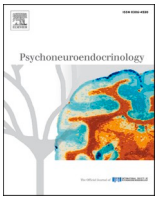
Psychoneuroendocrinology 143 (2022) 105839

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen



Allostatic load as a mediator of childhood maltreatment and adulthood depressive symptoms: A longitudinal analysis

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ARTICLE INFO

Keywords:
Depression
Allostatic load
Childhood Maltreatment
Longitudinal

ABSTRACT

Childhood maltreatment (CM) is associated with several negative outcomes in adulthood, including major depression. People who experience CM that go on to develop symptoms of major depression in adulthood tend to have earlier depressive symptom onset and greater symptom severity than those who do not experience CM. Studies have utilized allostatic load (AL) to understand how CM "gets under the skin" to contribute to depressive symptoms. However, studies largely utilize cross-sectional designs and limited biomarkers. The present study uses data from Wave 2 and Wave 3 of the Midlife Development in the United States study in regression-based analyses, examining if AL mediates the relationship between CM and the number of depressive symptoms in adulthood. AL was measured at Wave 2 using the system risk method with 27 biomarkers across seven different systems. CM was measured using the Childhood Trauma Questionnaire at Wave 2. Number of depressive symptoms were measured using the Composite International Diagnostic Interview-Short Form at Wave 3. Past month perceived stress, age, household income, education, sex, racial/ethnic identity, and current prescription medication use at Wave 2 were included as controls. Analyses identified that CM was associated with AL cross-sectionally, and that both CM and AL at were associated with the number of depressive symptoms prospectively. AL partially mediated the effects of CM on the number of depressive symptoms. The present study is the first to identify the mediating role of AL in the relationship between CM and adulthood depressive symptoms in a longitudinal design.

1. Introduction

Major depression is a highly prevalent mental health problem and a leading global cause of disability, affecting an estimated 332 million individuals, annually (World Health Organization, 2017). Additionally, major depression has been found to be comorbid or to increase the risk for developing several common health problems, including coronary heart disease, stroke, diabetes mellitus, and some forms of cancer (Miller et al., 2002; Jonas and Mussolino, 2000; Gold et al., 2020). These factors, in addition to an increasing economic burden, recorded as an increase by 21.5% from 2005 to 2010, underscore a need for improving the prevention and treatment approaches for major depression (Greenberg et al., 2015).

Among the risk factors for experiencing major depression, a history of childhood maltreatment (CM) has emerged as a strongly associated predictor, with half of all individuals who experience CM experiencing later major depressive symptoms in adulthood (Li et al., 2016; Nelson et al., 2017). Definitionally, CM may refer to several aspects of adverse childhood experiences including physical abuse by non-accidental means, sexual abuse including for an adult's gratification or financial gain, neglect such as the failure to provide minimal care or a lack of supervision, and thwarting of basic emotional needs on a persistent or extreme basis (Cicchetti and Toth, 2005). A history of CM has been associated with a greater risk for poor treatment response, increased chronic depressive symptoms, increased risk for suicide, and a greater risk for comorbid health conditions (Bernet and Stein, 1999; Arnow, 2004; Nanni et al., 2012; Tunnard et al., 2014). Thus, understanding the linkage between experiences of CM and major depressive symptoms is critical for improving treatment and prevention strategies for people currently experiencing depressive symptoms and those at risk for developing them.

One common theoretical approach for understanding how environmental factors such as CM get under the skin to create health problems like major depression is Allostatic Load (AL) theory. Through the lenses of AL, environmental events activate the body's stress response, causing a temporary shift in key biological mediators (typically markers

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https://doi.org/10.1016/j.psyneuen.2022.105839
Received 9 February 2022; Received in revised form 6 June 2022; Accepted 10 June 2022
Available online 15 June 2022

associated with the hypothalamic-pituitary-adrenal axis, sympathetic-adrenal-medullary) that allow for short-term adaptation to meet the environmental event (McEwen, 1998). Over the course of experiencing repeated or prolonged stressors, activation of biological mediators creates a wear and tear effect that shifts the homeostatic set point for those mediators (McEwen, 2003). The wear and tear effect on biological mediators, as well as the regions of the brain which are targeted by these mediators, help explain the association between environmental events and various mental health problems, including major depression (McEwen, 2000, 2003). Additionally, the targeting of the amygdala and hippocampus help explain the findings related to hippocampal volume loss only after the onset of major depression (McEwen, 2000; MacQueen et al., 2003).

Several converging lines of evidence, supported by AL theory, suggest that a history of CM may create a "wear and tear" effect on the body's regulatory systems that help explain depressive symptoms in adulthood. First, a reported history of CM before age 11 is associated with an increase in AL at age 40 as measured by a 9-item AL index (Widom et al., 2015). Second, several studies have identified that AL and depressive symptoms are cross-sectionally associated, with some studies identifying AL as a mediator that helps explain depressive symptoms. For instance, Kobrosly et al. (2013) identified that AL was associated with depressive symptoms in a sample of 2405 adults ages 60 and older, and these results were replicated in a sample of 125 adults ages 67–94 living in Rochester, New York (Kobrosly et al., 2014). Additionally, AL has been found to be associated with depressive symptoms in a sample of 2670 African American individuals at risk for coronary heart disease (Gillespie et al., 2019). Last, three studies suggest that AL multiple measures of predict future depressive symptoms. Juster et al. (2011) showed that a 10-item AL index predicts depressive symptoms at three years follow up, while Carbone (2020) showed that a 25-item AL index mediates the relationship between neighborhood safety and future depressive symptoms. Furthermore, Gale et al. (2015) showed that a 9-item AL index partially mediates the relationship between cognitive processing speed at age 16 and depression at age 36.

