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Childhood maltreatment and inflammation: Leveraging structural equation modeling to test the social signal transduction theory of depression

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ABSTRACT

Background: The experience of childhood maltreatment has long been understood to increase the risk for experiencing depressive symptoms and is often associated with an overall worse course of illness when these symptoms are elevated to a major depressive episode. Despite this, current treatments for depression continue to require a need for a greater understanding of the underlying mechanisms.

Method: We utilized structural equation modeling to test the effects of childhood maltreatment on inflammation and depressive symptoms. Inflammation was conceptualized as a latent variable, estimated by CRP, fibrinogen, IL-6, sICAM-1, sE-selectin, and TNF- α; whereas depressive symptoms were estimated using the subscales for the Center for Epidemiological Studies-Depression scale and childhood maltreatment was estimated using the subscales for the Childhood Trauma Questionnaire.

Results: Multivariate results identified that childhood maltreatment had a significant positive relationship with inflammation as well as depressive symptoms, and inflammation had a significant positive relationship with depressive symptoms. Notably, childhood maltreatment also had a significant positive relationship with perceived stress over the last month and this perceived stress had a positive relationship with depressive symptoms; however perceived stress had no relationship with inflammation.

Limitations: Data from the present study is cross-sectional, requiring replication with longitudinal data. Some measures such as childhood maltreatment were measured by self-report and should be replicated with verified reports.

Conclusions: These results provide support for the Social Signal Transduction Theory of Depression, emphasizing the importance of the immune system and inflammation as a relevant mediator between early social treats and adulthood depressive symptoms.

1. Introduction

Depression is one of the most common forms of mental health problems in the U.S. with an annual incidence rate of 8.3%, which is one of the highest rates globally (De Aquino et al., 2017). While the scientific literature on depression has expanded greatly over recent years, findings have been slow to generate improvements in treatment, with current frontline treatments only being effective in 30–50% of those experiencing depression(Roose and Schatzberg, 2005; Rush and Jain, 2018). The underwhelming treatment response is further underscored by findings that even subsyndromal levels of depression are likely to lead to a future depressive episode, and those that do experience depression are likely to experience an episode of moderate to severe symptom levels (Hasin et al., 2018; Rush and Jain, 2018; Lee et al., 2019) When these findings are considered in the context of additional epidemiological evidence that the fastest growing age group to experience depression in the U.S. are those between ages 12–25, the need to develop efficient and effective interventions is of extreme public importance for both current and future generations (Weinberger et al., 2017).

Of the many etiological factors associated with the experience of depressive symptoms, few rival the attention received by the investigation of adverse childhood experiences (ACE's). Beginning with seminal work by Felitti et al. (1998), the original ACE's study explored how various forms of abuse, neglect, family violence, and other forms of trauma or adversity might affect individuals mental and physical health into adulthood. Significant evidence for ACE's being positively associated with later adulthood depressive symptoms now exists, and with some additional evidence suggesting that the experience of ACE's may

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also be associated with increased inflammation into adulthood for those experiencing depressive symptoms (Chapman et al., 2004; De Venter et al., 2013; Iob et al., 2020).

Among the various forms of ACE's, the experience of childhood maltreatment may be one of the most salient factors for depression, with as many as 46% of those experiencing depression also endorsing a history of childhood maltreatment (Nelson et al., 2017). Indeed, childhood maltreatment has also been found to be associated with an overall worse course of depression, characterized by greater symptom severity, greater risk for multiple and persistent depressive episodes, higher risk for suicidal ideations, higher odds of chronic medical illness, and a decreased chance for a positive response to treatment (Nanni et al., 2012; Nelson et al., 2017). Thus, an understanding of how childhood maltreatment, specifically, is connected to depression may hold significant promise for the creation of new interventions that can provide significant relief to a broad number of those experiencing depression.

Of the possible explanations for the connection between childhood maltreatment and depression in adulthood, significant attention has been given to the dysregulation of various biological systems, especially as it pertains to the inflammation system. Indeed, several studies have identified the association between childhood maltreatment and upregulation of inflammation markers in adulthood (Danese et al., 2007; Coelho et al., 2014; Baumeister et al., 2016), as well as the experience of depression being associated with higher levels of various inflammation markers (Miller and Raison, 2016; Majd et al., 2020). Furthermore, a history of childhood maltreatment and a history of depression have both been found to be associated with medical pathology that are thought to have a strong inflammatory component such as various forms of heart disease (Whooley et al., 2007; Baldwin and Danese, 2019).

Slavich and Irwin's (2014) Social Signal Transduction Theory of Depression (SSTTD), a multilevel theory for the etiology, pathogenesis, and maintenance of depressive symptoms may provide significant theoretical backing for these connections. The SSTTD proposes that perception of social threat or adversity are processed by neural circuits associated with physical pain, which then cause an increase in inflammation through activation of the hypothalamic-pituitary-adrenal axis, sympathetic nervous system, and vagus nerve. The activation of these systems then leads to a cascade of biochemical signaling that is associated with changes at the genetic level, causing an upregulation of proinflammatory cytokines. This increase in proinflammatory cytokines is then thought to induce several depressive symptoms. Repeated activation of this system may cause the inflammation response to become sensitized, leading to low grade chronic inflammation and a heightened response to stress.

