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Depressive symptoms, childhood maltreatment, and allostatic load: The importance of sex differences

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ABSTRACT

Objective: Roughly half the individuals who experience childhood maltreatment also experience depressive symptoms in adulthood; however, many current treatments are ineffective. Allostatic load (AL) offers a method of exploring this relationship through the lens of biometric dysregulation that may explain these increased odds for depressive symptoms in adulthood. We attempted to expand the limited research base on AL, depressive symptoms, and childhood maltreatment by examining how these variables are associated in a U.S. community sample.

Method: Data were acquired through secondary analysis of the Midlife in the United States Refresher biomarker survey (n = 691). Depression severity, measured by the Center for Epidemiologic Studies Depression Scale, served as the dependent variable, while summed scores for the Childhood Trauma Questionnaire, and a 16 measure AL index served as independent variables. All analyses were stratified by sex (n male = 347, n female = 344). The Perceived Stress Scale was included to control for recent stress. An OLS regression was used to understand the relationship between depression and predictor variables before then being tested for the possible mediating role of AL.

Results: Comparison of OLS models yielded notable differences in predicting depressive symptoms between males and females, namely that while maltreatment was significant for both groups, AL was only significant for females. Mediation by allostatic load was not significant for males or females.

Conclusion: We explored the possible mediation of childhood maltreatment and adulthood depressive symptoms by AL. While our study did not confirm mediation, this was the first known study to explore these relationships in a U.S., community sample. Sex stratification reveals a clear need for accounting for sex differences in predictor variables for future studies.

1. Introduction

Roughly one in five individuals will experience major depression (MD) at some point in their lifetime, with most episodes qualifying as moderate or severe (Hasin et al., 2018). While as many as 70% of these individuals do get some form of treatment, findings from the Sequenced Treatment Alternatives to Relieve Depression revealed that current treatment methods may be inadequate for achieving remission in many individuals (Hasin et al., 2018; Rush et al., 2006). These factors expound upon recent estimates that MD is associated with an economic burden of 173–210 billion dollars annually (Greenberg et al., 2015). Notably, these statistics are associated with major depressive symptoms (MDS) severe enough to warrant a diagnosis of MD; however, significant deleterious health outcomes have also been associated with subsyndromal MDS including a general increased risk for psychiatric disorders, medical disease, and poorer overall quality of life (Goldney et al., 2004; Johnson et al., 2009; Koenig et al., 2006).

One factor largely associated with an increased odds of MDS is the experience of childhood maltreatment. Aversive childhood experiences studies have demonstrated a positive dose-response effect between childhood maltreatment and MDS later in life, with a later meta-analysis finding that half of all those who experience childhood maltreatment being affected by MDS (Chapman et al. 2004; Nelson et al., 2017). Specific to treatment, childhood adversity, which subsumes childhood maltreatment, has been found to be associated with treatment resistance as well as increased rates of suicidal behavior (Tunnard et al., 2013). Indeed, some evidence suggests individuals with adulthood MDS and childhood maltreatment may show superior treatment to psychotherapy

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over pharmacotherapy, and thus referral to the correct type of treatment may be critical to service providers for treatment planning (Nemeroff et al., 2003).

The need for an understanding of how childhood maltreatment and adulthood MDS are connected is clear from the epidemiological evidence; however, few findings have elucidated the biometric changes specific to this group. Therefore, the present study will utilize an allostatic load (AL) model to build an understanding of how these constructs are connected. In doing so, this will facilitate future research to help expand on the increase in health adversities experienced by this population, uncover future markers for treatment of MD, and identify resiliency factors for future treatment development (McEwen and Gregerson, 2019).

The term allostasis may take several different connotations. While some authors note it as entirely separate from homeostasis, others have defined it as a shift in philosophy about biometrics oriented around dynamic change rather than a specific norm (Juster et al., 2010). Irrespective of this philosophical difference, the phenomenon of AL, the over activation of the body's biological regulatory systems, has been implicated in both physical health and mental health outcome studies through a "wear and tear" effect (McEwen, 2000, 2003; Beckie, 2012). While AL studies are diverse in their selected biometrics and computational methods, many studies use a combination of markers accounting for differences across metabolic, cardiovascular, anthropometric, neuroendocrine, and immune systems (Juster et al., 2010).

Studies have been mixed in their findings on the relationship between AL and MDS. Previous research has identified that AL partially mediates the relationship between processing speed in adolescence and depressive symptoms in adulthood as well as the relationship between psychological distress and depression; is positively associated with affective and somatic symptom domains of depression; and is positively associated with overall symptom severity (Gale et al., 2015; Hinsta et al., 2016; Kobrosly et al., 2013, 2014). Additionally, some evidence has emerged that depressed individuals seeking emergency care may have higher AL than controls, that individuals currently taking psychotropic medications may have higher AL, and that metabolic components of AL may mediate the relationship between coronary heart disease and MDS in women (Gillespie et al., 2019; Juster et al., 2018; Kerr et al., 2020). With respect to treatment, some recent findings also suggest that AL, specifically metabolic and hypothalamic-pituitary-adrenal axis components, may be indicative of poorer response to selective serotonin reuptake inhibitors in those experiencing MDS (Hough et al., 2020). Counter to these findings though, other studies have found that the link between MDS and AL may weaken over time or when other variables such as age and sex are included (Juster et al., 2011), or that the link does not exist at all in some cases where health behaviors are accounted for (Rodriquez et al., 2018).

