aging*, *30*(1), 160–171. doi:10.1037/a0038544

Rao, U., Chen, L. A., Bidesi, A. S., Shad, M. U., Thomas, M. A., & Hammen, C. L. (2010). Hippocampal changes associated with early-life adversity and vulnerability to depression. *Biological Psychiatry*, *67*(4), 357–364. doi:10.1016/j.biopsych.2009.10.017

Reuben, A., Moffitt, T. E., Caspi, A., Belsky, D. W., Harrington, H., Schroeder, F., … Danese, A. (2016). Lest we forget: Comparing retrospective and prospective assessments of adverse childhood experiences in the prediction of adult health. *Journal of Child Psychology and Psychiatry*, *57*(10), 1103–1112. doi:10.1111/jcpp.12621

Rhee, T. G., Barry, L. C., Kuchel, G. A., Steffens, D. C., & Wilkinson, S. T. (2019). Associations of adverse childhood experiences with past-year DSM-5 psychiatric and substance use disorders in older adults. *Journal of the American Geriatrics Society*, *67*(10), 2085–2093. doi:10.1111/jgs.16032

Sachs-Ericsson, N. J., Sheffler, J. L., Stanley, I. H., Piazza, J. R., & Preacher, K. J. (2017). When emotional pain becomes physical: Adverse childhood experiences, pain, and the role of mood and anxiety disorders. *Journal of Clinical Psychology*, *73*(10), 1403–1428. doi:10.1002/jclp.22444

Schafer, M. H., Ferraro, K. F., & Mustillo, S. A. (2011). Children of misfortune: Early adversity and cumulative inequality in perceived life trajectories. *AJS; American Journal of Sociology*, *116*(4), 1053–1091. doi:10.1086/655760

Seifan, A., Schelke, M., Obeng-Aduasare, Y., & Isaacson, R. (2015). Early life epidemiology of alzheimer's disease - A critical review. *Neuroepidemiology*, *45*(4), 237–254. doi:10.1159/000439568

Sheridan, M. A., Peverill, M., Finn, A. S., & McLaughlin, K. A. (2017). Dimensions of childhood adversity have distinct associations with neural systems underlying executive functioning. *Development and Psychopathology*, *29*(5), 1777–1794. doi:10.1017/S0954579417001390

Shonkoff, J. P., Boyce, W. T., & McEwen, B. S. (2009). Neuroscience, molecular biology, and the childhood roots of health disparities: Building a new framework for health promotion and disease prevention. *JAMA*, *301*(21), 2252–2259. doi:10.1001/jama.2009.754

Short, A. K., & Baram, T. Z. (2019). Early-life adversity and neurological disease: Age-old questions and novel answers. *Nature Reviews. Neurology*, *15*(11), 657–669. doi:10.1038/s41582-019-0246-5

Slopen, N., Fitzmaurice, G., Williams, D. R., & Gilman, S. E. (2010). Poverty, food insecurity, and the behavior for childhood internalizing and externalizing disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*, *49*(5), 444–452. doi:10.1097/00004583-201005000-00005

Spitzer, R. L., Williams, J. B., Kroenke, K., Hornyak, R., & McMurray, J. (2000). Validity and utility of the PRIME-MD patient health questionnaire in assessment of 3000 obstetric-gynecologic patients: The PRIME-MD Patient Health Questionnaire Obstetrics-Gynecology Study. *American Journal of Obstetrics and Gynecology*, *183*(3), 759–769. doi:10.1067/mob.2000.106580

Stawski, R. S., Sliwinski, M. J., & Smyth, J. M. (2006). Stress-related cognitive interference predicts cognitive function in old age. *Psychology and Aging*, *21*(3), 535–544. doi:10.1037/0882-7974.21.3.535

Su, Y., D'Arcy, C., Yuan, S., & Meng, X. (2019). How does childhood maltreatment influence ensuing cognitive functioning among people with the exposure of childhood maltreatment? A systematic review of prospective cohort studies. *Journal of Affective Disorders*, *252*, 278–293. doi:10.1016/j.jad.2019.04.026

Swartz, J. R., Knodt, A. R., Radtke, S. R., & Hariri, A. R. (2015). A neural biomarker of psychological vulnerability to future life stress. *Neuron*, *85*(3), 505–511. doi:10.1016/j.neuron.2014.12.055

Tellegen. (1982). Brief manual for the Multidimensional Personality Questionnaire. Unpublished manuscript, University of Minnesota, Minneapolis.

Tracy, M., Salo, M., Slopen, N., Udo, T., & Appleton, A. A. (2019). Trajectories of childhood adversity and the risk of depression in young adulthood: Results from the Avon Longitudinal Study of Parents and Children. *Depression and Anxiety*, *36*(7), 596–606. doi:10.1002/da.22887

Trumpff, C., Marsland, A. L., Basualto-Alarcón, C., Martin, J. L., Carroll, J. E., Sturm, G., … Picard, M. (2019). Acute psychological stress increases serum circulating cell-free mitochondrial DNA. *Psychoneuroendocrinology*, *106*, 268–276. doi:10.1016/j.psyneuen.2019.03.026

Tun, P. A., & Lachman, M. E. (2006). Telephone assessment of cognitive function in adulthood: The brief test of adult cognition by telephone. *Age and Ageing*, *35*(6), 629–632. doi:10.1093/ageing/afl095

Van Assche, L., Van de Ven, L., Vandenbulcke, M., & Luyten, P. (2020). Ghosts from the past? The association between childhood interpersonal trauma, attachment and anxiety and depression in late life. *Aging & Mental Health*, *24*(6), 898–898. doi:10.1080/13607863.2019.1571017

Vannorsdall, T. D., & Munro, C. A. (2017). The link between childhood adversity and late-life mental health: Evidence for the influence of early-life experiences or illusory correlations?*International Psychogeriatrics*, *29*(3), 357–358. doi:10.1017/S1041610216002416

Williams, L. M. (1995). Recovered memories of abuse in women with documented child sexual victimization histories. *Journal of Traumatic Stress*, *8*(4), 649–673. doi:10.1007/BF02102893

Windle, M., Haardörfer, R., Getachew, B., Shah, J., Payne, J., Pillai, D., & Berg, C. J. (2018). A multivariate analysis of adverse childhood experiences and health behaviors and outcomes among college students. *Journal of American College Health: Journal of ACH*, *66*(4), 246–251. doi:10.1080/07448481.2018.1431892

Wolf, S., & Suntheimer, N. M. (2019). A dimensional risk approach to assessing early adversity in a national sample. *Journal of Applied Developmental Psychology*, *62*, 270–281. doi:10.1016/j.appdev.2019.03.004