Despite the epidemiologic and theoretical convergence of these lines of evidence, empirical studies that link childhood maltreatment to adulthood depression via inflammation are few and limited in their conclusions. In a study of German individuals who were currently hospitalized for mental health problems, allostatic load (which included C-reactive protein (CRP) as a measure of inflammation) mediated childhood maltreatment and adulthood depressive symptoms (Scheuer et al., 2018). Despite this, another study utilizing a community sample of non-institutionalized American individuals identified that allostatic load (which included CRP, interlukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) as measures of inflammation), was associated with depressive symptoms in females only, and childhood maltreatment did not have a significant relationship with allostatic load for either males or females (O'Shields and Gibbs, 2021). In turning to studies that evaluate inflammation only, a study lead by Danese et al. (2008) identified that childhood maltreatment was associated with adulthood depression and childhood maltreatment was associated with adulthood inflammation as measured by CRP; however, inflammation was not found to mediate the relationship between childhood maltreatment and depression. Additionally, Cohen-Woods and colleagues (2018) identified that a single-nucleotide polymorphism of the IL-6 gene increased the risk for recurrent depressive episodes in individuals exposed to moderate to severe childhood maltreatment. Furthermore, work by Zeugmann et al. (2013) identified that fibrinogen, but not CRP, IL-6, TNF-α, resistin, soluble *E*-selectin (sE-selectin), CD40ligand, or serum-amyloid A were elevated in individuals with a history of childhood maltreatment and depression. Lastly, a secondary analysis of cross-sectional data by Hostinar et al. (2015) identified that ACE's, including childhood maltreatment, and inflammation (as measured by CRP, IL-6, fibrinogen, sE-selectin, and soluble intercellular adhesion molecule-1 (sICAM-1)) were mediated by depressive symptoms.

1.1. Research questions

While previous studies have consistently identified that inflammation is associated with childhood maltreatment and adulthood depression in some capacity, measurement of inflammation has focused on an inconsistent selection of markers which may not accurately capture its relationship with depression. For instance, while CRP has been considered a strong indicator for the inflammation system and associated with several aspects of depression (Pariante, 2017; Felger et al., 2020). And some results have identified significant findings for other markers but not CRP in the context of depression (Zeugmann et al., 2013). Furthermore, studies have identified that markers such as intercellular adhesion ICAM-1, and *E*-selectin may be relevant components of the inflammation process associated with depression (van Dooren et al., 2016; Muller, 2019). Thus, the present study sought to answer several questions:

1) Can the association of childhood maltreatment and inflammation be confirmed when inflammation is measured broadly?
2) Is childhood maltreatment, inflammation, and recent stress associated with depressive symptoms in adulthood?
3) Does a relationship between childhood maltreatment, inflammation, and depressive in adulthood symptoms exist, as proposed in the SSTTD?

2. Method

2.1. Sample

The present study uses secondary cross-sectional data from the Midlife Development in the United States (MIDUS) data set, specifically, the combined samples from the biomarker subsets of Wave Two (n = 1255), collected from 2004 to 2009, and the Refresher Wave (n = 863), collected from 2012 to 2016 (Ryff et al., 2019; Weinstein et al., 2019). This resulted in a final sample of 2118 participants. Individuals were eligible for the biomarker subsets only if they provided data for the main study which collected information on sociodemographic qualities, psychosocial characteristics, and physical health. Individuals agreeable to participating in the biomarker subsection attended an overnight visit at University of Wisconsin, University of California Los-Angeles, or Georgetown University to collect additional psychological and biometric data. For a comprehensive review of the MIDUS project methodology, including sample recruitment and strategy, quality control, and spatial coverage please see Radler (2014) as well as publicly available documentation at the Inter-university Consortium for Political and Social Research (ICPSR) (Ryff et al., 2019; Weinstein et al., 2019). This study received approval from the institutional review board of the author group's home institution.

2.2. Measures

2.2.1. Depression

Depression was estimated as a latent variable using the four subscales of the Center for Epidemiologic Studies-Depression Inventory (CES-D), a widely utilized self-report measure for depressive symptoms (Radloff, 1977). The four subscales of the CES-D include measures of depressed affect, somatic activity, anhedonia, and interpersonal

challenge. Possible scores for the total CES-D range from 0 to 60, with greater values indicating greater severity of depressive symptoms. Prior testing of the CES-D has demonstrated criterion validity with symptom cut offs for major depressive episodes ranging from 16 or greater being indicative of a depressive episode (Smarr and Keefer, 2011). Evaluation of the CES-D's reliability has found moderate test-retest reliability and demonstrates adequate ability to detect change in depressive symptoms (Smarr and Keefer, 2011). Alpha for the CES-D using data from the present study was found to indicate acceptable internal consistency ($\alpha = 0.75$).