Despite the broadness of the literature base covering MDS and AL that has developed over the past decade, a paucity of studies have evaluated how early life events may affect this relationship. This oversight becomes even more concerning given that AL differences in maltreated youth have been identified as early as 8–10, that AL may mediate the relationship between childhood maltreatment and adulthood psychosis, and that childhood maltreatment has been found to predict AL thirty years later even while controlling for age, sex, and racial identity (Piotrowski et al., 2020; Rogosch et al., 2011; Widom et al., 2015).

Indeed, to date only one study has investigated childhood maltreatment and later MDS in adulthood using the AL framework. Scheuer et al. (2018) utilized a case-control model with a sample of 324 individuals experiencing moderate or greater MDS admitted to an inpatient psychiatric hospital compared to 261 non-depressed controls to conduct a mediation analysis between childhood abuse, AL, and adulthood MDS. Scheuer's (2018) AL index consisted of a 12-item composite measure of BMI, WHR, systolic blood pressure, diastolic blood pressure, basal plasma cortisol, triglycerides, total cholesterol, high density lipoprotein (HDL), total cholesterol/HDL, hemoglobin A1C (HGA1C), glucose, and C-reactive protein (CRP), which was coded dichotomously as the less healthy quartile each equaling one and then summed. Scheuer found that the AL model mediated the role between physical abuse and later MDS, but did not find significant results with respect to sexual abuse.

While Scheuer et al. (2018) study was an important step in understanding how childhood maltreatment and AL may contribute to the experience of MDS in adulthood, there were three key points we believed we could expand on:

1) We sought to expand the minimal research on childhood maltreatment, MDS, and AL by attempting to replicate Scheuer's (2018) results in a U.S. community sample.
2) We sought to improve the statistical control of the measurement of MDS with respect to AL and childhood maltreatment through inclusion of a measure aimed at the experience of recent stress.
3) We aimed to explore how the relationship between MDS, AL, and childhood maltreatment may differ across different Sexes.

2. Materials and methods

2.1. Sample and procedures

The present study utilizes data from the Midlife Development in the United States (MIDUS) data set, a nationally representative, longitudinal study composed by a multidisciplinary team with the main goal being to understand variations in health and age related diseases (Radler, 2014). More specifically, this study will utilize the MIDUS-Refresher wave, which was collected from 2011 to 2016, originally designed to replenish the large number of individuals lost between waves 1 and 2 of the main MIDUS study. Because of the biometric measurement component of the present study, Project 4, the biometric subsection of MIDUS-R, will be the primary data frame for this study.

From individuals who completed MIDUS-R, a sample of 863 individuals were drawn to form the Project 4 sample. Recruitment of participants took place in a two-stage process. Individuals were first mailed a recruitment packet which included a letter and brochure that described the study before calling the participants within the next few weeks to answer any questions and attempt to establish an appointment for participants to visit a clinical research unit at one of three universities as well as establish verbal consent for participation. Participants were asked to visit University of California: Los Angeles, University of Wisconsin, or Georgetown University depending on their location. Visits to clinical research units lasted two days, during which participant medical history, biospecimen, and self-report questionnaires were collected. Project 4 has a response rate of 42%, a mean participant age of 50.84 (SD = 13.41), relatively even sex distribution (52.1% female), and is predominantly White (70.6%). For a full review of the sampling methods and data collection procedures please see Love et al. (2010). Only individuals that provided complete information for the variables were included in this study, while all others were removed via case-wise deletion (N = 172). This resulted in a final sample of 691 participants.

2.2. Measures

2.2.1. Center for Epidemiologic Services Depression Scale

The present study utilizes the center for epidemiologic studies depression scale (CES-D) for measurement of MDS. The CES-D is a 20 item measure with each item allowing for a score of 0 (indicating rarely or none of the time), 1 (some or little of the time), 2 (moderately or much of the time), or 3 (most or all of the time). Scores are calculated by summing the items, resulting in a score range of 0–60 with higher scores indicating greater depressive symptomatology. Prior research has identified cutoffs of 16 or greater for determining if an individual is experiencing a depressive episode (Lewinsohn et al., 1997); however, because the aim of this study is to examine childhood maltreatment and

AL relative to overall MDS, scores here will be utilized as a continuous variable. Measures of internal consistency using the present sample yielded a Cronbach's alpha of 0.768 for the total sample, whereas alphas for the male-identifying and female-identifying respondents were found to be 0.786 and 0.745, respectively.

