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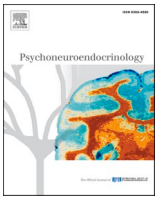

The mediating role of allostatic load in the relationship between early life adversity and cognitive function across the adult lifespan

Danielle D'Amico [a], Maya E. Amestoy [b], Alexandra J. Fiocco [a,*]

[a] Institute for Stress and Wellbeing Research, Department of Psychology, Ryerson University, Canada
[b] Graduate Department of Psychological Clinical Science, University of Toronto Scarborough, Canada

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ABSTRACT

Early life adversity is consequential for poor cognitive health in mid to late-life. Early life adversity is associated with higher allostatic load, a biological indicator of physiological dysregulation due to cumulative wear-and-tear from chronic stress. Higher allostatic load is also associated with poorer cognitive function across the lifespan. To date, a paucity of research has examined allostatic load as a mechanism through which early life adversity impacts cognition in adulthood. Using cross-sectional data from the Midlife in the United States (MIDUS) Study, the objective of the current study was to investigate the mediating role of allostatic load in the relationship between early life adversity and cognitive performance (global cognition, episodic memory, executive function) among middle-aged and older adults without cognitive impairment (n = 1541, M_{age}=53 ± 12, 53% female). Early life adversity was measured retrospectively using the Childhood Trauma Questionnaire. Allostatic load was composed of 20 biomarker proxies of neuroendocrine, metabolic, inflammatory, and cardiovascular systems, stratified by sex. Cognitive performance was evaluated using a battery of standardized neuropsychological tests. Controlling for age, education, and race, allostatic load significantly mediated the relationship between early life adversity and global cognition (β=−0.01, 95%CI [−0.01,−0.001]), and early life adversity and executive function (β=−0.01, 95%CI [−0.01,−0.001]), but not episodic memory. Findings did not change after controlling for lifestyle behaviours and current depression. Consistent with the biopsychosocial lifespan model of cognitive aging, findings suggest that early life adversity may become biologically embedded over time to negatively impact cognitive function in later adulthood in a domain-specific manner.

1. Introduction

The preservation of cognitive function across the adult lifespan is a key component of successful aging (Fiocco and Yaffe, 2010). Indeed, the maintenance of cognitive health is a precursor to other indices of well-being, including improved overall quality of life, functional status, independence, and a lower risk of developing a neurodegenerative disease such as dementia (Davis et al., 2010; Wu et al., 2020). As such, understanding the biopsychosocial factors that interact across the lifespan to facilitate healthy cognition is an important public health concern from a prevention, detection, and treatment standpoint. A substantial body of research suggests that the heterogeneity of cognitive aging is largely explained by modifiable risk factors (Zaninotto et al., 2018). Chronic stress is one such modifiable risk factor that is detrimental to cognitive function (Lupien et al., 2009).

Although chronic stress is consequential for cognitive function at all stages across the life course, early life (i.e., infancy, childhood, adolescence) has received a great deal of attention as a period during which the nervous system is particularly sensitive to the effects of stress (Meaney and Ferguson-Smith, 2010). Previous research has shown that greater levels of early life adversity are associated with poorer cognitive function in adulthood (Gold et al., 2021), faster rates of cognitive decline (Korten et al., 2014), and an increased risk of dementia (Donley et al., 2018). This is especially true for traumatic experiences in early life, such as maltreatment, abuse, and neglect (Nikulina and Widom, 2013).

The mechanism through which early life adversity impacts cognitive function in adulthood remains unclear but may be explained by the biological embedding of childhood adversity model, which proposes that when stress occurs during a sensitive developmental window, it calibrates how physiological systems operate throughout the life course (Hertzman, 1999). Namely, excessive levels of stress hormones (i.e., cortisol) in early life can harm the neurobiological development of the

* Correspondence to: Department of Psychology, Ryerson University, 350 Victoria Street, Toronto, ON, Canada.
E-mail address: afiocco@ryerson.ca (A.J. Fiocco).

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hypothalamic-pituitary-adrenal (HPA) axis (Anacker et al., 2014), the body's primary stress response system, which can lead to aberrant HPA maturation through childhood and a dysregulated HPA axis into adulthood (Herzog and Schmahl, 2018). This dysregulation can proliferate across the lifespan to impact cognitive health by priming risky health behaviours (e.g., poor diet, smoking, sedentary behaviour, social isolation) and shaping physiological responses to stress in adulthood (Frodl and O'Keane, 2013). For example, a recent study by Sheffler et al. (2021) found that higher levels of self-reported emotional stress reactivity mediated the relationship between early life adversity and global cognition among middle-aged and older adults. HPA axis dysregulation can also lead to wear-and-tear of other regulatory systems (e.g., the immune system; Silverman and Sternberg, 2012), which are central to a number of age-related health outcomes, including poor cognitive function. Indeed, Davis et al. (2019) found that the relationship between higher levels of childhood abuse and poorer global cognitive performance in later life was mediated by interleukin-6, a marker of systemic inflammation.

Although the aforementioned studies offer insight into the mechanisms through which early life adversity impacts cognitive function, they fail to capture how stress in early life accumulates over time through multisystem dysregulation to impact health outcomes across the lifespan. The biological embedding of early life adversity and its influence on cognitive function in adulthood may be better conceptualized using the allostatic load framework (Danese and McEwen, 2012). Allostatic load refers to multisystem physiological dysregulation due to cumulative wear-and-tear from chronic stress (McEwen, 1998). Specifically, chronic activation of the sympathetic-adrenal-medullary (SAM) and HPA axes (i.e., primary mediators) from chronic stress eventually leads to dysregulation of cardiovascular, immune, and metabolic systems (i.e., secondary mediators). The imbalance of these interconnected systems ultimately results in allostatic load, which, if maintained, can accumulate and lead to adverse effects on the brain and body (i.e., tertiary outcomes; Juster et al., 2010).