2.2.2. Childhood maltreatment

Childhood Maltreatment was estimated as a latent variable using the five subscales of the Childhood Trauma Questionnaire (CTQ), a self-report measure of retrospective abuse and neglect as self-reported during adulthood (Bernstein and Fink, 1998). The five subscales of the CTQ include measures of emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect, all with higher scores indicating greater history of childhood maltreatment. Possible scores for the total CTQ range from 25 to 125, with greater values indicating greater severity of reported childhood maltreatment. Prior testing of the CTQ has found it to be valid and reliable in both clinical and community settings (Bernstein et al., 1994; Scher et al., 2001). Alpha for the CTQ using data from the present study was found to indicate good internal consistency ($\alpha = 0.82$).

2.2.3. Inflammation

Inflammation was estimated as a latent variable using six biomarkers: CRP, fibrinogen, IL-6, sE-selectin, TNF-α, and sICAM-1. Selection of biomarkers was based on two complimentary lines of evidence. First, evidence for the inclusion of CRP, IL-6, fibrinogen, sICAM-1, and sE-selectin was drawn from a bifactor model of allostatic load (a measure of broad biological dysregulation) using the MIDUS data set which contained each of these measures in a subfactor measuring inflammation (Wiley et al., 2016). Second, the five initial markers, as well as TNF-α, have all been linked to both the experience of childhood maltreatment, adulthood depression, or both through a combination of theory and empirical evidence (Baumeister et al., 2016; Slavich and Irwin, 2014; Zeugmann et al., 2013; Hostinar et al., 2015; van Dooren et al., 2016; Muller, 2019; Wium-Andersen et al., 2013).

All six biomarkers were obtained via fasting blood draw before breakfast on the second day of their visit (Love et al., 2010). Serum was used to derive values for IL-6, TNF- α, CRP, sE-selectin, and sICAM-1, whereas citrated plasma was used to derive values for fibrinogen. Assay method, range, and mean levels can be reviewed in Table 1. Inter-assay and intra-assay coefficients of variability were less than 10% for all assays, with the sole exception of sE-selectin, which had an inter-assay coefficient of variability of 7.1–11.15%. Assay methods were consistent across both MIDUS Two and MIDUS Refresher. A full review of the laboratory methods is publicly available at ICPSR (Ryff et al., 2019; Weinstein et al., 2019).

Table 1
Inflammation markers.

	Assay method	Assay range	Mean (SD)
CRP	Immunoelectrochemiluminescence	0.014–216 μg/mL	2.99 (4.94) ug/mL
IL-6	Immunoelectrochemiluminescence	0.156–10 μg/mL	1.21 (3.62) pg/mL
Fibrinogen	Immunoturbidometric	2.8–4560 mg/mL	346.65 (82.40) mg/dL
TNF-α	Immunoelectrochemiluminescence	0.69–248 pg/mL	2.20 (1.21) pg/mL
sE-selectin	ELISA	1.25–80 ng/mL	42.34 (21.49) ng/mL
sICAM-1	ELISA	31–1000 ng/mL	279.45 (145.09) ng/mL

CRP: C-reactive protein; IL-6: interlukin-6; TNF-α: Tumor necrosis factor alpha; sICAM-1: intercellular adhesion molecule 1; ELISA: enzyme-linked immunosorbent assay.

2.2.4. Recent stress

Because a large portion of the evidence for the SSTTD is derived from laboratory studies in which inflammation is measured in response to a recent stressor, the Perceived Stress Scale was included as a measure of recent stress (Slavich and Irwin, 2014). The PSS is a ten item self-report measure aimed at measurement of perceived stress over the past thirty days in which participants respond via a likert scale ranging from never (0) to very often (4) (Cohen and Williamson, 1988). Prior testing of the PSS has acceptable reliability and validity in older adult samples, and some limited evidence suggests that PSS scores may be positively associated with levels of CRP, IL-6, and TNF-α (Main et al., 2009; Jiang et al., 2017). Alpha computed with data from the present study identified that the PSS demonstrated good internal consistency ($\alpha = 0.86$).

2.2.5. Controls

Body mass index (BMI) was included as a continuous measure, pre-calculated in its typical formulation (Kg/m^2). Age was included as a continuous variable with overall age range for the present sample being between 23 and 84 years of age. Current regular tobacco smoking status included as a categorical measure with "no current use (0)" being included as a reference group. Current use of antidepressant medications was included as a self-report categorical measure with "no current use (0)" being included as the reference group. Current use of non-steroidal anti-inflammatory drugs (NSAIDs) via oral consumption was included as a self-report categorical measure with "no current use (0)" being included as the reference group. Racial identity was assessed by asking participants "what are your main racial origins – that is, what race or races are your parents, grandparents and other ancestors" with possible responses including "White," "Black and/or African American," "Native American or Alaskan Native Aleutian Islander/Eskimo," "Asian," "Native Hawaiian or Pacific Islander," or "Other." Due to low cell size across racial identities other than White, racial identity was collapsed into "White (0)" and "non-White (1)" racial identities for analytic purposes. Participant sex was assessed by reporting of participants gender as either "male (0)" or "female (1)." Last, income was assessed via participant self-report, with values ranging from 0.00–300,000.00. Values above 300,000.00 were coded as 300,000.00 in the MIDUS data set to help protect the identity of participants.