Despite the converging evidence on the role of AL in explaining the connection between a history of CM and depressive symptoms in adults, only a small number of studies have examined CM, AL, and depressive symptoms, concurrently. Scheuer and colleagues (2018) utilized a case-control model, drawing adults experiencing depressive symptoms from an inpatient German hospital, finding that AL mediated the relationship between physical abuse and major depression, but not between sexual abuse and major depression. O'Shields and Gibbs, 2021 built on these findings, by attempting to generalize the results to an American community sample while disaggregating analyses by sex to account for differences between males and females. Sex-disaggregated models identified that recalled CM was not associated with AL for males or females (O'Shields and Gibbs, 2021). However, sex-disaggregated models also identified that AL was associated with depressive symptoms for females, but not for males (O'Shields and Gibbs, 2021). Thus far, Widom and colleagues (2015) have been the only group to study CM, AL, and depressive symptoms congruently using a longitudinal design. This work showed that while CM is associated with internalizing disorders (which includes depressive symptoms) in childhood and AL when measured 30 years later, internalizing disorders are not associated with AL. Further, Widom and colleagues (2015) did not test for depressive symptoms in adulthood, leaving key questions in causality unaddressed.

1.1. Rationale and research questions

While previous work has identified that CM is related to the experience of depressive symptoms in adulthood, the process by which this occurs is still unclear, and thus targets for future intervention strategies remain obscure. While some have identified that AL may mediate the relationship between types of CM and adulthood depressive symptoms, others have found conflicting results (O'Shields and Gibbs, 2021; Scheuer et al., 2018). The expectation that AL mediates the association between CM and depressive symptoms experienced in adulthood is theoretically tenable, although the only study examining these constructs prospectively did not measure depressive symptoms in adulthood (Danese and McEwen, 2012; Widom et al., 2015). Thus, the present study sought to answer two key questions:

1. Does AL predict future depressive symptoms in adulthood while controlling for the effects of CM?
2. Does AL mediate the relationship between CM and depressive symptoms experienced during adulthood using a longitudinal design?

2. Method

2.1. Sample

The present study is a secondary data analysis of the Midlife Development in the United States (MIDUS) study. Initiated in 1995, the MIDUS study conducted a multidisciplinary survey to understand differences in age related health and well-being in the U.S. (Brim et al., 2020). The present study draws on data from the biomarker sub-project (also referred to as Project 4) of the Wave 2 survey (collected from 2004 to 2009) and the Wave 3 main survey (collected from 2013 to 2014; Ryff et al., 2019a; Ryff et al., 2019b). The biomarker sub-project of Wave 2 collected data from 1255 participants who completed the main survey of Wave 2 and agreed for an overnight visit at either the University of Wisconsin, University of California Los-Angeles, or Georgetown University. This visit allowed for biospecimens collection and additional psychological testing. Of the 1255 biomarker sub-project participants, 945 followed up with the Wave 3 main survey, and thus were eligible for inclusion in the present study. Regrettably, 65 of these individuals had problematic electrocardiogram (ECG) data; with 25 individuals not being able to participate in ECG, 37 participating in ECG but having un-scorable data, and 3 participants not having ECG data reported by the technician. Because this ECG data was relevant to the measurement of AL in the present study, these individuals were removed, leaving a final analytic sample of 880 participants. On average, the analytic sample completed data collection for the biomarker sub-project in July of 2006 and data collection for the Wave 3 main survey in July of 2013, meaning there was an average of 7 years between waves of data collection for the analytic sample. For a review of the data collection timeline for the full MIDUS project, readers should refer to the MIUDS website (http://midus.wisc.edu/data/timeline.php).

2.2. Measures

Depressive Symptoms were assessed using the depression screener questions form the World Health Organization's Composite International Diagnostic Interview-Short From (CIDI-SF) (Kessler et al., 1998). The CIDI-SF was administered to MIDUS via phone from 2013 to 2014 as a part of the Wave 3 main survey. Testing of the CIDI-SF was initially validated using a nationally representative phone survey (Kessler et al., 1998).

The CIDI-SF is a combination of several short-form scales aimed at assessing eight CIDI syndromes, including major depressive episode. Participants first answer a set of stem questions specific to one of the eight disorders, and then move to more specific questions about each disorder or a different set of stem questions. Stem questions for major depressive episode assess whether participants experienced any two-week period in the past twelve months in which they 1) "nearly every day felt sad, blue or depressed" and 2) "lost interest in most things like work or hobbies or things you usually like to do for fun?" Participants who affirmed both these questions then answered whether they had experienced of fatigue, appetite disturbance, sleep disturbance, difficulty concentrating, decreased self-worth, and suicidal ideations.

Summation of both the stem questions and the six additional questions resulted in a continuous measure of the number of depressive symptoms ranging from 0 to 7. The depressive symptom measurement component of the CIDI-SF has been found to be superior to the Center for Epidemiological Surveys Depression Survey-8-item version, a common measure of depressive symptoms (Dang et al., 2020). Chronbach's alpha for the CIDI-SF based on data from the present sample was found to be 0.933, indicating excellent internal consistency.