While chronic stress is associated with poor health outcomes across the lifespan, adversity in early life may result in physiological responses that endure long after the initial threat has ceased by accumulating over time and becoming detrimental to lifelong health (Danese and McEwen, 2012). Previous research has shown that early life adversity is associated with higher allostatic load in adults (Misiak et al., 2021), even after accounting for adversity in adulthood (Su et al., 2019). A meta-analysis has also shown that higher allostatic load is associated with poorer cognitive function among adults (D'Amico et al., 2020a). Taken together, previous research suggests that allostatic load may be a plausible mechanism through which early life adversity impacts health in later life. Supporting this conjecture, a recent study by Atkinson et al. (2021) found that the relationship between early life adversity and multimorbidity among older adults was partially explained by higher levels of allostatic load. Allostatic load has also been found to mediate the relationship between early life adversity measured by childhood poverty and executive functioning among young adults (Evans et al., 2021; Evans and Schamberg, 2009). A paucity of research has examined whether allostatic load mediates the relationship between early life adversity and cognitive health throughout middle and older age.

Building on the extant literature, the objective of the current study was to examine the mediating role of allostatic load in the relationship between early life adversity and cognitive function (i.e., global cognition, episodic memory, and executive function) among middle-aged and older adults. It was hypothesized that allostatic load would significantly mediate the relationship between greater levels of early life adversity and poorer cognitive performance, such that higher early life adversity would be associated with greater allostatic load, and greater allostatic load would be associated with poorer cognitive performance across all cognitive domains of interest.

Given that previous research has found sex differences in the effect of both stress hormones and early life adversity on brain health (Sandman et al., 2018; Wolfova et al., 2021), sex-stratified models were conducted to explore whether the mediating role of allostatic load in the aforementioned relationships differs by sex. Further, in addition to total allostatic load, mediation by each allostatic load sub-component was conducted to explore whether mediating effects are driven by specific physiological systems.

2. Methods

2.1. Participants

Participants in this study were drawn from the second wave of the National Survey of Midlife in the United States (MIDUS II) study conducted in 2004–2006 and from the MIDUS Refresher study initiated in 2011. The MIDUS study is a longitudinal investigation of the interactive role of social, psychological, and behavioural factors on mental and physical health in middle and late-life (Brim et al., 2004; Radler and Ryff, 2010). In an effort to improve the representation of Black individuals and examine health in minority populations, a sample of Black individuals from Milwaukee, Wisconsin, were recruited to the MIDUS II and MIDUS Refresher studies, for a total of 5555 participants in the MIDUS II cohort and 4085 participants in the MIDUS Refresher cohort. Within the MIDUS studies, several sub-projects were initiated to allow for a more refined examination of specific study objectives. This included the Cognitive Project (Lachman et al., 2014) and the Biomarker Project (Love et al., 2010). A total of 1865 individuals participated in both of the sub-projects.

A total of 230 participants were excluded from analyses for meeting the following self-reported criteria: diagnosis of a neurological disorder, Parkinson's disease, a history of stroke, a history of a serious head injury, and/or having previously undergone chemotherapy or radiation treatment. Participants were then excluded from analyses if they were missing information on age, sex, educational attainment, or race ($n = 10$). Participants were also excluded from the final analyses if they were missing scores for early life adversity ($n = 12$), allostatic load ($n = 91$), or cognitive function ($n = 4$), for a final analytical sample of 1541. See Fig. 1 for a flowchart of the sample.

MIDUS data collection has been reviewed and approved by the Education and Social/Behavioural Sciences and the Health Sciences Institutional Review Boards at the University of Wisconsin-Madison. Additionally, ethics approval for secondary data analysis was approved by Ryerson University's Research Ethics Board (REB 2021–385).

2.2. Measures

2.2.1. Sociodemographic and health-related characteristics

The following self-reported variables were collected via phone interview and self-administered questionnaires: age; sex (male or female); highest achieved education level; race self-identified as White, Black/African American, Native American or Alaska Native Aleutian Islander/Eskimo, Asian, or other; a self-reported diagnosis of diabetes, hypertension, thyroid disease, and depression; use of prescription medication for depression or anxiety within the previous month (yes/no); perceived socioeconomic position indexed using the MacArthur Scale of Subjective Social Status (Adler et al., 2000); and current level of perceived stress measured using the 10-item Perceived Stress Scale (PSS-10; Cohen et al., 1983). Current level of physical activity was also assessed by asking participants '*Do you engage in regular exercise, or activity, of any type for 20 minutes or more at least 3 times/week?*' (yes/no). Participants were also asked if they currently smoke cigarettes regularly (yes/no), and frequency of alcohol intake within the previous month on a Likert-type scale ranging from 1 (*every day*) to 6 (*never*).

2.2.2. Early life adversity

The Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003) is a 25-item self-reported questionnaire that examines childhood

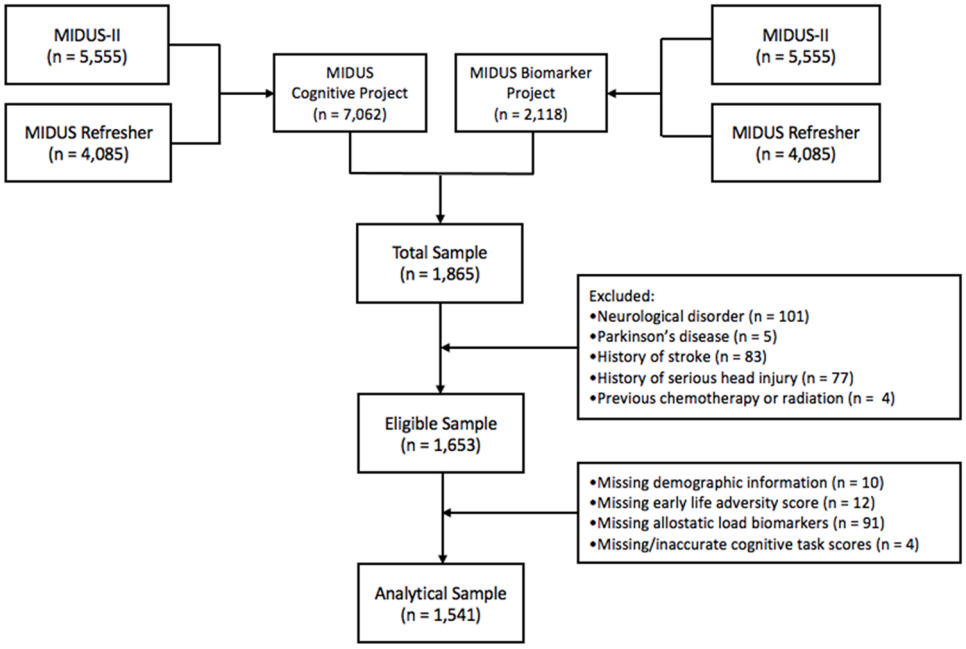

Fig. 1. Flowchart of the current sample.