2.2.2. Childhood Trauma Questionnaire

The childhood trauma questionnaire (CTQ) was selected as a measure of childhood maltreatment that is recalled during adulthood. The CTQ is a 28 item, self-report measure that can be divided into five subscales of trauma: emotional neglect, emotional abuse, physical neglect, physical abuse, and sexual abuse. A final section of the CTQ utilizes a three-question subsection to detect under reporting of traumatic experiences in the other five subscales. Each of the five maltreatment subscales has five questions with possible responses being scored as a five-point likert scale ranging from never (1) to very often (5). Therefore, every subscale has a possible score range of 5–25, with summation of scores across the five subscales ranging from 25 to 125. Prior psychometric testing of the CTQ that utilized a community sample of over 1000 adults has identified a test-retest reliability of 0.79 and 0.86 over a four month period (Scher et al., 2001). Testing or internal consistency using the present sample identified a Cronbach's alpha of 0.907 for the total sample, whereas alphas for the male-identifying and female-identifying samples were found to be 0.865 and 0.853, respectively.

2.2.3. Allostatic Load Index

AL was calculated using the Group Allostatic Load Index method which was originally postulated by (Seeman et al., 1997) and has become one of the most common methods of AL calculation (Juster et al., 2010). First we selected sixteen biomarkers, twelve of which were originally included in Scheuer et al.'s (2018) study. Because Scheuer et al.'s (2018) study was weighted heavily in terms of metabolic markers, and previously underutilized neuroendocrine and immune markers, we elected to add two neuroendocrine markers (norepinephrine and dehydroepiandrosterone) and two immune markers (interleukin-6 and tumor necrotic factor-α). These markers were selected based on prior literature that has identified these markers as being relevant to the measurement of MDS or AL (McEwen, 2003; Lamers et al., 2019). Each marker was then disaggregated by sex before being dummy coded so that the quartile indicating poorest health was coded as being equal to 1 (See Table 1 for quartile cutoffs and assay type). Dummy coded markers were then summed into an AL for each sex, each with a possible score ranging between 0 and16.

2.2.4. Perceived Stress Scale

Recent stress was measured via the Perceived Stress Scale. While AL related to childhood maltreatment has been found to be associated with long term changes that are detectable into adulthood, the finding that AL is also associated with childhood maltreatment during childhood raises the critical need for a recent measure of stress (Rogosch et al., 2011; Slopen et al., 2014; Widom et al., 2015). With this in mind, the perceived stress scale (PSS), a 10-item likert scale questionnaire with answers ranging from never (0) to very often (4), was selected for inclusion (Cohen and Williamson, 1988). The PSS is designed to assess the perception of stress during the last month, with higher scores indicating higher perceived stress. Measurement of internal consistency for the present sample yielded a Cronbach's alpha of 0.861 for the total sample, whereas alphas for the male-identifying and female-identifying respondents were found to be 0.867 and 0.922, respectively.

2.2.5. Medical history and treatment

Both having a prior medical condition and receiving current medical treatment are highly relevant to the present study. Many general medical conditions have been found to be comorbid with MD, such as diabetes mellitus and coronary artery disease, or may have a symptom pattern that has a similar behavioral expression to MD, such as hypothyroidism or Cushing's syndrome (Karlamangla et al. 2002; McEwen, 2000). Therefore, positive history of any medical condition that has been diagnosed by a physician was collapsed into a single dummy coded variable, with the absence of medical illness serving as the reference group. With respect to treatment, current pharmacotherapy is important to consider for both MD as well as general biometric measurement. For instance, some studies have found that treatment with an antidepressant, may be associated with changes in inflammatory biomarkers and neuroactive steroids, systems commonly used in AL indices (Hiles et al., 2012; Misiak et al., 2018; Zahed et al., 2017). Even more convoluting, some recent research on the utilization of anti-inflammatory medications on MD may result in a decrease in symptoms (Kohler et al., 2014). With these factors in mind, utilization of any medication was dummy coded, with no current medication usage serving as the reference group.

Table 1
Biometric variable cut offs for allostatic load index.

Biometric Variable	Assay Type	Variable Cut Off	
		Male	Female
Metabolic			
Fasting glucose	Enzymatic colorimetric	≥ 107 mg/dL	≥ 100.5 mg/dL
Hemoglobin A1C	Immunoturbidometric	≥ 5.8%	≥ 5.9%
Total cholesterol	Enzymatic colorimetric	≥ 197 mg/dL	≥ 207 mg/dL
High density lipoprotein	Enzymatic colorimetric	≤ 42	≤ 51
Cholesterol/high density lipoprotein	Calculated	≤ 0.236842	≤ 0.279416
Triglycerides	Enzymatic colorimetric	≥ 151 mg/dL	≥ 128 mg/dL
Anthropometric			
Waist hip ratio	Measured by nurse	≥ 1.013	≥ 0.886
Body mass index	Measured by nurse	≥ 32.45	≥ 34.37
Cardiovascular and Respiratory			
Systolic blood pressure	Measured by nurse while sitting	≥ 141	≥ 134
Diastolic blood pressure	Measured by nurse while sitting	≥ 87	≥ 82
Neuroendocrine			
Cortisol	High-pressure liquid chromatography tandem mass spectrometry	≥ 2.41 ug/dL	≥ 2.09 ug/dL
[a]Norepinephrine	High-pressure liquid chromatography tandem electrochemical detection	≥ 33.40 ug/dL	≥ 28.35 ug/dL
[a]Dihydroepiandrosterone	High-pressure liquid chromatography tandem mass spectrometry	≤ 2.2 ng/mL	≤ 2.6 ng/mL
Immune			
C-reactive protein	Immunoturbidometric	≥ 2.20 ug/mL	≥ 3.84 ug/mL
[a]Interleukin-6	Immunoelectrochemiluminescent	≥ 1.06 pg/mL	≥ 1.17 pg/mL
[a]Tumor necrotic factor- α	Immunoelectrochemiluminescent	≥ 2.38 pg/mL	≥ 2.31 pg/mL

[a] New to this study, not included in the Scheuer et al. (2018) study.

