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The effects of childhood maltreatment on social support, inflammation, and depressive symptoms in adulthood

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ABSTRACT

Rationale: Social Safety Theory (SST) suggests that social threats increase inflammation, exacerbating health risks, but that social support may decrease inflammatory signaling. One of the key health problems affected by both social forces and inflammation is major depression.
Objective: The present study sought to test aspects of the SST, to understand how social support and inflammation may mediate the effects of childhood maltreatment on depressive symptoms in adulthood.
Methods: This study utilized data from the national Midlife Development in the United States study (n = 1969; mean age 53; 77.2% White; 53.6% female) to model the effects of childhood maltreatment on depressive symptoms in adulthood and the potential serial mediating effects of social support and inflammation. Analyses were conducted via structural equation modeling, using the four subscales of the Center for Epidemiologic Studies Depression Scale to indicate depressive symptoms, the five subscales of the Childhood Trauma Questionnaire to indicate childhood maltreatment, and the Positive Relations Scale and a network level measure of support as indicators of social support. Inflammation was indexed using C-reactive protein (CRP). The model was estimated via maximum likelihood with robust standard errors and significance of indirect effects were assessed via a Sobel test.
Results: Childhood maltreatment was associated with increased depressive symptoms and CRP but decreased social support. Social support was associated with decreased depressive symptoms while CRP was associated with increased depressive symptoms. Assessing indirect effects yielded no serial mediation effect; however, a significant indirect effect from childhood maltreatment to depressive symptoms through social support was identified.
Conclusions: Analyses indicate mixed support for the SST with respect to depressive symptoms. Results highlight the role of social support in mitigating the effects depressive symptoms in adulthood; although, alternative strategies may be needed to decrease the effects of childhood maltreatment on inflammation as indexed by CRP.

Author note

Total word count including highlights (61), abstract (300), main text (5,328), references (2,499), and tables and figures (770) is 8958.

1. Introduction

Major depressive disorder (MDD) is a common mental health problem and leading cause of disability worldwide (Hasin et al., 2018). Regrettably, MDD onset is associated with potentially lifechanging consequences, including decreased lifespan after accounting for suicide, and increased risk for developing physical health morbidities (Otte et al., 2016; Gold et al., 2020). MDD is often recurrent in nature, and therefore an initial episode of MDD is associated with an increased risk for a future episode of MDD (Otte et al., 2016). Unfortunately, the onset of MDD is often insidious, where individuals who experience symptoms of MDD are 4.4 times more likely to experience recurrence within a one-year period (Horwath et al., 1992). Thus, MDD symptoms pose a significant public health threat, and understanding mechanisms that drive these symptoms may limit this threat through better directed treatment efforts.

Among social experiences, childhood maltreatment (CM) may be the most consequential for symptoms of MDD. A history of CM is associated both prospectively and retrospectively with MDD symptoms and those

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who experience CM have 2.66 to 3.73 times greater risk for developing a MDD episode in adulthood (Nelson et al., 2017; Kisely et al., 2018; Humphreys et al., 2020). Those with a history of CM who develop MDD have an overall worse prognosis, including earlier onset, a greater number of episodes, and a higher likelihood for comorbid mental health disorders (Bernet and Stein, 1999). Meta-analytic results suggest those with a history of CM are more than twice as likely to develop chronic or treatment-resistant MDD (Nelson et al., 2017). Individuals who develop chronic or recurrent MDD with a history of CM also tend to have a worse quality of life, higher risk for suicide, and greater risk for comorbidities (Medeiros et al., 2020).

However, social experiences may also have the potential to prevent MDD s. In a sample of 193 individuals receiving care for MDD, perceived social support (SS) was associated with lower MDD symptoms at 18-month follow up for those who were in full remission at the start of the study (LeskelÄ et al., 2006). In a sample of 946 adults recruited from primary care offices in Sweden, SS was associated with greater decrease in symptoms of MDD and greater treatment response after 12-weeks of internet based cognitive behavioral therapy, exercise, or treatment as usual (Hallgren et al., 2017). Last, in a UK sample of 71,117 adults surveyed during a COVID-19 lockdown period, daily face-to-face or phone/video contact was associated with lower symptoms of MDD (Sommerlad et al., 2022). Notably, results from a cross-lagged model that found romantic relationship conflict predicted psychological distress but not vice versa, establishing some support for the temporal ordering of associations between social relationships and mental health (Özdemir and Sağkal, 2021). Building on this, several additional studies show evidence for SS mediating the association between CM and symptoms of MDD, providing support SS as an intervention strategy to address symptoms of MDD (Sperry and Widom, 2013; Zhao et al., 2019; Struck et al., 2020).