Childhood Maltreatment was assessed using the Childhood Trauma Questionnaire-Short Form (CTQ-SF) (Bernstein and Fink, 1998). The CTQ-SF is a self-report measure of recalled CM, administered to MIDUS participants as a part of the Wave Two Biomarker project. The present study utilized the emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse subscales of the CTQ-SF, each of which has five statements where responses range from "never" (1) to "very often true" (5). Summation of these subscales (which included 25 total items) resulted in an overall measurement of CM with a possible range of 25–125. Prior testing of the CTQ-SF has identified high internal consistency and good test-retest reliability over a 2–6 month period (Bernstein et al., 1994). Chronbach's alpha for the CTQ based on data from the present sample was found to be 0.932, indicating excellent internal consistency.

Allostatic Load was measured using the dichotomization and summation method pioneered by Seeman and colleagues (1997). This method involves coding each individual measure as a "1" for the highest risk quartile while all others were coded as 0 for each individual biomarker. Markers in which high and low values could be considered high risk were coded so that the highest 12.5% and the lowest 12.5% were coded as 1. Markers selected for the present study included three sympathetic nervous system markers (epinephrine, norepinephrine, dopamine), five peripheral nervous system markers (high frequency heart rate variability, low frequency heart rate variability, root mean square successive difference, beat to beat interval, resting heart rate), two hypothalamic pituitary adrenal axis markers (cortisol, dehydroepiandrosterone sulfate[DHEAs]), six immune markers (C-reactive protein [CRP], interleukin-6 [IL-6], tumor necrosis factor-alpha [TNF-α], soluble intercellular adhesion molecule-1, sE-selectin, fibrinogen), two cardiovascular markers (systolic [BP], diastolic BP), three metabolic markers (fasting blood glucose, hemoglobin A1c [HbA1C], insulin resistance), and six lipid markers (high density lipoprotein [HDL], low density lipoprotein, total cholesterol to HDL ratio, triglycerides, waist to hip ratio [WHR], body mass index [BMI]). These markers were based on work by Carbone (2020), as well as O'Shields and Gibbs (2021), who had previously analyzed the role of AL using MIDUS data.

To mitigate bias that could be caused by differing number of markers across systems (i.e. two cardiovascular markers versus six immune markers), after dichotomization markers were then summed and divided by the total number of markers within that system, before being summed to create an overall measure of AL with a possible range of 0–7 (Gruenewald et al., 2012). The cut off for each marker, as well as the assay method, can be reviewed in Table 1. A comprehensive review of the laboratory methods for MIDUS is publicly available through ICPSR (Ryff et al., 2019a).

Covariates and demographics were measured during the Wave Two Biomarker project and included a measure of recent stress, reported race/ethnicity, reported sex, socioeconomic status, and prescription medication use.

Previous studies have identified a significant relationship between both recent stress and several biomarkers used in AL measurement, as well as between recent stress and depressive symptoms (Cristobal-Narvaez et al., 2020; Knight et al., 2021). Therefore, to control for the effect of general recent stress around the time that biomarker and CM data were collected, the Perceived Stress Scale (PSS) was included. The PSS is a measurement of perceived stress within the last 30 days and has a possible score range of 0–40 (Cohen et al., 1983). Cronbach's alpha for the PSS based on data from the present sample was found to be 0.860, indicating good internal consistency.

Table 1
Allostatic load cutoff values.

Marker	Sample Type & Assay Type	Cut Off Value
Immune		
CRP (ug/mL)	Serum via immunoelectrochemiluminescent	> 2.998
IL-6 (pg/mL)	Serum via ELISA assay	> 1.103
TNF-α (pg/mL)	Serum via immunoelectrochemiluminescent	> 2.409
Fibrinogen (ug/dL)	Citrated plasma via immunoturbidometric	> 386.000
sE-selectin (ng/mL)	Serum via ELISA assay	> 50.297
sICAM-1 (ng/mL)	Serum via ELISA assay	> 323.950
Sympathetic Nervous System		
Epin (ug/g)	High-performance liquid chromatography-electrochemical, adjusted for creatinine	> 2.466
Norep (ug/g)	High-performance liquid chromatography-electrochemical, adjusted for creatinine	> 32.432
Dopamine (ug/g)	High-performance liquid chromatography-electrochemical, adjusted for creatinine	> 175
Hypothalamic Pituitary Adrenal Axis		
DHEA-s (ug/g)	Serum via immunoelectrochemiluminescent	< 34 or > 193.5
Cortisol (ug/g)	Urine via enzymatic colorimetric assay and liquid chromatography-tandem mass spectrometry	< 4.9 or > 28
Parasympathetic Nervous System		
Pulse (beats per minute)	Measured by nurse	> 76
HFHRV (0.15–0.50 Hz)	Echocardiogram performed by technician	< 54.05
LFHRV (0.04–0.15 Hz)	Echocardiogram performed by technician	< 111.00
RMSSD	Calculated	< 11.835
SDRR (milliseconds)	Echocardiogram performed by technician	< 23.538
Metabolic		
Glucose (mg/dL)	Enzymatic colorimetric	> 104
HbA1C	Immunoturbidometric	> 6.1
HOMA-IR	Calculated	> 3.99
Cardiovascular & Respiratory		
Systolic BP	Measured by nurse while sitting	> 141
Diastolic BP	Measured by nurse while sitting	> 81
Lipid		
HDL	Serum via Enzymatic-colorimetric	< 42
LDL	Calculated	> 128.75
TC /HDL	Calculated	> 4.5
Triglycerides	Serum via Enzymatic-colorimetric	> 160
WHR	Measured by nurse	> 0.960
BMI	Calculated	> 32.21