2.2.6. Demographics

Several demographic variables were included due to prior finding as being covariates of either MD, AL, or childhood maltreatment. Participant's total household income including wages, pensions, social security, or other sources was included as a proxy for socioeconomic status based on prior findings that neighborhood affluence and degree of economic hardship may affect AL in adulthood (Patel, 2019; Slopen et al., 2014). Total household income ranged from 0.00 to 300,000 USD. The question "what are your main racial origins – that is, what race or races are your parents, grandparents, and other ancestors" was used as a proxy for participant racial identity. While White (n = 560), Black and/or African American (n = 52), Native American or Alaska Native (n = 15), Asian (n = 11), Native Hawaiian or Pacific Islander (n = 2), or other (n = 51) racial backgrounds were noted in the dataset, low prevalence in non-White groupings led to the need to dichotomize race as White (n = 560) and non-White (n = 131) for the purposes of this study. Racial identity as a necessary covariate is supported by pervasive epidemiological differences in mental health prevalence, especially with respect to MDS (Barnes and Bates, 2017). Participant age was included based on findings that both AL and MDS tend to increase with age (Luppa et al., 2012; McEwen, 2000). Ages ranged from 25 to 76. Finally, education was included to offer similar statistical control as Scheuer's (2018) model. While education levels were widely distributed in the analyzed sample, participant reporting of education level led to unequal cell sizes for some responses (ex:14 participants did not graduate high school while 147 had masters degrees), and so responses were re-categorized into no college degree (n = 218), college degree (n = 281), or graduate school degree (n = 192).

2.3. Analysis plan

We implemented a three-phase analysis plan focused around: 1) creation of a multivariate model, 2) attempting mediation of CTQ and CES-D by AL, and 3) attempting mediated moderation with CTQ and CES-D being mediated by AL, and CTQ and AL being moderated by age. Because some previous studies have discovered sex differences in AL and MDS, and there is wide interest sex differences in childhood maltreatment and MDS, we chose to disaggregate all analyses by self-reported sex (Clayton and Tannenbaum, 2016; Gallo et al., 2018; Gillespie et al., 2019; Juster et al., 2016) All analyses were disaggregated by sex and were performed by using SAS University Edition.

First, all variables were screened at the univariate and bivariate level before being entered into an OLS regression so that the relationship between variables could be examined in a multivariate model. Scores for the CES-D served as the dependent variable while AL index and CTQ scores served as the independent variables of interest, and PSS scores, age, household total income, racial identity, education level, current prescription medication use, and diagnosis of a medical condition served as relevant covariates. While many variables were skewed or kurtotic when examined through z transformation, residuals were evenly distributed at the multivariate level; therefore, variables were not transformed in favor of model parsimony and interpretability. Variance inflation factor was calculated for predictor variables and did not show any indication of multicollinearity. Additionally, a non-linear relationship was identified between CES-D scores and summed CTQ ($p < 0.01$) scores as well as CES-D scores and PSS scores ($p < 0.01$) for female participants and therefore their quadratic terms were included in all multivariate analyses. Similarly, male participants were also found to have a non-linear relationship between CES-D scores and PSS scores ($p < 0.001$) and a trend was identified between CES-D and CTQ scores ($p = 0.056$). Therefore, to allow for comparison between male and female multivariate models the same quadratic terms were included for both sexes.

The second phase of analyses sought to test if the mediating role of AL between childhood maltreatment and MDS could be replicated as initially was identified in Scheuer et al. (2018) prior model. We utilized the Baron-Kenney method to test for mediation and used the Sobel test to identify significance of mediation (Baron and Kenny, 1986). The mediation model was also stratified by sex and used the same predictor variables as the OLS model, including quadratic terms.

The third phase of analyses sought to test Scheuer's (2018) model further by examining if age moderated the relationship between childhood maltreatment and AL index by using a moderated mediation model. The moderation term was calculated through taking the product of CTQ scores and age. As with the other models this term was calculated separately for each sex. In line with the simple mediation model, we utilized the Baron-Kenney method with the Sobel test to identify significance.