Social Safety Theory (SST) provides a framework through which social relationships can be understood to affect health and behavior, particularly symptoms of MDD. Social Safety Theory has three key principles: 1) Humans have evolved with a disposition to foster social safety, that is relationships that foster inclusion, belonging, and connection to individuals who are friendly, emotionally supportive, and dependable (Slavich, 2020). Additionally, 2) social safety is beneficial for human health and behavior, while 3) social threats are harmful (Slavich, 2020). The effects of social safety and threat can be understood as a cascade of biological processes coalescing to influence the immune system and inflammatory process. Briefly, when the brain detects a threat, glucocorticoids, epinephrine, norepinephrine, and acetylcholine are released and bind to immune cells, increasing cytokine production. Cytokines are thought to act on the brain through three routes: 1) through the afferent vagus nerve (the neural route), 2) by crossing the blood brain barrier (the humoral route), and 3) through infiltration of monocytes via tumor necrosis factor-alpha signaling (the cellular route) (Slavich and Irwin, 2014; Miller and Raison, 2016). The targeting of the brain through these routes is thought to induce sickness behavior, a behavioral reaction to inflammatory signaling associated with symptoms of MDD including anhedonia, difficulty concentrating, fatigue, social withdrawal, and somnolence (Miller and Raison, 2016; Maes et al., 2012).

The repeated activation of these pathways is thought to cause a dysregulation of immune signaling, shifting the body towards a pro-inflammatory state. Repeated activation of these pathways is associated with changes in genomic expression of socially sensitive genes, leading to greater production of cytokines and increasing inflammatory signaling (Slavich and Cole, 2013). Additionally, repeated activation of sickness behavior can have neurodegenerative effects, helping to explain the chronicity of MDD (Maes et al., 2012). Further, life stress such as social threats have been found to alter mitochondrial signaling, exacerbating the metabolic cost of inflammatory signaling and helping to explain neuronal correlates of MDD as well as stress sensitization to MDD (Zitkovsky et al., 2021; Casaril et al., 2021; Morava and Kozicz, 2013). These factors help to explain the connection between CM and inflammation, as well as inflammation and symptoms of MDD (Osimo et al., 2020; Mac Giollabhui et al., 2021; Kerr et al., 2021).

SS may be able to decrease or mitigate inflammatory signaling. Meta-analytic results suggest that both SS and social integration are associated with overall lower levels of inflammation as measured by several molecules, including CRP (Uchino et al., 2018). Specific to SST, perceptions of SS among friends, family, and spouses are associated with decreased inflammation signaling as measured by several inflammatory molecules including CRP (Landvatter et al., 2022; Yang et al., 2014; Donoho et al., 2013). Further highlighting the relevance of SS perceptions, feelings of loneliness have been positively associated with inflammation when measured by CRP, IL-6, and fibrinogen (Nersesian et al., 2018). Thus, while the effects of CM on symptoms of MDD may be partially explained by both increased inflammation signaling and lower perceptions of SS, complimentary finding suggest that increased perceptions of SS may be associated with decreased symptoms of MDD via decreased inflammation signaling (Slavich and Irwin, 2014; Sperry and Widom, 2013; Hughes et al., 2014).

To date, two studies have reported findings on the associations between SS, inflammation, and symptoms of MDD. Among 164 breast cancer survivors, lower pre-treatment SS was associated with higher symptoms of MDD and inflammation as measured by IL-6. Further, lower perceptions of SS were associated with greater reports of pain and symptoms of MDD (Hughes et al., 2014). Only Runsten et al. (2014) have evaluated the association between social adversity (which included CM) and SS on inflammation and symptoms of MDD in a sample of 116 healthy, non-smoking Finnish women. Runsten et al. (2014) showed that women who reported lower levels of SS were found to have higher levels of CRP, a significant correlation between childhood adversity and symptoms of MDD disorder, and an interaction between childhood adversity and SS. However, no association was identified between symptoms of MDD and SS or CRP.