2.3. Analysis plan

A structural equation model was constructed to understand the effects of childhood maltreatment, inflammation, and recent stress on depressive symptoms. All continuous predictor variables were *Z*-transformed and centered prior to their inclusion in the model. Because data collected here are from a community sample, a non-normal distribution of predictors is to be expected. Therefore, the robust maximum likelihood with Satorra-Bentler correction estimation method was utilized. A measurement model was first estimated which included only latent variables: depression, childhood maltreatment, and inflammation. Covariance of predictors were determined via model fit indices and were restricted to covary within their respective latent variables. After establishment of the measurement model, the structural model was then estimated with maltreatment being regressed onto inflammation and recent stress, and maltreatment, recent stress, and inflammation being regressed onto depression. Recent stress was also regressed onto inflammation. Control variables were included in the structural model with their effects set to only predict the dependent variable. Additionally, descriptive statistics and a correlation matrix were drafted to better understand the nature of the variables included in the study. Because

continuous variables were *Z*-transformed for the multivariate model, variables included in the correlation matrix were also Z-transformed; however descriptive statistics are reported without transformation. Because of the high number of continuous measures, and therefore the high number of correlations tested, the Bonferroni correction based on 171 tests set significance for Pearson's r at 0.00029. Inspection of missing data revealed only 5.14% missingness throughout the analytic sample, and therefore missingness is unlikely to influence multivariate results (Bennett, 2001; Dong and Peng, 2013).

All analyses were performed in R with all structural equation analyses performed using the lavaan package (Rosseel, 2012; R Core Team, 2020).

3. Results

Most individuals were in middle to late adulthood (M = 53.02, SD = 12.55), relatively evenly split across male (n = 1163) and female sex (n = 953) and were predominately White in racial identity (n = 1511). Overall, the sample demonstrated low depressive symptoms (M = 15.37, SD = 5.39), with maximal scores for the sample topping out at 45 given a possible range of 0–60. Using the established cut off scores for the CES-D, the sample had higher rates of those not likely experiencing a current depressive episode (n = 1294) than those likely to be experiencing a current depressive episode (n = 817). Those likely to be experiencing a current depressive episode were also more likely to endorse current use of an antidepressant (n = 167) relative to those not likely to be experiencing a current depressive episode (n = 146), $\chi^2(1, N = 2111) = 33.25$, $p < 0.001$. Recalled maltreatment was also relatively low (M = 38.51, SD = 14.57) with maximal scores topping out at 121 given a possible score range of 25–125; however, a moderate degree of recent stress was noted in the sample with an average PSS score of 22.34 (SD = 6.34) given a possible range of 0–40. A full review of sample descriptives can be located in Table 2.

Table 2
Descriptive statistics.

	Raw mean (SD) or N	Range or %
CES-D	15.37 (5.39)	0–45
Depressed affect	2.09 (3.14)	0–20
Somatic complaints	9.208 (2.73)	0–12
Positive affect	3.68 (3.21)	0–18
Interpersonal challenge	0.45 (0.88)	0–6
CTQ	38.51 (14.57)	25–121
Emotional abuse	8.12 (4.19)	5–25
Physical abuse	7.05 (3.15)	5–25
Sexual abuse	6.63 (4.05)	5–25
Emotional neglect	9.83 (4.57)	5–25
Physical neglect	6.88 (2.75)	5–24
PSS	22.34 (6.34)	10–48
Age	53.02 (12.55)	25–84
BMI	30.02 (7.06)	14.99–77.58
Income	75,635.49 (61,970.02)	0.00–300,000.00
Tobacco smoking		
Current use	281	13.26%
No current use	1837	86.74%
Antidepressant		
Current use	315	14.39%
No current use	1803	85.61%
NSAID		
Current use	953	44.99%
No current use	1165	55.01%
Race/ethnic identity		
White	1591	75.33%
Non-White	521	24.66%
Sex		
Female	1163	54.91%
Male	955	45.09%

CES-D: Center for Epidemiologic Studies Depression Inventory; CTQ: Childhood Trauma Questionnaire; BMI: body mass index; PSS: Perceived Stress Scale. Range reported as actual score range for collected data.

3.1. Correlations

Bivariate analyses showed several notable correlations. Measures of maltreatment were found to have a weak but significant relationship with measures of depression including depressed affect and emotional abuse ($r = 0.28$, $p < 0.0001$), emotional abuse and somatic complaints ($r = 0.26$, $p < 0.0001$), emotional abuse and interpersonal difficulties ($r = 0.27$, $p < 0.0001$), and emotional neglect and positive affect ($r = -0.29$, $p < 0.0001$). Correlation coefficients across measures of childhood maltreatment and inflammation markers were also weak but significant, with notable relationships being identified between physical abuse and sE-selectin ($r = 0.10$, $p < 0.0001$), sexual abuse and CRP ($r = 0.10$, $p < 0.0001$), and sexual abuse and fibrinogen ($r = 0.10$, $p < 0.0001$). A similar trend was noted among measures of depression and inflammation in that weak correlations were observed between CRP and somatic complaints ($r = 0.09$, $p < 0.0001$), sE-selectin and somatic complaints ($r = 0.08$, $p = 0.0001$), sICAM-1 and somatic complaints ($r = 0.08$, $p < 0.0001$), and sE-selectin and positive affect ($r = -0.08$, $p = 0.0002$). A full review of correlations can be located in Table 3.