3. Results

3.1. Sample description and bivariate analyses

The analyzed sample consisted of 691 individuals, 344 of whom identified as female. Between sex groupings, differences were noted in MDS (male $M = 8.079$, $SD = 7.288$; female $m = 9.272$, $SD = 7.263$; $t(689) = -2.15$, $p < 0.05$), childhood maltreatment (male $m = 35.776$, $SD = 10.450$; female $m = 39.849$, $SD = 15.780$; $t(689) = -3.96$, $p < 0.001$), and recent stress (male $m = 21.411$, $SD = 6.139$; female $m = 22.973$, $SD = 6.079$; $t(689) = -3.39$, $p < 0.001$). No differences were noted in AL between male ($m = 3.855$, $SD = 2.585$) and female ($m = 3.824$, $SD = 2.697$) identifying participants ($t(689) = 0.042$, $p > 0.05$). A complete reporting of descriptive statistics, stratified by sex, can be reviewed in Table 2.

Bivariate analyses revealed several notable correlations across both sexes. For female participants both childhood maltreatment ($r = 0.348$, $p < 0.001$) and AL index ($r = 0.271$, $p < 0.001$) were found to have a significant correlation with MDS; however, childhood maltreatment ($r = 0.292$, $p < 0.001$), but not AL index ($r = 0.094$, $p > 0.05$) was significantly correlated with MDS for male participants. Notably, recent stress was found to have a significant correlation with MDS for both male ($r = 0.775$, $p < 0.001$) and female participants ($r = 0.715$, $p < 0.001$); although AL index was significant for recent stress for female participants ($r = 0.172$, $p < 0.01$), but not male participants ($r = 0.029$, $p > 0.05$). A complete reporting of correlation coefficients, stratified by sex, can be reviewed in Table 3.

3.2. Multivariate results

The OLS regression modeling MDS for male participants was significant ($F[12,334] = 55.61$, $p < 0.001$), accounting for 66.64% of the variance in depressive symptoms. Inspection of individual predictors revealed that only childhood maltreatment ($b = 0.329$, $p < 0.01$), recent stress ($b = -0.500$, $p < 0.05$) and their quadratic terms ($b = -0.003$, $p < 0.05$; $b = 0.029$, $p < 0.001$, respectively) were significant predictors for this model. Interpretation of the maltreatment main effects with the quadratic term did indicate a decrease in the effect of maltreatment as maltreatment scores increased, resulting in a less than one point change in MDS at any given value for childhood maltreatment within the analyzed sample score range while holding all other terms constant. Interpretation of the main effects of recent stress with the quadratic term indicates an increase in the effect of recent stress as recent stress increased, resulting in a 2.088 maximal increase in MDS while holding all other terms constant. The AL index was not a significant predictor of MDS score for the model.

The OLS regression modeling MDS for female participants was also significant ($F[12,331] = 41.52$, $p < 0.001$), accounting for 60.17% of the variance in depressive symptoms. As with the model for male participants, childhood maltreatment was found to be a significant predictor ($b = 0.213$, $p < 0.05$); however, recent stress was not significant. Also like the male model, the quadratic term for recent stress was significant ($b = 0.017$, $p < 0.01$); however, the quadratic term for

Table 2
Analyzed sample descriptive statistics and T-Tests.

Categorical Variable	Male		Female		
	N	%	N	%	
Race					
White	296	85.30	264	76.74	
Non-White	51	14.70	80	23.26	
Education					
No college degree	115	33.14	103	29.94	
College graduate	129	37.18	152	44.19	
Grad school graduate	103	29.68	89	25.87	
Currently taking a prescribed medication	233	67.15	251	72.97	
Has been diagnosed with a medical condition	281	80.98	288	83.72	
Continuous Variable	Male Only Analyzed Sample		Female Only Analyzed Sample		T-Test
	Mean (SD)	Range	Mean (SD)	Range	
MDS	8.073 (7.279)	0–43	9.262(7.251)	0–44	−2.15*
Maltreatment	35.842 (10.509)	25–83	39.893 (15.822)	25–97	−3.96***
AL index	3.855 (2.585)	0–11	3.819 (2.691)	0–12	0.042
Recent stress	21.387 (6.147)	10–43	22.961(6.065)	10–42	−3.39***
Household income	100,889.04 (70,917.99)	0–300,000	81,936.77 (60,521.67)	0–300,000	3.78***
Age	52.939 (14.216)	25–76	50.081 (12.867)	25–75	2.77**

MDS: Major Depressive Symptoms, AL: Allostatic Load, SD: Standard Deviation.
* P < 0.05,
** P < 0.01,
*** P < 0.001.

Table 3
Correlations of continuous variables.

Male Correlations						
	1	2	3	4	5	6
1. MDS	1.00					
2. Maltreatment	0.292***	1.00				
3. AL	0.094	0.059	1.00			
4. Recent stress	0.775***	0.284***	0.029	1.00		
5. Age	−0.166**	−0.078	0.280***	−0.193***	1.00	
6. Income	−0.179***	−0.215***	−0.142**	−0.106*	0.048	1.00
Female Correlations						
1. MDS	1.00					
2. Maltreatment	0.348***	1.00				
3. AL	0.271***	0.163**	1.00			
4. Recent stress	0.715***	0.280***	0.172**	1.00		
5. Age	−0.164**	0.009	0.204***	−0.224***	1.00	
6. Income	−0.083	−0.132*	−0.151**	−0.00003	−0.010	1.00

MDS: Major Depressive Symptoms, AL: Allostatic Load.
* P < 0.05,
** P < 0.01,
*** P < 0.001.

childhood maltreatment was not significant. Notably, increasing AL index (b=0.314, p < 0.01), racial identity as non-White (b = 1.633, p < 0.01), and obtaining an undergraduate degree were all significant predictors associated with an increase in MDS for female participants, while age (b = −0.045, p < 0.05) was associated with a decrease in MDS. Both the OLS regression models for male and female participants can be reviewed in Table 4.