CRP: C-reactive protein; IL-6: interleukin-6; TNF-α: tumor necrosis factor alpha; sE-selectin: soluble E-selectin; sICAM-1: soluble intercellular adhesion molecule-1; DHEA-S: dehydroepiandrosterone sulfate; Epin: epinephrine; Norep: norepinephrine; BMI: body mass index; WHR: waist hip ratio

Given epidemiologic evidence for racialized differences in both mental health and physical health problems that have an overlap in affected biological systems such as hypertension and coronary artery disease, self-reported race/ethnicity was included as a covariate (Mezuk et al., 2013). Race/ethnic identity was determined by asking participants "what is your main racial origins." Possible responses for racial/ethnic origin included White (n = 815), Black and/or African American (n = 23), Native American or Alaska Native Aleutian Islander/Eskimo (n = 12), Asian (n = 3), Other (n = 26), or Don't Know (n = 1). Because of low cell size for racial/ethnic identities other than White, identities were dichotomized into White (n = 815) and non-White (n = 65) groupings.

Because of significant differences in the occurrence of depressive symptoms across men and women, as well as sexual dimorphism in

several biological systems self-reported sex was included as a covariate (Altemus et al., 2014; Klein and Flanagan, 2016). Self-reported sex was determined by asking participants if they identified as male (n = 390) or female (n = 490).

Significant evidence has accumulated that socioeconomic status may be associated with differences in the development of health problems such as hypertension that may overlap with markers included in AL measurement, as well as the development of mental health problems such as major depression (Gavin et al., 2009; Marmot et al., 1991; Mezuk et al., 2013; Wang et al., 2010). Therefore, both household income and current education status were included as measures of socioeconomic status. Income was included as a measure of the participant's total household income from wage, pension, social security, and other sources. Possible values for participant income ranged from $0 to a top-coded value of $300,000.00 USD. Education was included as an ordinal measure with 12 levels ranging from "no school/some grade school" to "PhD, EdD, MD, DDS, LLB, LLD, JD, or other professional degree."

Because prior research has identified a significant positive association between age and AL, participant self-reported age in years was included as a continuous variable, with values ranging from 34 to 83 (Crimmins et al., 2003).

Last, self-reported participant prescription medication use was included as a dichotomous measure. The decision to control for the effects of medications, broadly, was based on the wide number of biological systems used in the measurement of AL, as well as the wide number of therapeutic medications outside antidepressant medication class that may have an antidepressant effect (Kohler et al., 2016; Pecina et al., 2019).

2.3. Analysis plan

The present study utilized a series of regression-based analyses to assess if a history of CM and AL were associated with future depressive symptoms, and if AL was a mediator of this relationship between while controlling for additional factors. Thus, the first model included AL as the dependent variable with CM as the independent variable of interest, as well as including recent stress, age, education, non-White racial/ethnic identity, income, reported female sex, and affirmation of prescription medication use as relevant covariates. Based on the continuous nature of the AL variable, this model was run as an ordinary least squares (OLS) regression, and produced a normal distribution of residuals. Variance inflation factors did not indicate multicollinearity among predictors included in the model.

To assess if self-reported history of CM and AL were associated with future depressive symptoms a second regression model was created, which included the same covariates as the OLS model. Because the dependent variable was count based and demonstrated overdispersion (M=0.619, σ^2 =3.080) a generalized linear model fit to a negative binomial distribution was utilized. Residual deviance (254.28, df=813) was improved relative to the null model (318.51, df=822), and the comparison of the log likelihood for the negative binomial model against the nested poison model continued to support the interpretation of the negative binomial model (log likelihood = 6.710 e^{-197}, df=11). This was further supported by the negative binomial model's superior Akaike Information Criterion (AIC= −1112.827) relative to that of the nested poison model (AIC= 2029).

Mediation analyses were hypothesized to find that AL at Wave 2 would mediate the relationship between recalled CM at Wave 2 and number of depressive symptoms at Wave 3. Mediation analysis was modeled accordingly, and covariates were held continuous across the model as they were in the regression models. Causal mediation analyses were simulated 10,000 times using the default quasi-Bayesian Monte Carlo method with robust standard errors (Tingley et al., 2014).

All analyses were completed in R v.4.0.5, with the MASS package v.7.3–54 being used to assess the negative binomial regression model, and the Causal Mediation Analysis package v.4.5.0 package being used to assess the possible mediational relationship of AL between recalled CM and depressive symptoms (R Core Team, 2021; Tingley et al., 2014; Venables and Ripley, 2002). Additional univariate and bivariate statistics were also calculated to help characterize the analyzed sample. Correlation coefficients were calculated for all continuous variables included in the regression models using Pearson's *r*. Because previous studies had taken steps to evaluate potential sex differences, mean comparisons for continuous variables across sexes were tested using t-tests (Scheuer et al., 2018; O'Shields and Gibbs, 2021). Further, to test the sensitivity of results around AL calculation using general versus sex-specific cut-offs, multivariate results were repeated using an AL index with sex-specific cut-offs as has been seen in Scheuer and colleagues (2018). Last, because of the attrition in participants between the completion of the Wave 2 Biomarker Project and the Wave 3 main survey, univariate statistics were calculated separately for completers vs non-completers and can be reviewed in supplemental Table 1.