1.1. Present study

The present study sought to test components of SST by modeling how experiences of CM may affect symptoms of MDD into adulthood through SS and inflammation. To date, the effects of CM on symptoms of MDD and perceived SS on symptoms of MDD have been well documented. Similarly, the potential for CM and perceived SS to be associated with inflammation and symptoms of MDD has also received strong support. Despite this, models testing the effects of SS in the association between inflammation and symptoms of MDD, as well as between CM, inflammation, and symptoms of MDD, are few. What studies are available have small samples sizes or do not test the effects of CM (i.e. general social adversity), constraining the external validity of available results evidence (Runsten et al., 2014). Using the SST as guidance we examined three research questions concurrently:

1. Does perceived SS mediate the association between CM and MDD symptoms?
2. Does inflammation mediate the association between CM and symptoms of MDD ?
3. Does SS serially mediate the association between CM and MDD symptoms through inflammation ?

2. Method

2.1. Sample

This study utilizes data from the Midlife Development in the United States (MIDUS) study. We pooled data from the main survey and biomarker sub-project of Wave 2 (main: 2004–2006; biomarker: 2004–2009) and the Refresher Wave (main: 2011–2014; biomarker: 2012–2014) (Ryff et al., 2021; Ryff et al., 2017; Ryff et al., 2022a;

Weinstein et al., 2019). The main survey was completed by participants in their own home, with completers being prompted to follow up for a two day stay at either the University of California Los Angeles, University of Wisconsin, or Georgetown University hospitals for the biomarker sub-projects. Biomarker sub-projects included the completion of additional psychosocial inventories as well as biological variable capture in the morning of the second day of their visit. The Milwaukee African American sample projects for Wave 2 (2005–2006) and the Refresher Wave (2012–2013) were also included, which sampled Black and/or African American identifying residents of the Milwaukee area to improve the racial/ethnic representation of the MIDUS study (Ryff et al., 2022b, 2022c). The full data set for MIDUS 2 and MIDUS Refresher main survey and biomarker sub-project completers, including the Milwaukee samples, resulted in a data frame of 2118 individuals.

2.2. Measures

Depressive symptoms. Depressive symptoms were measured using the 20-item Center for Epidemiologic Studies Depression (CES-D) scale, assessed during the biomarker sub-project. (Radloff, 1977). The CES-D is composed of four subscales: Depressed Affect (7-items), Positive Affect (4-items), Somatic Complaints (7-items), Interpersonal (2-items). For each item participants respond via Likert scale as 0 "rarely or none of the time", 1 "some or a little of the time", 2 "occasionally or moderate amount of the time", or 3 "most or all of the time." The potential score range for the CES-D is from 0 to 60. Studies exploring the construct validity of the CES-D shows similarity to other common measures of depressive symptoms such as the Beck Depression Inventory, the Hamilton Rating Scale for Depression, and the Zung Self-Rating Depression Scale (Shafer, 2006).

Maltreatment. We utilized the 25-item childhood trauma questionnaire-short form (CTQ) to measure recalled experiences of CM, assessed during the biomarker sub-project (Bernstein et al., 1998). The CTQ uses five subscales to measure experiences of emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse prior to the age of 18. Each subscale uses five prompts with each response ranging from 1 "never true" – 5 "very often true". The potential scale range of the CTQ is between 25 and 125, with greater scores indicating more recalled experiences of CM. Measurement of recalled abuse and neglect has been found to be unaffected by participation in psychotherapy despite a reduction in psychopathology (Paivio, 2001). The CTQ has been widely used in several studies, particularly those investigating the association between CM and depressive symptoms in adulthood (Humphreys et al., 2020).