3.2. Structural equation model

Factor loadings for measures of both Depression and Childhood Maltreatment were found to be above 0.50; however, factor loadings for Inflammation were mixed with IL-6 (0.150), sICAM-1 (0.253), TNF-α (0.250), and sE-selectin (0.270) demonstrating poor loadings, while CRP (0.682) and Fibrinogen (0.630) demonstrated acceptable loadings. Covariance among predictors were determined by model fit indices, with the final measurement model demonstrating excellent model fit ($\chi^2 = 289.207$ (df = 80), $\chi^2/df = 3.61$, CFI = 0.974, TLI = 0.966, RMSEA = 0.036 (95% CI [0.032–0.040]), SRMR = 0.029).

The structural equation model without any control variables demonstrated excellent model fit indices ($\chi^2 = 3338.002$ (df = 120), $\chi^2/df = 7.268$, CFI = 0.976, TLI = 0.965, RMSEA = 0.038 (95% CI [0.033–0.042]), SRMR = 0.027). Inspection of regression coefficients showed that childhood maltreatment (b = 0.109, $p < 0.001$), inflammation (b = 0.160, SE = 0.05), and recent stress (b = 0.599, $p < 0.001$) each demonstrated a significant relationship with depression. Furthermore, childhood maltreatment was found to have a significant relationship with both recent stress (b = 0.363, p < 0.001) and inflammation (b = 0.082, $p < 0.01$); however, recent stress did not demonstrate a significant relationship with inflammation ($p = 0.11$).

The structural model with control variables included also showed acceptable model fit indices, although model fit is slightly worse with their inclusion ($\chi^2 = 1628.32$ (df = 212), $\chi^2/df = 7.680$, CFI = 0.867, TLI = 0.844, RMSEA = 0.059 (0.056–0.061), SRMR = 0.069). Regression coefficients showed similar findings with the prior model in that that there was a significant positive relationship between childhood maltreatment and inflammation (b = 0.064, $p < 0.01$) and between childhood maltreatment and recent stress (b = 0.363, $p < 0.001$). With respect to depression, maltreatment (b = 0.090, p < 0.001), recent stress (b = 0.581, p < 0.001), and inflammation (0.139, p < 0.001) each had a significant positive relationship, indicating that an increase in each of these variables was associated with an increase in depressive symptoms. Additionally, inspection of control variables revealed that racial identity other than White (b = 0.067, $p < 0.05$), BMI (b = 0.026, $p < 0.05$), antidepressant use (b = 0.114, $p < 0.01$), current tobacco smoking status (b = 0.179, $p < 0.001$) had a significant positive relationship with depression, while reported female sex (b = −0.063, p < 0.05) and income (b = −0.036, p < 0.01) both had a significant negative relationship with depression. Notably, recent stress did not have a significant relationship with inflammation ($p = 0.130$), nor did age ($p = 0.918$) or NSAID use ($p = 0.904$) with depression. A full review of regression coefficients can be located in Table 4 and a corresponding path diagram can be seen in Fig. 1.

Table 3
Correlations.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1.CES-D-DA	–																		
2. CES-D-SC	**0.65**	–																	
3. CES-D-I	**0.50**	**0.45**	–																
4. CES-D-PA	**−0.53**	**−0.42**	**−0.30**	–															
5.EA	**0.28**	**0.26**	**0.27**	**−0.206**	–														
6.PA	**0.20**	**0.16**	**0.18**	**−0.149**	**0.67**	–													
7.EN	**0.23**	**0.21**	**0.20**	**−0.304**	**0.66**	**0.49**	–												
8.PN	**0.20**	**0.20**	**0.19**	**−0.217**	**0.52**	**0.51**	**0.62**	–											
9.SA	**0.19**	**0.167**	**0.15**	**−0.125**	**0.45**	**0.42**	**0.33**	**0.32**	–										
10.CRP	0.06	**0.09**	0.07	−0.06	**0.08**	**0.08**	0.05	**0.08**	**0.10**	–									
11.IL-6	0.02	0.04	−0.01	−0.03	0.007	0.006	−0.002	0.01	0.03	**0.10**	–								
12.Fibrinogen	0.08	0.06	0.05	−0.05	0.05	0.07	0.05	**0.09**	**0.10**	**0.46**	0.07	–							
13.sE-selectin	0.07	**0.08**	0.07	**−0.08**	0.04	**0.10**	0.03	**0.09**	0.03	**0.16**	0.07	**0.15**	–						
14.sICAM-1	0.04	**0.08**	0.03	−0.05	0.03	0.05	0.03	0.03	0.01	**0.11**	0.04	**0.09**	**0.18**	–					
15.TNF-a	−0.009	0.009	−0.003	−0.02	−0.02	−0.0005	−0.02	0.02	0.01	**0.12**	0.05	**0.08**	**0.12**	**0.49**	–				
16.PSS	**0.64**	**0.60**	**0.44**	**−0.60**	**0.30**	**0.18**	**0.26**	**0.22**	**0.19**	0.05	0.03	0.04	0.06	0.03	−0.02	–			
17.BMI	**0.10**	**0.11**	**0.09**	**−0.11**	**0.11**	**0.15**	0.07	0.07	**0.17**	**0.33**	**0.09**	**0.32**	**0.25**	0.07	**0.10**	**0.09**	–		
18.Age	**−0.16**	**−0.12**	**−0.18**	**0.10**	**−0.14**	**−0.12**	−0.07	−0.03	−0.07	−0.01	0.04	**0.15**	**−0.08**	0.004	**0.10**	**−0.20**	−0.04	–	
19. Income	**−0.13**	**−0.14**	**−0.09**	**0.12**	**−0.11**	**−0.12**	**−0.09**	**−0.13**	**−0.12**	−0.06	−0.05	**−0.13**	**−0.10**	**−0.08**	−0.07	**−0.12**	**−0.09**	−0.07	–