3. Results

3.1. Univariate and bivariate analyses

Univariate statistics for the analyzed sample are presented in Table 2. The analyzed sample was predominately White in racial/ethnic identity (92.61%), female in reported sex identity (55.68%), and of middle to late adulthood in age (M=53.87, SD=10.97). Interpretation of mean education levels revealed that most participants had at least some college level education (M=7.82, SD=2.42), and most participants had a mean total household income of $79,226.38 USD. Depressive symptoms were generally low (M=0.61, SD=1.75). Recalled history of CM was similarly low with a mean of 37.54 (SD=14.10). AL was found to have a mean level of 1.54 (SD=0.92) with maximal reported scores topping out at 4.33.

Calculation of Pearson's correlation coefficient identified several notable bivariate relationships. Depressive symptoms at Wave 3 were found to have a significant positive relationship with recalled history of CM ($r = 0.286$, $p < 0.001$). AL did not have a significant relationship with depressive symptoms at wave 3 ($r = 0.058$, $p > 0.05$); however, a significant relationship was identified between AL and recalled history of CM ($r = 0.095$, $p < 0.01$). Notably, an additional correlation between AL as it is included in the present study and an AL index (possible range: 0–27) which did not include the division process from Gruenwald (2012) was also tested, and the two measures were found to be highly correlated ($r = 0.95$, $p < 0.001$). Several mean comparisons across sexes were tested, revealing that males (m=1.668, SD=1.450) had greater average AL relative to females (m=1.450, SD=0.922) $t(846) = 3.456$, $P < 0.01$, while females (m=0.761, SD=1.944) had greater average

Table 2
Descriptive statistics.

	M (SD) or Frequency	Response Range or %
Depressive Symptoms	0.61(1.75)	0–7
Maltreatment	37.54(14.10)	25–114
Allostatic Load	1.54(0.92)	0–4.35
Recent Stress	21.44(6.05)	10–48
Income	79,226.38(61,746.80)	0.00–300,000.00
Age	53.87(10.97)	34–83
Education	7.82(2.42)	0–12
Race/Ethnicity		
White	815	92.61%
non-White	65	7.39%
Sex		
Male	390	44.31%
Female	490	55.69%
Prescription Medication Use		
Affirmed	636	72.27%
Denied	244	27.73%

number of depressive symptoms relative to males (m=0.441, SD=1.944) t(878) = −2.698, P < 0.05. A correlation matrix of all continuous variables included in multivariate analyses can be reviewed in Table 3, while mean comparisons across male and female participants can be reviewed in supplemental Tables 2 and 3.

3.2. Regression models

The OLS regression model assessing the relationship between recalled history of CM at Wave 2 and AL at Wave 2 while including covariates accounted for 11.12% of the variance in AL. A significant positive relationship between CM and AL was identified, with a single point increase in CM being associated with a 0.007 (SE=0.002, p < 0.001) increase in AL. Notably, a significant negative relationship was identified with reported sex, indicating that self-reported female sex was associated with a 0.275 (SE=0.062, p < 0.001) decrease in AL.

The negative binomial regression model assessing the relationship between AL at Wave 2, recalled CM at Wave 2, and depressive symptoms at Wave 3 demonstrated significant results. Both recalled CM (IRR=1.022, 95% CI=[1.004–1.044]) and AL (IRR=1.102, 95% CI=[1.003–1.216]) had a significant positive relationship with depressive symptoms, indicating that a rise in CM or a rise in AL were both associated with an increased number of depressive symptoms. Notably, female identity trended towards significance (p = 0.051) but did not rise above the p < 0.05 threshold.

The regression analyses indicate that AL at Wave 2 partially mediates the relationship between recalled CM at Wave 2 and number of adulthood depressive symptoms at Wave 3 (See Fig. 1). Analysis of the proportion of the effects identified that the total effect of recalled CM on the number of depressive symptoms was 0.0059 (p < 0.01, 95% CI: [0.004–0.01]). Of this total effect, 0.0052 (95% CI: [0.004–0.01], p < 0.01) was found to be the direct effect, whereas 0.0007 (p < 0.01, 95% CI: [0.003–0.01]) was found to be the indirect effect Thus, causal mediation analysis indicates that 10.26% (95% CI: [0.02–0.32], p < 0.01) of the effect of recalled CM on number of depressive symptoms is mediated by AL.

3.3. Sensitivity to allostatic load calculation method

To test the sensitivity of multivariate results relative to the use of sex-specific cut-off scores in the process of creating an AL index (See supplemental Table 4). The OLS models predicting AL both accounted for 11% of the variance in AL; however, sex was only a significant predictor for the general AL cut-off model (b= −0.275, p < 0.001), not for the sex-specific cut-off model (b= −0.082 p = 0.201). Notably, comparison of negative binomial models predicting the number of depressive symptoms found that the significance of AL as a predictor was reduced to a trend when using the sex-specific cut-off AL index (p = 0.095) (See supplemental table 5). Mediation analysis using the sex-specific AL index was found to mediate a lower proportion of the effect of CM on number of depressive symptoms (8.86%), although results were still significant (p = 0.026, 95% CI: [0.008–0.29]) Table 4.