maltreatment prior to the age of 18. The CTQ is comprised of 25 items rated on a five-point Likert-type scale ranging from 1 (*never*) to 5 (*very often*), with seven items reverse-scored so that higher scores on each item indicate more severe maltreatment. The CTQ can be divided into five subscales (i.e., physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect) each comprising five summed items with higher scores reflecting greater levels of maltreatment. To calculate a total early life adversity score, each of the five sub-scores were classified for severity on four levels (i.e., 0 = none to minimal, 1 = slight to moderate, 2 = moderate to severe, and 3 = severe to extreme) based on validated cut-off criteria from Bernstein et al. (2003). The total score was then derived by summing each of the five severity sub-scores, yielding a total score ranging from 0 to 15, with higher scores reflecting greater levels of early life adversity.

2.2.3. Biomarkers

Comprehensive biological assessments were conducted during overnight visits at three General Clinical Research Centers (UCLA, University of Wisconsin – Clinical and Translational Research Core, and Georgetown University), and samples were shipped to the MIDUS Biocore Laboratory for assay. For the purpose of the current study, data from 20 biomarkers were obtained to index functioning of the neuroendocrine, immune, metabolic, and cardiovascular systems. For details regarding biomarker measurement, collection protocols, and assay procedures, see Love et al. (2010). Biomarkers measuring cardiovascular function included systolic and diastolic blood pressure (SBP; DBP). Measures of neuroendocrine functioning included overnight urinary measures of epinephrine, norepinephrine, and cortisol, as well as dehydroepiandrosterone sulfate (DHEA-S). Indicators of immune system function included insulin-like growth factor 1 (IGF-1), C-reactive protein (CRP), fibrinogen, tumor necrosis factor (TNF) alpha, interleukin-6 (IL-6), E-selectin, and intracellular adhesion molecule-1 (ICAM-1). Measures of metabolic activity included high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), waist-hip ratio (WHR), glycosylated hemoglobin (HbA1c), urinary creatinine, and the homeostasis model of insulin resistance (HOMA-IR).

Allostatic load index was calculated using the count-based method, stratified by sex (Juster et al., 2010). Specifically, each biomarker was scored using high-risk quartile cut-offs stratified by sex (i.e., upper or lower quartiles depending on whether low or high values confer a greater risk for health). For all participants, each biomarker was then assigned a score of 0 (*did not pass threshold*) or 1 (*passed threshold*) depending on the biomarker's risk ranking. These scores were then summed across all biomarkers for a total score ranging from 0 to 20. A total multi-system allostatic load score, along with sub-scores for cardiovascular, immune, metabolic, and neuroendocrine systems, were computed for each participant. Higher total scores indicate greater allostatic load, or physiological dysregulation as a result of chronic stress. See Table 1 for a list of biomarkers included in each allostatic load sub-system and their respective cut-off scores for the total sample and stratified by sex.

To ensure that mediation effects were not a result of the allostatic load index calculation, two alternative calculation methods were employed for sensitivity analyses: 1) count-based method without stratification by sex (Juster et al., 2010), and 2) summation of z-scores for each of the 20 biomarkers (Juster et al., 2010).

2.2.4. Cognitive function

Cognitive functioning was assessed at MIDUS II using The Brief Test of Adult Cognition by Telephone (BTACT; Tun and Lachman, 2006), a battery of neurocognitive tasks designed to assess seven areas of cognitive functioning that are sensitive to aging. These included the Rey Auditory-Verbal Learning Test to assess immediate and delayed verbal episodic memory; the backward digit span task to assess working memory span; the category fluency test to measure verbal fluency; the number series completion task to measure inductive reasoning; the backwards counting task to assess speed of processing; and the Stop and Go Switch Task to measure attention switching. See Tun and Lachman (2006) for a detailed description of the test battery administration. The BTACT has demonstrated good construct validity (Lachman et al., 2014).

A global cognitive composite score was derived by summing the z-scores for each of the seven neurocognitive task scores. In addition to this, two summary scores, an episodic memory score and an executive function score, were created based on previous exploratory and confirmatory factor analyses of the BTACT item scores (see Lachman et al., 2010). The episodic memory score was calculated by summing the z-scores for the immediate and delayed word list recall. The executive

Table 1
High risk quartile cut-offs used to calculate allostatic load for the total sample and stratified by sex.

System and Respective Biomarkers	High-risk cut point		
	Females	Males	Total sample
Neuroendocrine			
DHEA-S (μg/mL)[a]	≤ 42.25	≤ 74.00	≤ 55.00
Urinary cortisol (μg/g of creatinine)	≥ 27.29	≥ 23.00	≥ 25.74
Urinary epinephrine (μg/g of creatinine)	≥ 18.26	≥ 19.91	≥ 19.64
Urinary norepinephrine (μg/g of creatinine)	≥ 143.35	≥ 149.54	≥ 146.10
Immune			
IGF-1 (ng/mL)[a]	≤ 90	≤ 109	≤ 100
CRP (μg/mL)	≥ 4.07	≥ 2.39	≥ 3.19
IL-6 (pg/mL)	≥ 3.43	≥ 3.20	≥ 3.29
TNF-alpha (pg/mL)	≥ 2.39	≥ 2.46	≥ 2.44
Fibrinogen (mg/dL)	≥ 404.0	≥ 369.0	≥ 388.5
ICAM-1 (ng/mL)	≥ 325.65	≥ 320.77	≥ 321.46
E-selectin (ng/mL)	≥ 48.58	≥ 52.62	≥ 49.63
Cardiovascular			
SBP (mmHg)	≥ 141	≥ 141	≥ 141
DBP (mmHg)	≥ 80	≥ 86	≥ 83
Metabolic			
WHR (waist cm: hip cm)	≥ 0.89	≥ 1.01	≥ 0.97
HbA1c (%)	≥ 6.1	≥ 6.1	≥ 6.1
LDL (mg/dL)	≥ 125	≥ 124	≥ 125
HDL (mg/dL)[a]	≤ 49	≤ 38	≤ 43
TG (mg/dL)	≥ 134	≥ 164	≥ 148
Urinary creatinine (mg/dL)	≥ 90.05	≥ 135.63	≥ 114.00
HOMA-IR ((glucose × insulin)/405)	≥ 4.11	≥ 4.84	≥ 4.31

Notes. CRP = C-reactive protein; DBP = diastolic blood pressure; DHEA-S = dehydroepiandrosterone sulfateHbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; HOMA-IR = homeostasis model of insulin resistance; ICAM-1 = intracellular adhesion molecule-1; IGF-1 = insulin-like growth factor 1; IL-6 = interleukin-6; LDL = low-density lipoprotein; SBP = systolic blood pressure; TG = triglycerides; TNF-alpha = tumor necrosis factor alpha; WHR = waist-to-hip ratio.