Variables 1–4 are subscales of the Center for Epidemiological Studies – Depression (CES—D), variables 5–9 are subscales of the Childhood Trauma Questionnaire, variables 10–15 are inflammation markers.
CES-D-DA: depressed affect; CES-D-SC: somatic complaints; CES-D-I: interpersonal difficulties; CES-D-PA: positive affect; EA: emotional abuse; PA: physical abuse; EN: emotional neglect; PN: physical neglect; SA: sexual abuse, CRP: C-reactive protein; IL-6: interlukin-6; TNF-α: Tumor necrosis factor alpha; sICAM-1: intercellular adhesion molecule; PSS: perceived stress scale; BMI: body mass index.
Bolded correlation coefficients are significant at least at $p < 0.00029$.

Table 4
Multivariate models.

	Structural model without controls $n = 2062$ b(SE)	Structural model with controls included $n = 2009$ b(SE)
PSS		
Maltreatment	0.363 (0.029)**	0.363 (0.028)**
Inflammation		
Maltreatment	0.082 (0.027)**	0.064 (0.021)**
PSS	0.026 (0.016)	0.022 (0.015)
Depression		
Inflammation	0.160 (0.070)*	0.139 (0.052)**
PSS	0.599 (0.024)**	0.581 (0.024)**
Maltreatment	0.109 (0.020)**	0.090 (0.020)**
BMI	–	0.026 (0.013)*
Current tobacco smoking	–	0.179(0.046)**
Anti-depressant use	–	0.114 (0.040)**
NSAID use	–	0.003 (0.025)
Age	–	0.001 (0.012)
Income	–	−0.036 (0.012)**
Non-white race	–	0.067 (0.033)*
Female sex	–	−0.062 (0.027)*

PSS: Perceived Stress Scale; BMI: body mass index; NSAID: non-steroidal anti-inflammatory drug.
* $p < 0.05$.
** $p < 0.01$.

4. Discussion

The present study sought to build on the small number of studies examining the role of childhood maltreatment and inflammation in the experience of depressive symptoms in adulthood. While some studies have examined how individual markers of inflammation may be important predictors of depression, it is also well understood that biological systems are dynamic and act in concert (Danese et al., 2008; Zeugmann et al., 2013). Thus, the study of a single marker may not yield a holistic representation. The novel analyses presented here identified that the experience of childhood maltreatment is associated with a broad upregulation of the broader inflammation system, and that experiences of childhood maltreatment and increased inflammation are both associated with depressive symptoms in adulthood. Furthermore, the present analyses also showed how recent stress may be relevant, suggesting that childhood maltreatment is associated with the experiences of recent stress in adulthood and recent stress is associated with depressive symptoms; however, recent stress is not associated with inflammation.

Results of this study can be viewed as building on the work of Hostinar et al. (2015) who also utilized the MIDUS data set to examine how adverse childhood experiences and recent stress may impact several mediators which then influence adulthood inflammation. Notably, Hostinar et al. (2015) work examined adulthood depressive symptoms as a possible mediator, identifying that both recent life and aversive childhood experiences were associated with depressive symptoms, and that these depressive symptoms were associated with adulthood inflammation. Several differences should be considered in that 1) the present study includes a greater number of individuals from the MIDUS data set, 2) the present study included TNF- α in its measurement of inflammation, 3) Hostinar et al. (2015) broadly measured aversive childhood experiences whereas the present study focused on the phenomenon of childhood maltreatment. However, an important finding surrounding the results of both studies is the hypothesis that inflammation and depression may be bi-directional in their effects, as has been theorized by others (Beurel et al., 2020). If inflammation and depressive symptoms do indeed have a bi-directional effect, then the combined treatment of both constructs may be essential to achieving sustained remission of depressive symptoms. This has been supported by the successful use of concurrent anti-depressant and anti-inflammatory medications in the treatment of depressive symptoms for individuals