4. Discussion

The present study is the first to our knowledge that explores AL as a potential mediator between recalled CM and depressive symptoms experienced in adulthood using a longitudinal design. Our analyses identified that AL may mediate between 8.86% and 10.26% of the effects of CM on depressive symptoms over an average of seven years later, dependent on the use of a general quartile vs sex-specific quartile cut off method.

When interpreting results of the present study, it is critical to consider how AL was formulated. Early work that studied AL via an index focused on 10 markers: systolic and diastolic BP, WHR, HDL, total cholesterol, HbA1C, DHEA-S, cortisol, noradrenaline, and adrenalin (Seeman et al., 1997; for rationale of each marker see Table 1 of McEwen, 2000). Widom and colleagues' (2015) work identifying that CM is related to internalizing problems and AL utilized four of the original markers (systolic and diastolic BP, HDL, HbA1C) while including five new measures (total cholesterol to HDL ratio, CRP, albumin, creatinine clearance, and peak air flow). Work by Scheuer and colleagues (2018) who identified that AL mediated the relationship between physical abuse and depressive symptoms adhered more closely to the original formulation employed by Seeman and colleagues (1997), excluding DHEA-S, noradrenaline, and adrenalin, while also including CRP, total cholesterol to HDL ratio, triglycerides, and BMI. O'Shields and Gibbs (2021) who identified that AL was associated with depressive symptoms in females included each of the markers in Scheuer and colleagues' (2018) work while adding back DHEA-S and norepinephrine and also including IL-6 and TNF-α. Thus, while differences in associations between the constructs of CM, AL, and depressive symptoms have varied over time, these differences should be considered in relation to differences in AL formulation across studies. The present study formulated AL based on these previous studies and work by Carbone (2020), who identified that AL mediated the relationship between neighborhood perceptions and the presence or absence of depression. This formulation included important components such as parasympathetic nervous system markers, additional immune markers, dopamine, and insulin resistance. Because O'Shields and Gibbs (2021), Carbone (2020), and the present study each draw their sample from the MIDUS study, it may be worth considering that differences in associations may be related to AL formulation. Further studies that evaluate the impact of environmental events on various systems (i.e. immune, parasympathetic nervous system, or metabolic), rather than studying overall AL as an index, may provide important insights.

Additionally, the role of AL as a potential mediator should be considered carefully within the context of potential sex differences. Widom and colleagues (2015) used only a general cut-off derived from biomarker levels across the entire sample. Although, Scheuer and colleagues (2018) calculated AL using the risk-based quartile method with sex specific cut-off's where mean differences were determined per marker. O'Shields and Gibbs (2021) furthered this approach by calculating an AL index for each sex independently, with both sexes having different cut-offs at every marker, and then analyzing multivariate results disaggregated by sex. The present study first identified that AL using a general cut-off for the entire sample had a significant association

Table 3
Correlations among continuous variables.

	1	2	3	4	5	6	7
1. Depressive symptoms	–						
2. Maltreatment	0.286 * **	–					
3. Allostatic load	0.058	0.095 * *	–				
4. Recent Stress	0.301 * **	0.314 * **	0.010	–			
5. Income	-0.087 *	-0.101 * *	-0.086 *	-0.083 *	–		
6. Age	-0.140 * **	-0.145 * **	0.231 * **	-0.197 * **	-0.184 * **	–	
7. Education	-0.064	-0.112 * *	-0.110 * *	-0.085 *	0.293 * **	-0.088 * *	–