3.3. Mediation and moderated mediation analyses

Mediation of childhood maltreatment and MDS by AL for male participants was tested via the Baron-Kenney method as can be seen in Fig. 1. While a significant relationship was identified for the main effects between childhood maltreatment and MDS (b = 0.329, p < 0.01), no significant relationship was identified for the main effects between childhood maltreatment and AL (b = −0.015, p = 0.824). Consistent with the OLS model, the main effects between AL and MDS were found to be insignificant (b = 0.150, p = 0.122). Utilizing the path coefficients, the Sobel test revealed that simple mediation of maltreatment and MDS by AL was insignificant for male participants (z = −0.212, p = 0.832). A moderated mediation model was utilized with age moderating the relationship between maltreatment and AL. Age was not found to be a significant moderator (b = 0.0004, p = 0.603) and the main effects between maltreatment and AL remained insignificant (b = −0.044, p = 0.620). A Sobel test confirmed that the moderated mediation model was also insignificant (z = −0.466, p = 0.641).

Mediation of childhood maltreatment and MDS by AL for female participants was tested through the same procedures as the male participants, and the corresponding path coefficients can be reviewed in Fig. 2. As with the male participants, a significant relationship was identified for the main effects between childhood maltreatment and MDS (b = 0.213, p < 0.05), but not between childhood maltreatment and AL (b = −0.080, p = 0.088). Breaking with the prior model, the main effects between AL and MDS were significant (b = 0.314, p < 0.01) however the Sobel Test revealed that mediation was still insignificant (z = −1.486, p = 0.137). Also like the male participant model, age was implemented as a moderator for the relationship between maltreatment and AL in a moderated mediation model. Age was an insignificant moderator (b = 0.0005, p = 0.467) for the main effects between maltreatment and AL (b = −0.110, p = 0.079), and a Sobel test

Table 4
Multivariate statistics.

Male Model ($F = 55.61$)*** $R^2 = 0.6664$			**Female Model** ($F = 41.67$)*** $R^2 = 0.6017$	
Variable	B	SE	B	SE
Maltreatment	0.329**	3.285	0.213*	0.089
Quadratic Term	−0.003*	0.001	−0.001	0.0008
AL Index	0.150	0.096	0.314**	0.104
Recent stress	−0.500*	0.210	−0.057	0.267
Quadratic Term	0.029***	0.004	0.017**	0.005
Age	−0.012	0.019	−0.045*	0.022
Race/Ethnicity (White = 0)	0.378	0.661	1.633**	0.616
Income	−0.000007	0.000003	−0.000002	0.000004
Prior medical condition (no condition = 0)	−0.838	0.707	1.409	0.793
Currently taking prescription medication (no medication = 0)	0.309	0.598	1.180	0.625
College graduate (some college or less = 0)	−0.013	0.580	1.277*	0.618
Graduate school graduate (some college or less = 0)	0.616	0.662	0.047	0.719

AL: Allostatic Load.
* $P < 0.05$,
** $P < 0.01$,
*** $P < 0.001$.

found the model as a whole to be insignificant ($z = -1.520$, $p = 0.128$).

4. Discussion

4.1. Primary findings

The present study examined the relevance of childhood maltreatment and adulthood AL in predicting adulthood MDS, and is the first study to do so in a U.S., community sample. Stratification by sex highlighted that childhood maltreatment was relevant for both male and female identifying participants; however, AL was only significant for female participants in multivariate models. Attempted mediation analysis and moderated mediation analysis of AL on the relationship between childhood maltreatment and adulthood MDS were insignificant across both sexes, a conflicting finding with the current literature (Scheuer et al., 2018).

While the results of this study do not support the mediation findings of Scheuer et al. (2018), which we attempted to extend from a hospitalized sample to a community sample, there are some key discrepancies that may account for this difference. Chiefly, Scheuer's sample coming from an inpatient psychiatric hospital would most likely be associated with greater overall depressive symptoms, and theoretically may also be associated with a greater degree of biological dysregulation (Miller et al., 2009). For our sample, the maximum value for CES-D scores in the study was 44.00 out of a possible 60.00. While some differences in AL index construction are notable between the two studies, the AL index employed here uses 16 biomarkers and thus should allow for greater detection of biometric dysregulation associated with MDS, not less. Therefore, differences in AL construction are not likely related to the lack of mediation in the present study. When further examining these findings across previous research that has identified an increased AL in individuals presenting for emergency care that were also experiencing depressive symptoms, it is possible that AL may function differently across different settings (Juster et al., 2018).