[a] lower quartile used as the high-risk cut point.

function score was calculated by summing the z-scores for working memory, verbal fluency, inductive reasoning, processing speed, and attention switching. Higher total scores on each of the composite measures are indicative of better global cognitive performance, episodic memory, and executive functioning. If a participant was missing a score or the task was flagged due to test disruption or interview equipment failures for more than half of the cognitive tasks in a given domain (i.e., 4 or more out of 7 for global cognition, 2 out of 2 for episodic memory, and 3 or more out of 5 for executive function), the composite score was not calculated (n = 4 for global cognition and executive function; n = 71 for episodic memory). Among participants with legitimate scores for at least half of the cognitive tasks in a given domain, a composite score was still calculated with available data.

2.3. Statistical analyses

All analyses were performed using SPSS v23. Pearson bivariate correlational analyses were conducted to determine the associations between age, sex, race, educational attainment, alcohol intake, early life adversity, allostatic load, cognitive function, physical activity, smoking status, and depression. Race was treated as a binary variable in the statistical models (i.e., White/non-White) due to the small number of non-White participants. PSS-10 scores, diabetes, hypertension, thyroid disease, use of prescription medication for depression or anxiety, and perceived socioeconomic position were treated as descriptive variables.

A total of three primary mediation models were conducted using PROCESS Macro (Hayes, 2017) with early life adversity as the independent variable, allostatic load as the mediator variable, and cognitive function (i.e., global cognition, episodic memory, or executive function) as the dependent variable. To correct for non-normality among the independent, mediator, and dependent variables, mediation was evaluated by comparing the observed indirect effect to 5000 bootstrapped resamples, whereby each simulated dataset was constructed by random sampling from the observed dataset with replacement. Based on the distribution of the resampled datasets, 95% confidence intervals were generated for the total, direct, and indirect effects (p-value <0.05). All models were adjusted a priori for sociodemographic factors including age, educational attainment, and race. A fully adjusted model was also conducted controlling for current depression and lifestyle factors including physical activity, alcohol intake, and smoking status.

Sensitivity analyses were conducted to ensure that any possible mediating effects were not driven by the calculation method for allostatic load (i.e., sex-stratified count-based method). Specifically, two alternative calculations (original count-based method and the sum of z-score method) were assessed as independent mediators in the partially and fully adjusted mediation models. All sensitivity analyses were adjusted a priori for sex, in addition to all aforementioned model adjustments.

To address exploratory questions pertaining to sex-specific associations, the three aforementioned primary mediation models were conducted among males and females separately. Furthermore, to explore whether mediating effects are driven by specific physiological systems, each of the four allostatic load sub-system scores were entered as independent mediating variables in the aforementioned models.

3. Results

3.1. Participant characteristics

A summary of participant sociodemographic and health-related characteristics, including descriptive statistics for allostatic load, early life adversity, and cognitive performance, are shown in Table 2. Briefly, the average age of the sample was 53.4 (SD = 12.4) years and 53.3% were female. The majority of participants were White (82.3%), 78.4% had at least some post-secondary education, and perceived socioeconomic position was moderate with a mean score of 4.4 out of a possible score of 10. Based on scores from the PSS-10, participants reported, on average, moderate levels of perceived stress within the previous month (mean = 21.9, SD = 6.1). Twenty-five percent of the sample reported a previous diagnosis of depression and 13.8% reported taking prescription medication for depression or anxiety within the previous month. On average, participants reported low levels of early life adversity, with a mean CTQ score of 2.4 (SD = 3.3) out of a possible 15. Allostatic load was also low, with a mean score of 5 (SD = 2.9) out of a possible 20. Frequency distributions of CTQ total scores and allostatic load total scores are presented in Supplementary Figure 1a and 1b, respectively.

3.2. Bivariate correlations

Table 3 displays the Pearson bivariate and point-biserial correlations between sociodemographic and lifestyle variables, current depression, allostatic load and its sub-scores, early life adversity, and cognitive function. Older age was associated with lower early life adversity ($r = -0.10$, $p < .001$), higher total allostatic load ($r = 0.22$, $p < .001$), and lower composite scores for global cognition ($r = -0.39$, $p < .001$), episodic memory ($r = -0.28$, $p < .001$), and executive function ($r = -0.35$, $p < .001$). Compared to males, females had higher early life adversity scores ($r = -0.11$, $p < .001$), higher episodic memory composite scores ($r = -0.27$, $p < .001$), and lower executive function composite scores ($r = 0.10$, $p < .001$). Higher educational attainment was associated with lower early life adversity ($r = -0.14$, $p < .001$), lower total allostatic load ($r = -0.19$, $p < .001$); lower sub-scores for cardiovascular ($r = -0.10$, $p < .001$), metabolic ($r = -0.17$, $p < .001$), and immune function ($r = -0.21$, $p < .001$); higher neuroendocrine sub-scores ($r = 0.11$, $p < .001$), and higher composite scores for global cognition ($r = 0.37$, $p < .001$), episodic memory ($r = 0.22$, $p < .001$),

Table 2
Participant sociodemographic and health-related characteristics for the total sample and stratified by sex.