Social support. We included two measures of SS, assessed during the main survey: the Positive Relations with Others (PRO) scale and the MIDUS Social Support (MSS) scale (Ryff, 1989; Ryff and Keyes, 1995; Ryff et al., 2017, 2021). The PRO scale is a 7-item subscale of the Psychological Well-Being scale in which participants respond to prompts via a 7-point Likert scale ranging from 1 "strongly agree" to 7 "strongly disagree." Example prompts include: "maintaining close relationships has been difficult and frustrating for me" and "I have not experienced many warm and trusting relationships with others." Potential scores for the PRO ranged from 7 to 42. The MSS scale is an average level of network SS based on Likert scale responses to 4 prompts regarding friends, 4 prompts regarding family, and 6 prompts regarding a spouse or partner. Examples include: "how much does your [friend, family, spouse or partner] really care about you?" and "can you rely on [your friend, family, spouse or partner] for help if you have a serious problem?" Potential responses included: 1 "a lot," 2 "some," 3 "a little," 4 "not at all." Responses were reverse coded as appropriate and mean responses for friends, family, and spouse or partner scales were averaged together, returning a scale range between 1 and 4 indicating overall support. Because not all forms of network support may be relevant for each participant (for instance spousal/partner support), responses were included for all individuals that provided responses for at least two of the three network scales. Higher scores for both SS measures indicated greater perceived SS. Both measures have previously been utilized in tests exploring social relationships and inflammation using the MIDUS data set (Elliot et al., 2018).

Inflammation. We utilized CRP as an index for inflammation, collected during the biomarker sub-project. CRP is an acute phase inflammatory protein released from the liver via stimulation by IL-6 (Sproston and Ashworth, 2018). CRP has seen utility as an important marker for inflammatory processes, including the release of cytokines IL-6 and TNF-α which are considered highly relevant to studies investigating inflammation and depressive symptoms (Haapakoski et al., 2015; Sproston and Ashworth, 2018). Fasting blood samples were collected from participants prior to breakfast on the second day of their campus visit. Samples were stored between −60° and −80° Celsius, shipped on dry ice to the Tracy Lab at the University of Vermont, and stored at −65° Celsius until assayed. Citrated plasma was used to measure CRP levels via BNII nephelometer from Dade Behring via particle enhanced immunonepholometric assay. The assay range for this method is 0.157–1100 μg/mL, with an inter-assay coefficient of variation (CV) between 2.1 and 5.7% and an intra-assay CV between 2.3 and 4.4%. Any samples that fell below the assay range used serum samples to re-assay via CRP via immunoelectrochemiluminescence using a high-sensitivity assay kit (Meso Scale Diagnostics #K151STG). This method had an assay range of 0.014–216 μg/mL, with an inter-assay CV between 4.72 and 5.16% and intra-assay CV between 2.2 and 4.1%.

Controls. We included ten control variables, supported by current guidelines for studies investigating associations between inflammation and depressive symptoms (Horn et al., 2018). Sex was included dichotomously as male or female based self-report. Racial/ethnic identity was based on participant's self-identification as White, Black and/or African American, Native American or Alaska Native, Aleutian Islander/Eskimo, Asian, Native Hawaiian or Pacific Islander, other, don't know, or refused to answer. To allow for appropriate cell size, racial/ethnic identity was dichotomized into White and non-White identities. Age was included as a continuous variable with potential values ranging from 25 to 84. Household income was included as a continuous measure ranging from $0-$300,000 USD, with incomes above $300,000 top coded to protect participant anonymity. Education was included as an ordinal measure ranging from 1 (no school/some grade school) - 12 (PhD, EDD, DDS, LLB, JD, or other professional degree). Past month alcohol consumption was measured ordinally ranging from 0 to 5, with 0 indicating no drinking in the past month and 5 indicating daily drinking in the past month. Tobacco smoking status was included categorically as Current Tobacco Smoking, History of Tobacco Smoking, and No Tobacco Smoking. Current use of antidepressant was measured as confirmed or denied antidepressant use. Current use of non-steroidal anti-inflammatory drugs (NSAID) was measured as confirmed or denied antidepressant use. Body mass index (BMI) was included as a continuous measure, obtained by a nurse upon arrival to the clinical research unit. Racial/ethnic identity, income, and education were included based on responses during the main survey. Age, sex, tobacco smoking status, past month alcohol consumption, NSAID use, antidepressant use, and BMI were included based on data from the biomarker sub-project.

2.3. Analytic strategy

Of the 2118 participants in the data frame, 133 were removed due to CRP levels greater than 10 μg/mL per an increased risk of ongoing physical illness (Shine et al., 1981; Pepys and Hirschfield, 2003; Mac Giollabhui et al., 2020). Sixteen individuals were removed for not providing enough social support network data. Of the remaining 1969 participants, 1914 provided complete data. Univariate analyses of all variables explored means, standard deviation, and frequencies within the data. Bivariate associations among continuous measures were tested via Spearman's rho per the non-normal distributions of experiences of CM, depressive symptoms, and CRP in the general population.