Overall, this study does support a connection between maltreatment experienced in childhood and MDS in adulthood that has already been well established by the literature (Chapman et al., 2004; Nelson et al., 2017); however, in breaking with prior literature that had identified a significant relationship between AL and childhood maltreatment, our findings were mixed (Rogosch et al., 2011; Slopen et al., 2014; Widom et al., 2015). At the bivariate level childhood maltreatment was associated with AL in female identifying participants only, and while this association persisted into the multivariate regression model, childhood maltreatment did not predict AL in a mediation model even when attempting to moderate by age.

Our results here also highlight the importance of sex differences in future AL studies. While Scheuer et al.'s (2018) study did check for sex differences across each biomarker as we did, the choice here to stratify all analyses by sex highlights an important gap in our understanding of sex differences in the experience of childhood maltreatment and adulthood MDS. Indeed, it has been well understood that at least either a

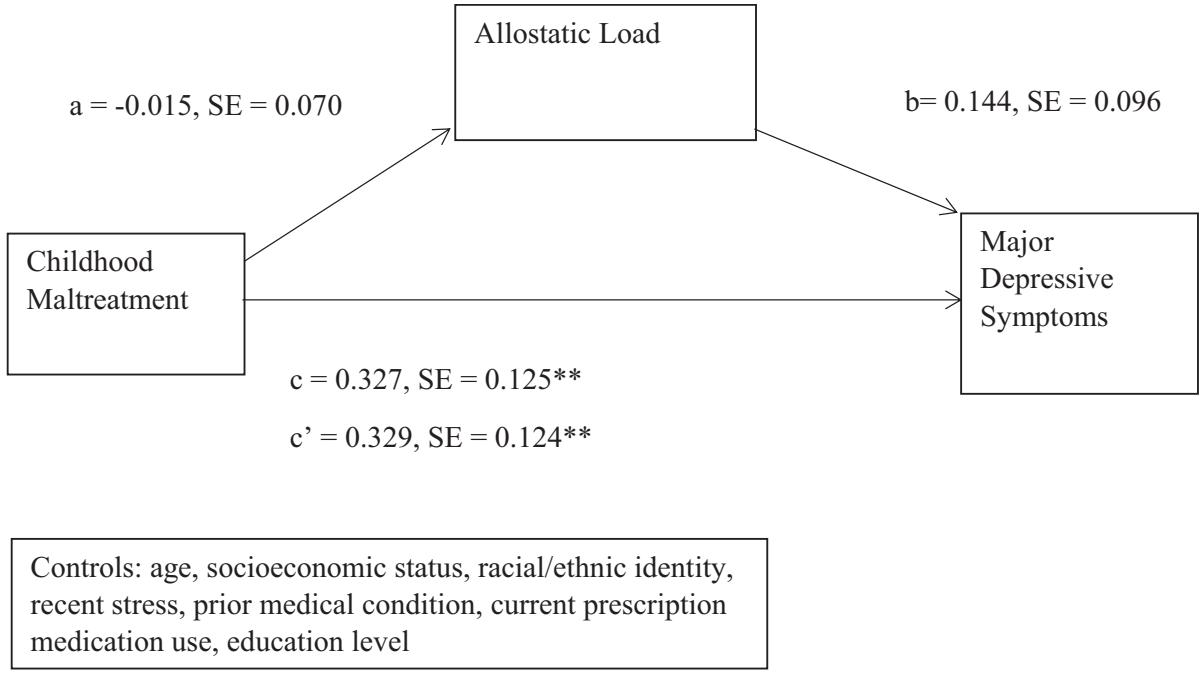

Fig. 1. Male Mediation Model. Path coefficients for the mediation of allostatic load on the relationship between childhood maltreatment and major depressive symptoms (n = 347). *p < 0.05, **p < 0.01, ***p < 0.001.