	Mean ± SD (range) or % (n)		
	Total sample (n = 1541)	Females (n = 822)	Males (n = 719)
Age in years	53.4 ± 12.4 (25 – 84)	53.2 ± 12.0 (25 – 84)	53.9 ± 12.8 (25 – 82)
Race (%)			
Asian	0.9 (14)	1 (8)	1.1 (8)
Black and/or African American	10.9 (168)	13.1 (109)	7.8 (56)
Native American or Alaska Native Aleutian Islander/ Eskimo	1.6 (25)	3.4 (28)	3.2 (23)
White	82.3 (1269)	76.2 (626)	83.4 (600)
Other	4.2 (65)	6.2 (51)	4.2 (30)
Educational attainment (%)			
Did not complete high school	3.4 (53)	3.4 (28)	3.4 (25)
High school (or equivalent)	18.1 (280)	21.8 (179)	14.0 (101)
Some college	15.1 (232)	18.7 (154)	20.5 (148)
College diploma or associate's degree	8.4 (130)	8.0 (66)	8.9 (64)
Bachelor's degree	24.1 (371)	23.2 (191)	25.0 (180)
Some graduate school	3.8 (58)	3.3 (27)	4.3 (31)
Master's degree	17.5 (270)	17.8 (146)	17.2 (124)
Doctoral or professional degree	5.0 (77)	3.8 (31)	6.4 (46)
Perceived socioeconomic position	4.4 ± 1.8 (1 – 10)	4.6 ± 1.8 (1 – 10)	4.2 ± 1.7 (1 – 10)
Diabetes (% yes)	9.7 (150)	9.3 (76)	10.3 (74)
Hypertension (% yes)	35.5 (543)	34.9 (285)	36.1 (258)
Thyroid disease (% yes)	12.7 (195)	18.8 (154)	5.7 (41)
Depression (% yes)	25.0 (381)	30.8 (250)	18.4 (131)
Medication for depression or anxiety (% yes)	13.8 (212)	20.1 (148)	10.3 (64)
PSS-10 score	21.9 ± 6.1 (10 – 48)	22.3 ± 6.2 (10 – 48)	21.3 ± 5.9 (10 – 44)
Regular physical activity (% yes)	77.5 (1195)	76.9 (632)	78.3 (563)
Current smoking (% yes)	14.6 (175)	13.6 (88)	15.8 (87)
Alcohol intake (%)			
Everyday	8.0 (124)	4.7 (39)	11.8 (85)
5–6 days/week	5.8 (90)	3.4 (28)	8.6 (62)
3–4 days/week	10.8 (167)	8.8 (72)	13.2 (95)
1–2 days/week	18.7 (288)	17.8 (146)	19.7 (142)
< 1 day/week	25.6 (395)	29.3 (241)	21.4 (154)
Never	31.0 (477)	36.0 (296)	25.2 (181)
CTQ score (early life adversity)	2.4 ± 3.3 (0 – 15)	2.7 ± 3.6 (0 – 15)	1.9 ± 2.8 (0 – 14)
Allostatic load total score	5.0 ± 2.9 (0 – 16)	5.0 ± 2.9 (0 – 15)	5.1 ± 2.8 (0 – 16)
Neuroendocrine system sub-score	1.01 (0 – 4)	1.00 (0 – 4)	1.03 (0 – 4)
Cardiovascular system sub-score	0.51 (0 – 2)	0.52 (0 – 2)	0.50 (0 – 2)
Metabolic system sub-score	1.79 (0 – 7)	1.78 (0 – 7)	1.81 (0 – 7)
Immune system sub-score	1.72 (0 – 7)	1.72 (0 – 7)	1.58 (0 – 7)
Global cognition composite (range)	-2.9 – 1.8	-2.8 – 1.8	-2.3 – 1.8
Episodic memory composite (range)	-2.8 – 3.6	-2.8 – 3.6	-2.4 – 3.4
Executive function composite (range)	-3.3 – 1.9	-3.3 – 1.8	-2.7 – 1.9

Notes. CTQ = Childhood Trauma Questionnaire; PSS-10 = 10 item Perceived Stress Scale; SD = standard deviation

and executive function ($r = 0.35$, $p < .001$). Compared to non-White individuals, White individuals had lower early life adversity scores ($r = -0.12$, $p < .001$); lower total allostatic load scores ($r = -0.10$, $p < .001$); lower metabolic ($r = -0.08$, $p < .001$) and immune ($r = -0.13$, $p < .001$) allostatic load sub-scores; and higher composite scores for global cognition ($r = 0.22$, $p < .001$), episodic memory ($r = 0.10$, $p < .001$), and executive function ($r = 0.24$, $p < .001$). Compared with those without current depression, those with current depression had higher early life adversity scores ($r = 0.29$, $p < .001$), higher total allostatic load ($r = 0.10$, $p < .001$), and higher metabolic ($r = 0.08$, $p = .003$) and immune ($r = 0.09$, $p = .001$) allostatic load sub-scores. Those who reported that they were currently smoking had higher early life adversity scores ($r = 0.13$, $p < .001$), higher allostatic load total scores ($r = 0.15$, $p < .001$), higher metabolic ($r = 0.11$, $p < .001$) and immune ($r = 0.11$, $p < .001$) allostatic load sub-scores, and lower composite scores for global cognition ($r = -0.06$, $p = .04$) and executive function ($r = -0.06$, $p = .04$). Those currently engaging in regular physical activity had lower early life adversity scores ($r = -0.06$, $p = .02$); lower allostatic load total scores ($r = -0.17$, $p < .001$); lower metabolic ($r = -0.16$, $p < .001$) and immune ($r = -0.14$, $p < .001$) allostatic load sub-scores; and higher composite scores for global cognition ($r = 0.07$, $p = .01$), episodic memory ($r = 0.06$, $p = .02$), and executive function ($r = 0.06$, $p = .02$). Greater alcohol intake was associated with greater early life adversity ($r = 0.05$, $p = .04$), higher total allostatic load ($r = 0.15$, $p < .001$), higher metabolic ($r = 0.18$, $p < .001$) and immune ($r = 0.13$, $p < .001$) allostatic load sub-scores, lower neuroendocrine allostatic load sub-scores ($r = -0.05$, $p = .05$), and lower composite scores for global cognition ($r = -0.07$, $p = .01$) and executive function ($r = -0.11$, $p < .001$).