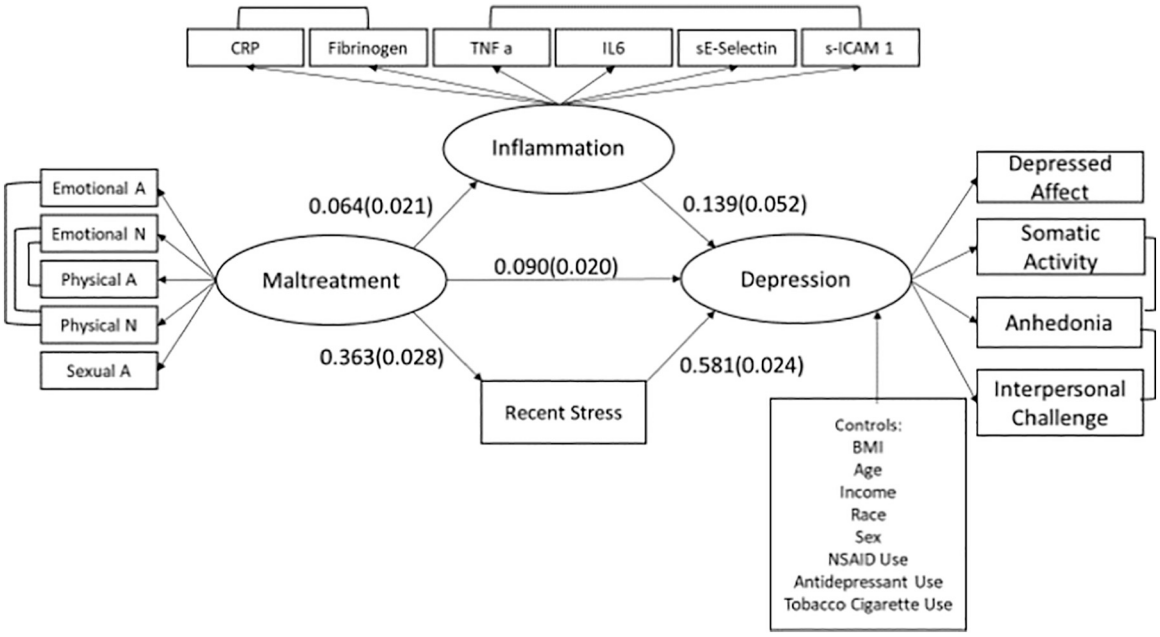

Fig. 1. Path model
All path coefficients reported are significant at least at the 0.05 level with the exception of control variables which are not reported on here. See Table 4 for a full review of coefficients.
Coefficients are reported as b(se).

with CRP levels greater than 3 mg/L (Kohler et al., 2016). Furthermore, a need to treat both inflammation and depressive symptoms, concurrently, may help explain the mixed results of cognitive-behavioral therapy in effectively reducing the depressive symptoms of individuals with higher levels of inflammation (Lopresti, 2017). While neither inflammation nor depression should be viewed in a vacuum as isolated targets for treatment where holistic treatment methods are possible, the current lack of effective treatments may signal a need for more comprehensive treatment strategies.

The present study also confirms the finding that childhood maltreatment has broad aversive consequences that are felt during adulthood, including depressive symptoms, inflammation, and perceptions of recent stress; however, the precise reasoning for this phenomenon is still unclear. Some evidence supports that the experience of childhood maltreatment may be associated with several neurological changes that may then help explain the experience of depressive symptoms. For instance, frontal EEG asymmetry in survivors of moderate to severe childhood maltreatment has been found to be associated with low-grade inflammation in adulthood (Hostinar et al., 2017). However, it should also be considered that survivors of childhood maltreatment may be at an increased risk for experiencing further trauma in adulthood (Gama et al., 2021). This process of being exposed and re-exposed to traumatic events may alter an individual's cognitive understanding of the world or themselves, which may help explain why childhood maltreatment is associated with increased perceptions of recent stress in the present study (Kaysen et al., 2005; Jopling et al., 2020). Thus, the experience of childhood maltreatment may represent a significant etiological marker, the identification of which should be of high priority for early intervention to attenuate or prevent future major depressive episodes and commonly comorbid diseases (Chu et al., 2021). Indeed, some evidence for this approach has already been identified in the use of a 10-day course of hydrocortisone for adults within 12 h of experiencing physical trauma, which was associated with lower rates of future depressive symptoms compared to the placebo group (Delahanty et al., 2013).