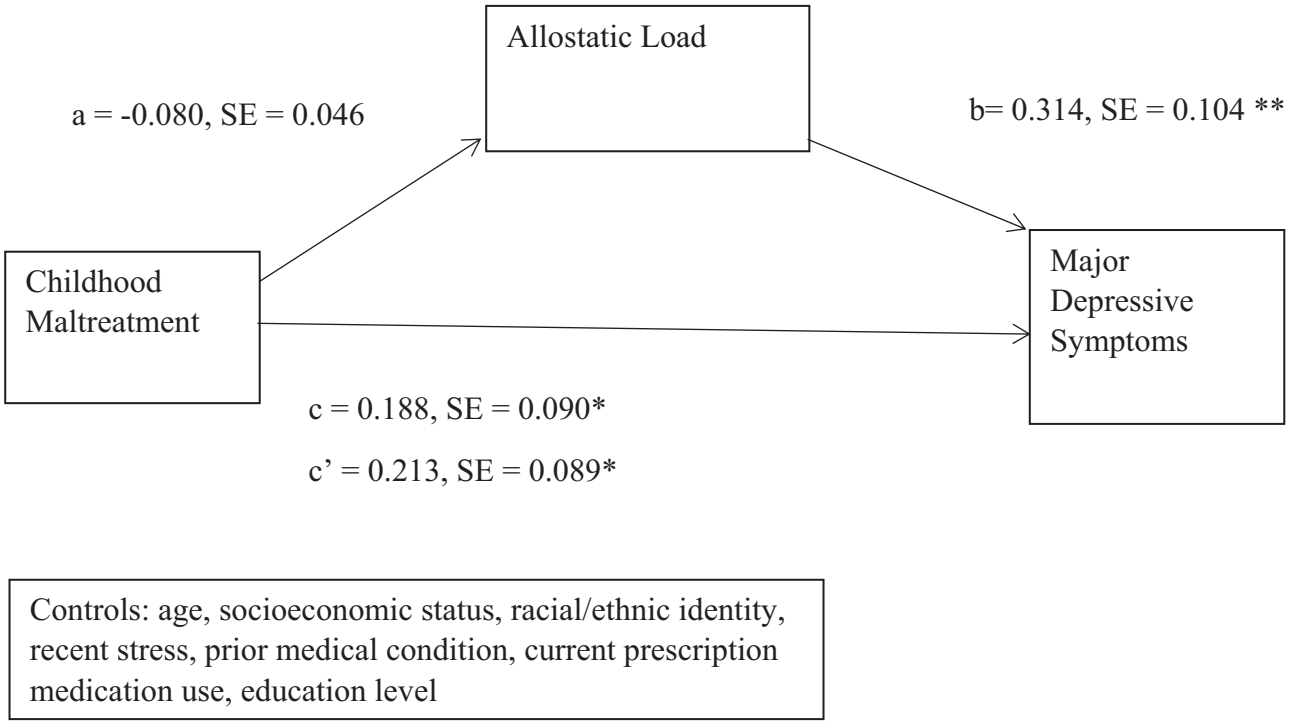

Fig. 2. Female Mediation Model. Path coefficients for the mediation of allostatic load on the relationship between childhood maltreatment and major depressive symptoms (n = 344). *p < 0.05, **p < 0.01, ***p < 0.001.

dichotomous gender or sex identification should be accounted for in models assessing for the role of AL on MDS; however, prior models have focused largely on including binary gender or sex as a covariate which does not allow for an investigation of sex differences with respect to individual variable main effects (Gale et al., 2015; Kobrosly et al., 2013, 2014; Juster et al., 2011; Rodriquez et al., 2018). Indeed, Gillespie et al. (2019) who utilized a sex stratification approach to examine the relationship between AL, MDS, and coronary heart disease in male and female African Americans identified that only metabolic marker components of their AL index partially mediated the relationship between MDS and coronary heart disease, and that this was only significant for females. Therefore, as our results suggest, it seems plausible that AL may function differently across different drc groupings, and that more precise techniques that evaluate specific markers instead of broad system dysregulation may improve the ability to detect mediation.

4.2. Limitations and future directions

While the present study meaningfully advances the conversation around childhood maltreatment, AL, and MDS, there are several limitations that should be considered when interpreting results. First, this study utilizes a cross-sectional design. While some evidence exists that changes in AL relative to the experience of childhood maltreatment are detectable into adulthood, the same cannot be said for studies evaluating the link between AL and MDS (Juster et al., 2011; Widom et al., 2015). Studies that are able to utilize a longitudinal design could ameliorate this weakness in the research. Second, due to limitations of the data, we collapsed individuals from various non-White identities into a single grouping: People of Color. The assumption that all individuals who are People of Color have the same experience is inaccurate especially within the context of long studied U.S. epidemiological discussions (see Franzini et al., 2001, for a discussion of the Hispanic paradox; see Mezuk et al., 2013, for a discussion of the Black-White paradox). A recent study of individuals disaggregated by both sex and race identified AL differences among groupings and thus, an understanding of how socio-cultural forces around these demographic variables interact to affect the relationship between AL, childhood maltreatment, and MDS could bring forward important findings for future intervention and prevention (Bey et al., 2018). Third, throughout our study we have utilized the term "sex"; however, gender, as a sociocultural construct, and sex, as a biological marker, may be easily conflated. Due to limitations of the data in this secondary analysis we were only able to include participant's sex; however, we would like to highlight that some studies have found meaningful results when evaluating how gender and sex may affect AL (Juster et al., 2016). Finally, many of the psychosocial measures employed here are self-response measures. Importantly, some recent findings have identified that recall of childhood maltreatment and the actual experience of childhood maltreatment may different outcomes with respect to later mental health problems (Baldwin et al., 2019). Therefore, it is recommended that future studies attempt to take both individual's recall of previous maltreatment along with written case records into account so as to understand how AL may be affected differently across these two reporting types.

5. Conclusion

We attempted to expand upon the initial findings of Scheuer et al. (2018) that AL mediated the relationship between childhood maltreatment and MDS. We could not replicate Scheuer's findings, which were initially discovered using a sample from an inpatient psychiatric hospital, in a community sample; however, because we were able to stratify all analyses by sex we were able to identify clear differences in what variables are significant in the development of MDS in adulthood. We suggest several additional ways to improve our current understanding of these constructs including longitudinal studies, stratification by gender and sex, and stratification by sex and race/ethnicity. Through these investigative methods we can build a stronger understanding of new treatment targets for those affected by childhood maltreatment and MDS.

Disclosure

The authors declare no conflict of interest in the preparation or publication of the work presented here. All authors have approved the final article.

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.

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