Structural equation modeling tested the potential mediating and serially mediating effects of SS and CRP on the association between CM and depressive symptoms. A measurement model was estimated with the four subscales of the CES-D serving as indicators of Depressive Symptoms, the five subscales of the CTQ serving as indicators of Maltreatment, and the PRO scale and MSS scale serving as indicators of Social Support. Indicators for the latent constructs were entered into the model simultaneously. Given the expected right-skew distribution of CM, depressive symptoms, and CRP levels in the general population we chose to use a robust maximum-likelihood (MLR) estimation method using the Yuan-Bentler correction. Model fit indices were used to assign covariance between CES-D subscales and between CTQ subscales during the establishment of the measurement model. We then added path coefficients with Maltreatment predicting Social Support, CRP, and Depressive Symptoms, as well as Social Support and CRP predicting Depressive Symptoms, and Social Support predicting CRP using a structural equation model. We then tested the model while controlling for the effects of covariates on Depressive Symptoms. Because MIDUS top-codes income at $300,000.00 USD, creating a bimodal distribution rather than an expected right skew, income was z-transformed to improve model convergence. Full information maximum likelihood estimation was utilized to minimize the influence of missing data.

To account for the influence of removing individuals with CRP levels above 10 μg/mL a sensitivity analysis was conducted by repeating covariate adjusted multivariate analyses with these individuals included (Mac Giollabhui et al., 2020). The same 16 participants were removed from the sensitivity analyses due to low social support network data. Of the remaining 2102 participants, 2041 provided complete data for the present analyses. All analyses were conducted using R version 4.1.2, with structural equation modeling being conducted with the Lavaan package (R Core Team, 2021; Rosseel, 2012).

Three main indirect effects consistent with the research questions were tested using a Sobel test. This included 1) the potential mediating effect of Social Support on the association between Maltreatment and Depressive Symptoms (Maltreatment → Social Support → Depressive Symptoms), 2) the potential mediating effect of CRP on the association between Maltreatment and Depressive Symptoms (Maltreatment → CRP → Depressive Symptoms), and 3) the potential serial mediating effects of Social Support through CRP on the association between Maltreatment and Depressive Symptoms (Maltreatment → Social Support → CRP → Depressive Symptoms). To allow for comparison, significance testing of indirect effects was conducted for both the main model and the sensitivity analysis model.

3. Results

3.1. Univariate and bivariate description

The sample had a mean age of 53 years, identified as predominantly White (76.9%), and had relatively even gender representation (male = 46.4%; female = 53.6%). The sample had a mild degree of depressive symptoms (m = 15.286, SD = 5.186) and CM (m = 38.100, SD = 14.098). SS was high among the sample with a mean of 3.412 (SD = 0.496) for support within their network and mean 40.094 (SD = 7.194) for positive relations. Mean CRP levels were 2.166 (SD = 2.173), indicating a one standard deviation increase in CRP was then associated with having chronic systemic inflammation. A full review of sample descriptive statistics can be located in Table 1.

There were several significant bivariate associations for the key variables of interest. Overall depressive symptoms were associated with CM ($\rho = 0.230$, $p < 0.001$) and CRP ($\rho = 0.091$, $p < 0.001$). In addition, there was a negative association between depressive symptoms and social network support ($\rho = -0.140$, $p < 0.001$) and the PRO scale ($\rho = -0.181$, $p < 0.001$). Experiences of CM were positively associated with CRP ($\rho = 0.082$, $p < 0.001$), while a negative association was noted between CM and the MSS scale ($\rho = -0.350$, $p < 0.001$). For a comprehensive description of bivariate associations as well Cronbach's α for relevant scale and subscales, see Table 2.

Table 1
Sample descriptive statistics.