p < 0.05 * , p < 0.01 * *, p < 0.001 * **

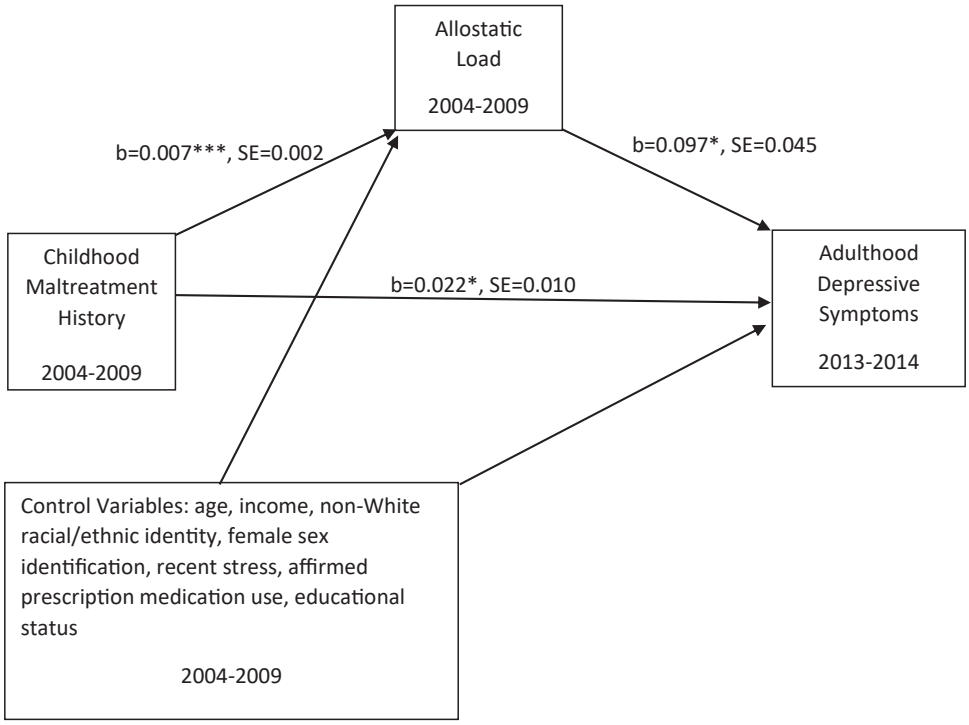

Fig. 1. Allostatic load as a mediator of the effect of childhood maltreatment on adulthood depressive symptoms.

Table 4
Multivariate Results.

	Allostatic Load F= 12.83 (814), r^2 = 0.11 N = 823		Depressive Symptoms 2x loglikelihood= −1112.82, df= 813 N = 823	
	b (SE)	T	b (SE)	IRR, 95% CI: [2.5%– 97.5%]
Allostatic Load	–		0.097(0.045) *	1.102, [1.003–1.216]
Maltreatment	0.007(0.231) * **	3.373	0.022(0.010) *	1.022, [1.004–1.044]
Recent Stress	0.001(0.005)	0.348	0.111(0.024) * **	1.117, [1.063–1.179]
Age	0.017(0.003) * **	5.928	-0.052 (0.015)* **	0.948, [0.920–0.976]
Income	-0.0000003 (0.0000005)	-0.699	0.0000001 (0.000002)	1.000, [0.999–1.000]
Education	-0.035(0.013) * *	-2.727	-0.048 (0.063)	0.952, [0.840–1.079]
Sex (male=0)	-0.275(0.062) * **	-4.417	0.598(0.307)	1.819, [0.840–1.079]
Race(White=0)	0.177(0.118)	1.499	-0.774 (0.582)	0.461, [0.153–1.641]
Prescription Medication Use	0.243(0.070) * **	3.434	0.536(0.347)	1.710, [0.834–3.444]

Allostatic Load model measured by ordinary least squares regression whereas the Depressive Symptoms model was measured by generalized linear model fit to a negative binomial distribution. Direct comparison across beta values should be made with caution.
$p < 0.05$ * , $p < 0.01$ * *, $p < 0.001$ * **

with depressive symptoms. However, when AL was measured using sex-specific cut-offs, AL showed only a trend relationship with depressive symptoms. Thus, while differences in formulation methods of AL should be heavily scrutinized when comparing results across studies, it should also be considered how sex differences may influence associations with AL. Further inspecting sex differences in the present analytic sample through mean comparisons included as supplemental analyses identified that females had greater mean depressive symptoms but lower mean AL relative to males. This replicates findings by Honkalampi et al. (2021) who showed that AL tends to be higher in males in a general community sample in Finland but is still higher overall for those being treated for major depression in an outpatient setting. This may explain why the sex-specific AL index only trended towards significance in the present study, as well as why a case-control design as implemented by Scheuer and colleagues' (2018) study found significant results. Although, it should also be considered that males and females have some inflammation and anthropometric dimorphism, both of which influence HPA-axis responsivity (Baumeister et al., 2016; Klein and Flanagan, 2016; Lu, 2007). Therefore, while females may have had lower mean AL, it should be considered that interactions between biological systems may be different across sexes.

Differences in CM measurement across studies should also be considered carefully. Our analyses, Scheuer and Colleagues (2018), and O'Shields and Gibbs (2021) each use a retrospective measure of CM, but Widom and Colleagues (2015) were able to obtain court records so as to allow for a more objective, prospective measure of CM. Meta-analytic results that account for the combined results of 16 studies have identified that there is poor agreement between retrospective and more objective, prospective reports of CM, with only 56% of those with recalled CM having a confirmed case of CM (Baldwin et al., 2019). Thus, it has been argued that reported retrospective and prospective CM may represent different samples. Therefore, it may be called into question if the association between CM and AL or between CM and depressive symptoms would be stronger if the present analysis could select for confirmed cases of CM (Baldwin et al., 2019). Despite this, work by Danese and Widom (2020) comparing retrospective vs prospective reports of CM found that risk for various forms of psychopathology, including major depression, was significantly associated with a retrospective report of CM, regardless of if the participant's recall was objective or not, or type of maltreatment documented. Furthermore, an objective history of CM was minimally linked to a risk for psychopathology in the absence of a subjective recall of CM even in severe cases (Danese and Widom, 2020).