3.3. Mediation models

Controlling for age, education, and race, there was a statistically significant indirect effect of allostatic load in the relationship between early life adversity and global cognition ($\beta = -0.01$, 95% BCa CI [−0.01, −0.002]), which remained statistically significant in the fully adjusted model ($\beta = -0.01$, 95% BCa CI [−0.01, −0.001]). See Fig. 2a. Allostatic load did not significantly mediate the relationship between early childhood adversity and episodic memory in the partial adjusted model ($\beta = -0.003$, 95% BCa CI [−0.01,.001]) or fully adjusted model ($\beta = -0.004$, 95% BCa CI [−0.01,.0002]). See Fig. 2b. Lastly, there was a statistically significant indirect effect of allostatic load in the relationship between early life adversity and executive function in the partially adjusted model ($\beta = -0.01$, 95% BCa CI [−0.02, −0.003]) and in the fully adjusted model ($\beta = -0.01$, 95% BCa CI [−0.01, −0.001]). See Fig. 2c.

Sensitivity analyses revealed that the aforementioned findings did not change using alternative calculations for the allostatic load index. Please see Supplementary Figure 2a and 2b.

3.4. Exploratory analyses

When stratifying the fully adjusted primary mediation models by sex, there was no statistically significant indirect effect of allostatic load in the relationship between early life adversity and global cognition or episodic memory in males or females. There was a statistically significant indirect effect of allostatic load in the relationship between early life adversity and executive function among females ($\beta = -.008$, 95% BCa CI [−0.02, −0.001), but not males. See Supplementary Figure 3a-c for the detailed path estimates of the partially and fully adjusted models.

In the fully adjusted models, there was no statistically significant indirect effects of neuroendocrine, cardiovascular, metabolic or immune sub-system scores in the relationship between early life adversity and global cognition, executive function, or episodic memory. See Supplementary Figure 4a-c for details path estimates of the partially and fully adjusted models.

4. Discussion

The current findings support a mediating role of allostatic load in the relationship between early life adversity and both global cognitive function and executive function. Aligned with the study hypotheses, greater early life adversity was associated with higher allostatic load, and higher allostatic load was associated with both poorer global

Table 3
Pearson bivariate correlations between the variables of interest.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Age (1)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Sex (2)	.03	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Education (3)	-0.06[a]	.07[b]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Race (4)	.11[c]	-0.09[b]	.13[c]	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Alcohol (5)	-0.07[b]	-0.21[c]	-0.14[c]	-0.12[c]	–	–	–	–	–	–	–	–	–	–	–	–	–
Smoking (6)	-0.15[c]	.03	-0.21[c]	-0.14[c]	-0.01	–	–	–	–	–	–	–	–	–	–	–	–
PA (7)	-0.01	.02	.10[c]	.10[c]	-0.06[a]	-0.01[b]	–	–	–	–	–	–	–	–	–	–	–
Depression (8)	-0.09[c]	-0.15[c]	.01	.003	.03	-0.12[c]	.10[c]	–	–	–	–	–	–	–	–	–	–
ELA (9)	-0.10[c]	-0.11[c]	-0.14[c]	-0.12[c]	.05[a]	.13[c]	-0.06[a]	.29[c]	–	–	–	–	–	–	–	–	–
AL total (10)	.22[c]	.01	-0.19[c]	-0.10[c]	.15[c]	.15[c]	-0.17[c]	.10[c]	.10[c]	–	–	–	–	–	–	–	–
AL NE (11)	.24[c]	.01	.11[c]	.04	-0.05[a]	.03	.01	.04	-0.05	.31[c]	–	–	–	–	–	–	–
AL CV (12)	.11[c]	-0.02	-0.10[c]	-0.03	.01	.01	-0.04	-0.02	.03	.40[c]	.04	–	–	–	–	–	–
AL MET (13)	.02	.01	-0.17[c]	-0.08[b]	.18[c]	.11[c]	-0.16[c]	.08[b]	.11[c]	.71[c]	-0.11[c]	.12[c]	–	–	–	–	–
AL IMM (14)	.17[c]	.00	-0.21[c]	-0.13[c]	.13[c]	.14[c]	-0.14[c]	.09[b]	.10[c]	.75[c]	-0.05[a]	.12[c]	.37[c]	–	–	–	–
GC (15)	-0.39[c]	-0.04	.37[c]	.22[c]	-0.07[b]	-0.06[a]	.07[b]	.02	-0.06[a]	-0.24[c]	-0.06[a]	-0.09[c]	-0.14[c]	-0.22[c]	–	–	–
EM (16)	-0.28[c]	-0.27[c]	.22[c]	.10[c]	.03	-0.03	.06[a]	.05	.002	-0.13[c]	-0.001	-0.05[a]	-0.08[b]	-0.14[c]	.70[c]	–	–
EF (17)	-0.35[c]	.10[c]	.35[c]	.24[c]	-0.11[c]	-0.06[a]	.06[a]	-0.002	-0.07[b]	.23[c]	-0.07[b]	-0.09[c]	-0.14[c]	-0.20[c]	.91[c]	.36[c]	–

Notes. AL = allostatic load; CV = cardiovascular; EF = executive function; ELA = early life adversity; EM = episodic memory; GC = global cognition; IMM = immune; MET = metabolic; NE = neuroendocrine; PA = physical activity

[a] $p < .05$
[b] $p < .01$
[c] $p < .001$

cognition and executive functioning. However, allostatic load was not found to be a mediator of the relationship between early life adversity and episodic memory. Exploration of the allostatic load sub-systems suggests that the aforementioned mediation models are not driven by specific sub-components of the allostatic load index. Finally, differential mediation effects by sex suggest a mediating role of allostatic load in the relationship between early life adversity and executive function among females, but not males.

The aforementioned direct associations between allostatic load and early life adversity, and allostatic load and cognition are aligned with previous systematic reviews (D'Amico et al., 2020a; Misiak et al., 2021). Current findings are also consistent with previous mediation models conducted in late adolescence and early adulthood (Evans et al., 2021; Evans and Schamberg, 2009), supporting the theoretical conjecture that stress in early life becomes biologically embedded over time through multisystem physiological dysregulation, which negatively impacts health outcomes throughout the lifespan (Berens et al., 2017; Danese and McEwen, 2012; Herzog and Schmahl, 2018). The current work builds on these findings by suggesting that the cognitive health consequences of stress in early life may extend beyond the immediate timescale of childhood and adolescence and proliferate throughout adulthood and into later life. This supports current models of cognitive aging, which posit that cognitive aging is a lifelong developmental process, anchored in early experiences and extending across the lifespan (Livingston et al., 2020; McEwen, 2003).