	Mean (SD) or N	Range or %
Depressive Symptoms (sum)	15.286 (5.186)	0–45
Depressed Affect	1.966 (3.078)	0–20
Positive Affect	9.271 (2.693)	0–12
Somatic Complaints	3.608 (3.163)	0–18
Interpersonal	0.442 (0.862)	0–6
Maltreatment (sum)	38.100 (14.098)	25–121
Emotional Abuse	8.048 (4.090)	5–25
Physical Abuse	6.973 (3.026)	5–25
Sexual Abuse	6.523 (3.886)	5–25
Emotional Neglect	9.755 (4.504)	5–25
Physical Neglect	6.822 (2.700)	5–24
Social Support	3.412 (0.496)	1.125–4.000
Positive Relations	40.094 (7.194)	9–49
C-Reactive Protein	2.166 (2.173)	0.020–10
Body Mass Index	29.515 (6.522)	14.990–77.580
Alcohol Consumption	1.569 (1.547)	0–5
Never smoked tobacco	1116	56.67%
Former tobacco smoking	602	30.57%
Current tobacco smoking	251	12.74%
Affirmed Antidepressant Use	281	14.3%
Affirmed NSAID Use	886	45.0%
Sex (male)	915	46.4%
Age	53.121 (12.577)	25–84
Race/Ethnicity (other than white)	449	22.8%
Income	77,288.890 (62,414.061)	0-300,000.00
Education	7.818 (2.506)	1–12

3.2. Measurement model

Factor loadings estimated by exploratory factor analysis showed that predictors for Depressive Symptoms, Maltreatment, and Social Support all loaded onto their respective factors, with the lowest absolute value factor loading being 0.496. Inclusion of CRP into the exploratory factor analysis did not change which predictors loaded onto their respective factors or drop any factor loading below an absolute value of 0.4 (see Table 3). CRP did not load onto any factor and had a uniqueness of 0.973. Covariance among predictors were determined by model fit indices, with the final measurement model demonstrating a significant model chi-square ($\chi^2 = 169.306$ (df = 33), $\chi^2/df = 5.130$), but otherwise excellent model fit indices (CFI = 0.977, TLI = 0.961, RMSEA = 0.046, SRMR = 0.028).

3.3. Structural equation models

The structural equation model without control variables demonstrated similar model fit indices to the measurement model, with a significant model chi-square test ($\chi^2 = 230.592$ (df = 42), $\chi^2/df = 5.490$), but otherwise excellent model fit indices (CFI = 0.969, TLI = 0.951, RMSEA = 0.048, SRMR = 0.029). Regressions for the model showed that Maltreatment (b = 0.097, SE = 0.024, $p < 0.001$) and Inflammation (b = 0.096, SE = 0.023, $p < 0.001$) both had a significant positive association with Depressive Symptoms, while Social Support had a negative association with Depressive Symptoms (b = −3.437, SE = 0.269, $p < 0.001$). While Maltreatment had a significant association with both Inflammation (b = 0.074, SE = 0.020, $p < 0.001$) and Social Support (b = −0.047, SE = 0.006, $p < 0.001$), Inflammation and Social Support had no significant association.

Adjusting for covariates showed overall worse model fit indices, though still within an acceptable range ($\chi^2 = 1297.537$ (df = 163), $\chi^2/df = 7.960$, CFI = 0.859, TLI = 0.828, RMSEA = 0.060, SRMR = 0.062). Maltreatment (b = 0.069, SE = 0.024, $p < 0.01$), Inflammation (b = 0.057, SE = 0.026, $p < 0.05$), and Social Support (b = −3.367, SE = 0.268, $p < 0.001$) continued to demonstrate an association with