In addition to the consideration of retrospective vs prospective measurement of CM, it should also be considered how subconstructs of CM are lumped together or split apart. Our analyses, Widom and colleagues (2015), and O'Shields and Gibbs (2021) each used a measure of CM that combines aspects of abuse and neglect into a single measure; however, it has been argued that abuse and neglect have differing impacts on neurobiological development (Sheridan and McLaughlin, 2014). Indeed, experiences of deprivation such as neglect by a caregiver, have been associated with reduced cortical thickness and volume in areas critical for complex social interactions such as the prefrontal cortex, the superior and inferior parietal cortex, and the superior temporal cortex. Further, experiences of threat such as physical, emotional, or sexual abuse, have been associated with several changes in the amygdala including increased dendritic spines, elevated basal activity in response to a novel or stressful task, and deficits in inhibitory regulation. In this light, the Scheuer and colleagues (2018) study may be more precise in assessing associations of CM and AL given that their use of the Early Trauma Inventory only allowed for the assessment of threats, not deprivation. However, the experience of both deprivation and threat may create a synergistic effect in individuals who experience early life deprivation and may have an already greater response to the experiences of psychosocial stress. This response may be prolonged due to heightened amygdala responsivity (Sheridan and McLaughlin, 2014). This combined deprivation and threat dysregulation is supported by early thinking around AL which hypothesized some individuals to have a heightened and prolonged stress response, causing other allostatic systems to have to compensate for this response and eventually create a "wear and tear effect" (McEwen, 2000) Thus, future studies should continue to study the association between CM and AL using a combined measurement of abuse and neglect but may benefit from comparisons between a no-CM group, abuse only group, neglect only group, and abuse and neglect group.

Last, analyses presented here may have implications for the development of prevention and treatment efforts for major depression. Theorizing on a pathophysiological model of major depression as it relates to AL has focused on how repeated activation of allostatic systems is associated three key changes in the brain: 1) hyperactivity of the amygdala, 2) leading to HPA axis dysregulation, 3) followed by hippocampal and prefrontal cortex volume loss (McEwen, 2003). This is supported by findings that the hippocampal volume loss in people experiencing major depression is thought to occur early in the course of major depression, but not before it occurs (MacQueen et al., 2003). Importantly experiences of early threat are also associated with decreased hippocampal volume, but this effect is often not present until adulthood (McLaughlin et al., 2014; Tottenham and Sheridan, 2009). Thus, the finding that AL mediates the relationship between CM and depressive symptoms is theoretically supported and may point towards a potential use as a marker for treatment. Although, it should also be considered that AL indices based on biological mediators may underestimate the mediational effect of AL due to an inability to account for key changes in the brain that are implicated in the prior experience of maltreatment and a current depressive symptom. Future research aiming to advance the clinical utility of AL may benefit from assessing interventions' effects on biological mediators commonly used in AL indices and their relationship with key brain regions such as the amygdala and hippocampus in individuals who have experienced CM. Development of such interventions may hold potential for preventing the onset of depressive symptoms in adulthood for some individuals who experience CM, or to reduce the occurrence of commonly associated comorbidities such as coronary artery disease or bone density loss for those that do go on to develop depressive symptoms (McEwen, 2003).

4.1. Limitations

While the present study makes significant contributions to the understanding of how a history of CM contributes to adulthood depressive symptoms, results should be considered within the context of several limitations. First, many of the measures utilized here are self-report and therefore may be subject to forms of bias. This is especially important in the context of CM research given recent findings that substantiated reports of CM have been found to predict inflammation more strongly as measured by CRP than individual recall (Osborn and Widom, 2020). Future studies may wish to prioritize a design in which case records for CM can be verified. Second, the MIDUS study is known to be lacking in its ability to detect differences across various racial/ethnic groups. While the MIDUS research group attempted to rectify this through the collection of a convenience sample of Black and/or African American identifying individuals around the city of Milwaukee, cell size across racial/ethnic groupings was still insufficient to analyze outside of a White or non-White binary. Third, several hundred individuals were lost to attrition between completion of the Wave 2 biomarker project and the main Wave 3 survey. It should be considered that individuals lost to attrition may be fundamentally different from participants that followed up, potentially biasing results. Fourth, a degree of consideration should be given to how AL is being conceptualized across studies. The present study includes a greater number of biomarkers in its AL index relative to other studies at the intersection of CM, AL, and depressive symptoms, and while the markers selected here overlap with other studies of AL and depression, future studies may consider more sophisticated methods (Carbone, 2020; O'Shields and Gibbs, 2021; Scheuer et al., 2018; Widom et al., 2015). For instance, work by Wiley et al. (2017) demonstrated that AL may be modeled as a latent construct with a bifactor structure, while work by Liu et al. (2021) has demonstrated how Item Response Theory can be used to capture greater variability in AL models. Still other new models have been used to analyze how various markers of the immune system are related to specific depressive symptoms using network analysis (Fried et al., 2020; Moriarity et al., 2021). Given that the present study better provides limited grounds for causal inference through a longitudinal design, future studies should focus on more sophisticated analytic techniques so as to uncover more specific targets for treatment and prevention that cannot be identified through the broad measurement of AL as an index. Last, AL was only included at Wave 2 and depressive symptoms were only included at Wave 3, and therefore potential bidirectional effects cannot be accounted for nor can an empirical temporal ordering that does not rely on theoretical inference.

4.2. Conclusion

A history of CM has been well documented as being associated with poor health outcomes later in life, including morbidities across both the physical and mental health spectrum. The present study sought to expand on the work of previous studies that had explored the possible mediation of the relationship between CM and depressive symptoms experienced in adulthood by AL using a longitudinal design. Analyses presented here support that AL partially mediates this relationship, being associated with depressive symptoms an average of seven years prospectively.

Conflict of interest statement

We confirm that this work is original, has not been published elsewhere, and is not under consideration for publication elsewhere. We have no conflict of interest to disclose. No funding sources are associated with the work presented here.

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