The current findings suggest that early life adversity impacts cognitive function through allostatic load in a domain-specific manner. Namely, allostatic load was found to mediate the relationship between early life adversity and executive function, but not episodic memory. A plausible mechanism for the null associations found for episodic memory is that frontal lobe-dependent tasks (i.e., executive functions) are more sensitive to normal age-related changes in comparison to hippocampal-dependent tasks (i.e., episodic memory), which tend to exhibit greater variation among the eldest older adults and are implicated in pathological cognitive changes such as amnestic mild cognitive impairment and, eventually, Alzheimer's disease (Halliday, 2017). This is consistent with the frontal lobe hypothesis of aging, which suggests that cognitively intact older adults may show disproportionate age-related changes to the prefrontal cortex while presenting with healthy neural functioning of non-frontal regions (West, 2000). This speculation is especially relevant for the current sample, which is comprised of non-impaired adults between the ages of 25 and 84, with relatively high levels of cognitive functioning. However, previous research suggests that early life adversity is particularly potent for stress-sensitive regions including the hippocampus, such that adults experiencing higher levels of early life adversity have smaller hippocampal volumes (Calem et al., 2017). Accordingly, the cognitive domain-specific impacts of early life adversity through allostatic load warrants further investigation.

Exploratory analyses suggest that the meditating role of allostatic load in the relationship between early life adversity and cognitive function is not driven by any specific allostatic load sub-component. This finding is aligned with recommendations to consider biomarkers across multiple interconnected physiological systems (Fiocco et al., 2019; McEwen, 2003), especially in the context of cognitive health and age-related changes in cognition, which are complex and dynamically unfold over time. Moreover, the impacts of chronic stress across the life course due to early life adversity are reflected across multiple biological systems. Therefore, biological signatures that incorporate multiple biological systems may be a more robust predictor of cognitive function and

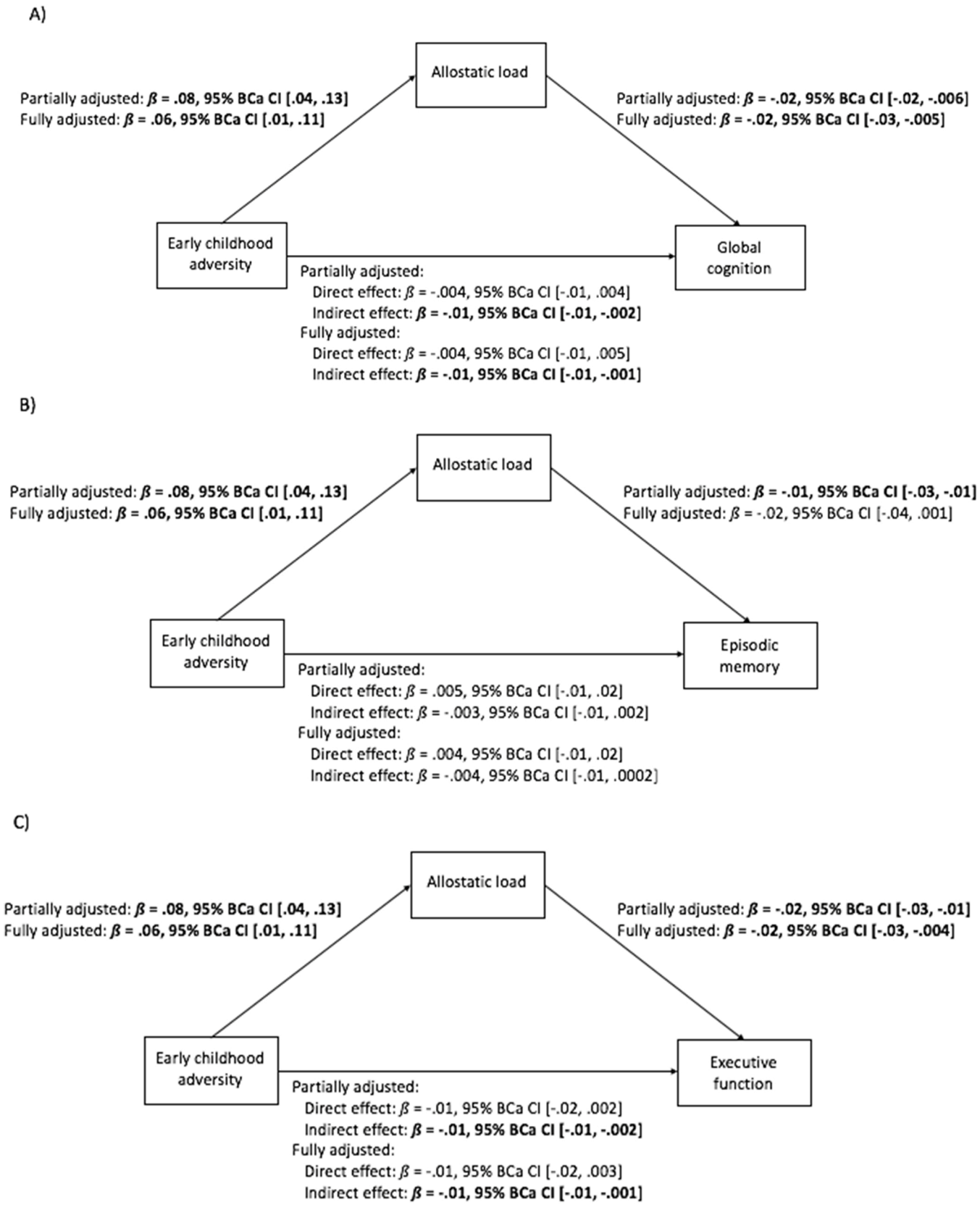

Fig. 2. Mediation models for A) global cognition (partially adjusted: R^2 =.32, $F(5, 1535) = 145.71$, $p < .001$; fully adjusted: $R^2 = .27$, $F(9, 1173) = 48.7$, $p < .001$); B) episodic memory (partially adjusted: R^2 =.14, $F(5, 1531) = 48.08$, $p < .001$; fully adjusted: $R^2 = .11$, $F(9, 1169) = 16.85$, $p < .001$); and C) executive function (partially adjusted: R^2 =.29, $F(5, 1535) = 127.45$, $p < .001$; fully adjusted: $R^2 = .25$, $F(9, 1173) = 44.24$, $p < .001$). Partially adjusted models controlled for age, education, and race. Fully adjusted models further controlled for current depression and lifestyle factors including physical activity, alcohol intake, and smoking. Bolded estimates are significant at $p < .05$.