Further, the examination of the association between childhood maltreatment and adulthood inflammation at both the bivariate and multivariate level replicates several notable findings. Indeed, childhood maltreatment has been associated with increased CRP in adulthood as well as several proinflammatory cytokines; however, inconsistencies have been noted in the literature (Danese et al., 2007; Danese et al., 2008; Coelho et al., 2014; Palmos et al., 2019). A review of inflammatory markers and childhood maltreatment by Coelho et al. (2014) highlights that some inconsistencies in the association between the type of childhood maltreatment experienced and the upregulation of specific inflammatory markers may be due in-part to differences in trauma assessment measures across studies. The present study utilized the CTQ, a widely employed measure of recalled childhood maltreatment that has been used in several studies to evaluate the association between maltreatment and inflammation in adulthood. Despite this, the present study was not able to replicate the association between maltreatment and TNF-α or maltreatment and IL-6, both of which have mixed findings (Coelho et al., 2014). Although, the present study did confirm an association between fibrinogen and maltreatment, particularly as it pertains to a history of physical neglect and sexual abuse. This finding replicates previous work by Zeugmann et al. (2013) who identified that fibrinogen levels in adulthood are significantly associated with a history of physical neglect as measured by the CTQ in a group of 25 individuals who were hospitalized with severe depressive symptoms. Additionally, Bruassoulis et al. (2007) have identified that a history of childhood maltreatment was associated with increased sE-selectin and sICAM-1 in individuals being treated for sepsis or acute respiratory distress syndrome relative to active controls receiving ventilator treatment; however, the present study only identified significant findings for sE-selectin, not sICAM-1. Thus, findings presented here seem to indicate that while a broad measurement of maltreatment and inflammation may have utility, future work focused on precision may benefit from interrogating individual inflammatory molecules and their associations with specific high stress environmental events.

Last, the differences in association between childhood maltreatment and inflammation, and recent stress and inflammation raises important questions for how stress responsivity is understood. Previous studies identified that childhood maltreatment was associated with several neurological changes that were implicated in sensitization for social

stress such as frontal EEG asymmetry, and alterations in dorsolateral and ventromedial prefrontal cortex activation (Hostinar et al., 2017; Zhong et al., 2020). Thus, results from the present study offer an important discrepancy in that recent stress was not associated with inflammation; however, it should be considered that this may be due to how the PSS measures stress. Indeed, the PSS measures stress perception broadly over the last month, asking participants about their ability to "control irritations" and "if things were going their way," and not necessarily measuring social stress, specifically (Cohen and Williamson, 1988). This point is underscored by previous findings that only interpersonal stress (not non-interpersonal stress), has been associated with increased cytokine reactivity in a sample of adolescent girls (Slavich et al., 2020). Thus, the differential associations between recent stress and the experience of childhood maltreatment confirms the SSTTD model assumptions that only interpersonal stress is associated with inflammation (Slavich and Irwin, 2014).

4.1. Limitations

Despite the notable strengths of the present study, results should be interpreted within the context of several limitations. From a methodological standpoint, the present study utilizes a cross-sectional design with many self-reported measures. Future studies should attempt to replicate analyses using longitudinal data or objective reports of childhood maltreatment such as Child Protective Services case records to strengthen the causal inference of associations presented here (Maxwell and Cole, 2007; Newbury et al., 2018; Osborn and Widom, 2020). Additionally, the MIDUS data set lacks ability to highlight racial/ethnic health disparities, given the low numbers of multiple racial/ethnic groups. Future studies may benefit from replication of analyses of the present study, disaggregated across multiple racial/ethnic groupings, to better understand how the social environment affects groups differently to create health inequities (Mezuk et al., 2013). Furthermore, various sex hormones, as well as adherence to socialized gender roles have been identified as affecting stress response, and may be critical for explaining health disparities, requiring a more careful analysis of gender beyond the traditional male/female dichotomy examined here (Derry et al., 2015; Slavich and Sacher, 2019; Kerr et al., 2020; Keenan et al., 2021). Last, the present study accounts for the variance in overall depressive symptoms but does not account for the presence or absence of specific symptom clusters or subtypes of major depression. Future studies may benefit from the use of a case-control design to control for the presence of a major depressive episode, specific depressive symptom subtypes, or a higher likelihood of receiving antidepressant treatment which may be linked with state-specific upregulation of inflammatory markers (Syed et al., 2018; Beurel et al., 2020). Further, the use of non-recursive structural equation modeling to account for the potentially joint-sustaining effects of health problems strongly linked to inflammation and major depression (Gold et al., 2020).

4.2. Conclusion

Major Depression represents a major health problem for a significant portion of the U.S. population and often occurs more frequently and severely when individuals have a history of childhood maltreatment. The analyses presented in the present study confirm prior findings of the field while also offering further support to the SSTTD. Future studies may seek to build on the analyses presented here through use of longitudinal design, improving racial/ethnic representation, disaggregating analyses based on various demographic characteristics, or analyzing the effects of reported maltreatment against confirmed case records.

CRediT authorship contribution statement

JO conceptualized the study, completed all statistical analyses, and drafted the abstract, main text, and tables of the paper. DP assisted with the literature review, as well as the drafting of the introduction and results sections of the paper. OM provided oversight for the study conceptualization, data analytic process, and drafting. All authors provided critical revisions to the manuscript, approved the final version, and consented to its publication.

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Conflict of interest

All authors deny any conflicts of interest.

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