Table 2
Correlation matrix of continuous variables.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1 CESD	0.891																		
2 DA	0.651***	0.855																	
3 PA	−0.030	−0.504***	0.785																
4 SC	0.789***	0.573***	−0.440***	0.733															
5 I	0.459***	0.409***	−0.301***	0.393***	0.569														
6 CTQ	0.230***	0.309***	−0.289***	0.297***	0.265***	0.930													
7 EA	0.271***	0.293***	−0.194***	0.293***	0.265***	0.801***	0.871												
8 EN	0.148***	0.254***	−0.295***	0.234***	0.218***	0.867***	0.622***	0.894											
9 PA	0.135***	0.133***	−0.108***	0.147***	0.152***	0.592***	0.485***	0.383***	0.791										
10 PN	0.149***	0.223***	−0.238***	0.222***	0.197***	0.699***	0.445***	0.594***	0.352***	0.961									
11 SA	0.150***	0.169***	−0.106***	0.146***	0.111***	0.500***	0.364***	0.284***	0.303***	0.282***	0.942								
12 MSS	−0.136***	−0.252***	0.311***	−0.232***	−0.239***	−0.350***	−0.262***	−0.382***	−0.174***	−0.266***	−0.127***	0.861							
13 Pos R	−0.181***	−0.312***	0.413***	−0.323***	−0.302***	−0.322***	−0.243***	−0.361***	−0.146***	−0.243***	−0.073**	0.569***	0.782						
14 CRP	0.091***	0.088***	−0.072**	0.112***	0.078***	0.082***	0.070**	0.040	0.069**	0.087***	0.051*	−0.016	0.008	–					
15 Inc	−0.079***	−0.110***	0.128***	−0.131***	−0.071**	−0.118***	−0.092***	−0.083***	−0.080***	−0.137***	−0.086***	0.053*	0.076***	−0.139***	–				
16 BMI	0.073***	0.089***	−0.090***	0.098***	0.100***	0.094***	0.072**	0.048*	0.125***	0.073**	0.062**	−0.078***	−0.052*	0.444***	−0.053*	–			
17 Age	−0.126***	−0.188***	0.114***	−0.109***	−0.195***	−0.096***	−0.149***	−0.068**	−0.116***	0.005	−0.048*	0.107***	0.168***	0.039	−0.105***	0.020	–		
18 ETOH	0.023	−0.022	0.033	0.014	−0.013	−0.032	−0.041	0.006	−0.050*	−0.028	−0.054*	0.018	−0.005	−0.118***	0.168***	−0.134***	0.026	–	
19 Educ	−0.040	−0.066**	0.136***	−0.118***	−0.069**	−0.135***	−0.062**	−0.078***	−0.133***	−0.164***	−0.085***	0.051*	0.055*	−0.173***	0.378***	−0.134***	−0.021	0.138***	–

CESD: Center for Epidemiological Studies Depression scale; DA: Depressed Affect; PA: Positive Affect: SC: Somatic Complaints; I: Interpersonal; CTQ: Childhood Trauma Questionnaire; EA: Emotional Abuse; EN: Emotional Neglect; PA: Physical Abuse; PN: Physical Neglect; SA: Sexual Abuse; MSS: MIDUS Social Support; Pos R: Positive Relationships; CRP: C-reactive protein; Inc: Income (z-transformed); BMI: Body Mass Index; ETOH: Alcohol; Educ: Education status.

Cronbach's α is presented on diagonals for scale and subscale variables.

*<0.05.

**<0.01.

***<0.001.

Table 3
Exploratory factor analysis.

	Factor 1	Factor 2	Factor 3	Uniqueness
Depressed Affect	0.917	–	–	0.218
Positive Affect	−0.476	–	–	0.600
Somatic Complaints	0.768	–	–	0.413
Interpersonal	0.508	–	–	0.665
Emotional Abuse	–	0.854	–	0.260
Physical Abuse	–	0.797	–	0.426
Sexual Abuse	–	0.519	–	0.362
Emotional Neglect	–	0.706	–	0.531
Physical Neglect	–	0.659	–	0.724
Positive Relations	–	–	0.759	0.340
Social Support	–	–	0.683	0.474
CRP	–	–	–	0.979

Depressive Symptoms. Similarly, Maltreatment continued to have a significant association with Social Support (b = −0.048, SE = 0.006, p < 0.001) and Inflammation (b = 0.070, SE = 0.020, p < 0.001), while no association was identified between Inflammation and Social Support. Age (b = −0.017, SE = 0.004 p < 0.001), income (b = −0.098, SE = 0.048, p < 0.05), and current education level (b = −0.049, SE = 0.021, p < 0.01) had a negative association with Depressive Symptoms, while racial/ethnic identity other than White (b = 0.442, SE = 0.133, p < 0.001), current tobacco smoking (b = 0.598, SE = 0.199, p < 0.01), and current antidepressant use (b = 0.904, SE = 0.174, p < 0.001) were associated increased Depressive Symptoms. All comparative fit indices and model coefficients can be reviewed in Tables 4 and 5. See Fig. 1 for a corresponding path diagram of the adjusted structural equation model.