a more appropriate endpoint of early life adversity compared to individual biomarkers or physiological systems considered in isolation. It should be noted, however, that the independent mediating role of metabolic and immune biomarkers, but not cardiovascular or neuroendocrine biomarkers, were statistically significant before controlling for lifestyle behaviours and current depression. This finding is partially aligned with previous studies showing that accelerated declines in cognitive performance are associated with combined cardiovascular and metabolic markers, but not with combined markers of neuroendocrine and immune function (Goldman et al., 2006; Seeman and Crimmins, 2001). This may be due to greater predictive value of the secondary mediators of allostatic load, which extend from wear-and-tear of the primary mediators and, thus, reflect more extensive physiological dysregulation. Consideration of lifestyle behaviours, however, indicate that metabolic and immune dysfunction stemming from early life adversity may be modulated by lifestyle choices later in life including smoking, alcohol intake, and physical activity. However, this assertion is purely speculative and additional work is needed to understand if the mechanism through which early life adversity impacts cognitive function is, in fact, driven by specific allostatic load components.

Exploratory sex-based analyses provided support for an effect modification by sex. Specifically, the current study found that the relationship between early life adversity and executive function was mediated by allostatic load among females and not males when stratifying the model, even when using sex-specific cut-off scores when calculating the allostatic load index. This aligns with previous research which has found that elevated stress hormones have a greater effect on cortical thinning in females compared to males (Sandman et al., 2018) and that childhood socioeconomic position, as a proxy measure for early life adversity, is a stronger predictor of cognitive function in females compared to males (Wolfova et al., 2021). Atkinson et al. (2021) also found that the mediating effect of allostatic load in the relationship between early life adversity and multimorbidity in older adulthood was stronger in middle-aged and older women compared to men. This may be due to more adverse experiences in early life among females compared to males, which was observed in the present study and has been previously reported (Haahr-Pedersen et al., 2020), rendering females more vulnerable to adverse outcomes as a result of early life adversity compared to males. These findings, however, should be taken as hypothesis-generating results, as the investigation of sex differences in the present study was exploratory in nature. Therefore, future research is needed to corroborate these results, and examine specific mechanisms of action that underlie potential sex differences. It should also be noted that there was a statistically significant indirect effect of allostatic load in the relationship between early life adversity and global cognition in the entire sample, but no significant indirect effect was found for global cognition when stratifying the model by sex. It is possible that this is not due to true sex differences and may instead be the result of lower power to detect significant effects due to the smaller sample size. Indeed, there were only 822 females and 719 males in the partially adjusted models and 640 females and 543 males in the fully adjusted models. Nonetheless, the current study supports the growing need for sex- and gender-based analyses in aging research.

The present study highlights the importance of considering protective factors that may moderate the relationship between early life adversity and allostatic load, and the relationship between allostatic load and cognitive function. Although adjusting for physical activity, alcohol intake, and smoking did not alter the results, the effect sizes were relatively small and the models only accounted for 11–27% of the variance in cognitive performance, suggesting that other key modifiable factors (e.g., social isolation, dietary intake) may also mediate the relationship between early life adversity and cognitive function. Indeed, coping mechanisms that reduce social isolation, such as social engagement and seeking social support, may buffer the association between early life adversity and allostatic load (Friedman et al., 2015; Horan and Widom, 2015), and should be considered in future research. Factors that build cognitive reserve, including educational attainment in adulthood, have also been shown to buffer the association between early life adversity and cognitive function (Friedman et al., 2015); however, all models in the current study controlled for education. It should also be noted that the measures used to assess physical activity, smoking, and alcohol intake were each made up of a singular item, and future work should use more granular measures to assess lifestyle behaviours.

Although less work has directly examined protective factors that may buffer the relationship between allostatic load and cognitive function, recent findings have shown that healthy lifestyle behaviours may moderate the association between psychosocial stress and cognitive function in later life (D'Amico et al., 2020b; Ihle et al., 2020). Future work is needed to examine lifestyle-based moderators of cumulative physiological wear-and-tear from early life stress and cognitive health outcomes across the lifespan. From a prevention-based perspective, it may be more advantageous to apply risk reduction strategies before early life adversity leads to the accumulation of allostatic load over time, which may be more difficult to reverse. A systematic review of intervention-based studies found preliminary evidence that allostatic load as an endpoint may be malleable to the effects of psychosocial and pharmacological interventions (Rosemberg et al., 2020). This remains a critical line of future investigation in the context of stress across the lifespan and cognitive aging.

Although these findings are important and novel, the current study is not without limitations. First, the cross-sectional nature of the study design prevents causal claims from being made about the relationship between early life adversity, allostatic load, and cognitive function. Although early life adversity theoretically occurs decades before the accumulated index of biological stress and cognitive function, participants with poorer cognitive function may be less accurate in the reporting of childhood events. The retrospective recall of events in early life, however, is an inherent limitation of studies using self-report measures of childhood, especially among older adults. Moreover, observed effects may have been underestimated due to the characteristics of the current sample. On average, the current sample reported relatively low levels of childhood adversity and presented with a low total allostatic load score. Consequently, additional research is needed to examine the interplay between early life adversity, allostatic load and cognitive functioning in samples that have experienced greater levels of childhood adversity. Furthermore, additional research is needed to examine whether the type of adversity (e.g., emotional vs. physical abuse) modifies these associations.

5. Conclusion

Despite the aforementioned limitations, the results from this study suggest that early life adversity is consequential for cognitive function across the adult lifespan and may be biologically embedded through physiological dysregulation due to cumulative chronic stress. The current findings lend support for recommendations of targeting early life as a critical window for prevention and intervention for healthy aging (Oveisgharan et al., 2020). Future research is needed to understand resilience factors that may reduce physiological dysregulation due to chronic stress and buffer the effects of early life adversity on cognitive health outcomes in order to promote a healthy aging population. Transdisciplinary collaboration across scientists, health care providers, policy makers, and individuals with lived experience is crucial to move this endeavour forward.

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CRediT authorship contribution statement

Danielle D'Amico: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Visualization. **Maya E. Amestoy:** Formal analysis, Data curation, Writing – review & editing, Visualization. **Alexandra J. Fiocco:** Supervision, Writing – review & editing. All authors have read and approved the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105761.

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