3.4. Mediation analysis

Testing the significance of the indirect effects of Social Support and CRP on the association between Maltreatment and Depressive Symptoms yielded mixed findings. Social Support was found to have a significant indirect effect on the association between Maltreatment and Depressive Symptoms (z = 6.748, SE = 0.161, p > 0.001). However, CRP did not have a significant indirect effect on the association between Maltreatment and Depressive Symptoms (z = 1.857, SE = 0.003, p < 0.05), nor did Social Support and CRP have a significant serial mediation effect (z = −0.987, SE = 0.011, p < 0.05). All indirect effects can be reviewed in Table 6.

3.5. Sensitivity analysis

To test the sensitivity of multivariate results to the inclusion of CRP levels above 10, we reran the structural equation model adjusted for covariates including participants with CRP levels greater than 10 μg/mL. This expanded sample shifted mean CRP levels to 2.999 (SD = 4.954) with the highest CRP level being 79.300. Mean depressive symptoms for the expanded sample were 15.367 (SD = 5.322). Findings were similar between the sensitivity model and the adjusted structural equation model, however Inflammation was no longer significantly associated with Depressive Symptoms (p = 0.492). Significance of results was otherwise unaltered, including the significant association between Maltreatment and Inflammation and the non-significant association between Social Support and Inflammation. No changes in the directionality of associations were noted, nor the significance of indirect effects.

Table 4
Model fit indices for tested models.

	Measurement Model	Main Model	Adjusted for Covariates	Sensitivity Analysis
Chi sqr (df)	169.306 (33)	230.592 (42)	1297.537 (163)	1204.553 (163)
Chi sqr/df	5.130	5.490	7.960	7.389
CFI	0.977	0.969	0.859	0.874
TLI	0.961	0.951	0.828	0.847
RMSEA	0.046	0.048	0.060	0.056
SRMR	0.028	0.029	0.062	0.062
Loglikelihood	−47663.422	−51993.078	−50458.822	−55696.766
AIC	95414.844	104082.156	101035.644	111511.533
BIC	95660.597	104350.249	101363.504	111843.183
Adjusted BIC	95520.807	104197.751	101176.061	111655.736

Table 5
Multivariate models.

	Main Model	Adjusted for Covariates	Sensitivity Analysis
	b(SE)	b(SE)	b(SE)
Depressive Symptoms			
←Social Support	−3.437 (0.269)***	−3.367 (0.268)***	−3.246 (0.264)***
←CRP	0.096 (0.023)***	0.057 (0.026)*	0.008 (0.011)
←Maltreatment	0.097 (0.024)***	0.069 (0.024)**	0.066 (0.023)**
←Age	–	−0.017 (0.004)***	−0.017 (0.004)***
←Income	–	−0.098 (0.048)*	−0.095 (0.047)*
←Education	–	−0.049 (0.021)*	−0.051 (0.020)**
←Sex (male)	–	−0.168 (0.105)	−0.193 (0.102)
←Race/ethnicity (non-White)	–	0.442 (0.133)***	0.434 (0.127)***
←Alcohol consumption	–	0.037(0.032)	0.029 (0.031)
←Current tobacco smoking	–	0.598 (0.199)**	0.582 (0.187)**
←Former tobacco smoking	–	0.031 (0.106)	0.082 (0.104)
←NSAID use	–	−0.038 (0.097)	−0.017 (0.094)
←Antidepressant use	–	0.904 (0.174)***	0.817 (0.165)***
CRP			
←Social Support	0.216 (0.186)	0.208 (0.188)	0.241 (0.486)
←Maltreatment	0.074 (0.020)***	0.070 (0.020)***	0.136 (0.056)*
Social Support			
←Maltreatment	−0.047 (0.006)***	−0.048 (0.006)***	−0.051 (0.006)***

CRP: C-reactive protein.
*P < 0.05.
**P < 0.01.
***P < 0.001.

4. Discussion

The recognition of how social relationships can shape health has grown tremendously in recent years, with an increasing focus on the role of inflammation (Miller and Raison, 2016; Slavich, 2020). The present study is the first to concurrently explore how CM as a form of early life social threat affects perceived SS in adulthood, and how these relate to the connection between inflammation and depressive symptoms. Surprisingly, our analyses did not identify that CRP mediated the effects of CM on depressive symptoms, nor did we find evidence that perceptions of SS were associated with decreased depressive symptoms through CRP. However, results do underscore the important potential for SS as a target for mitigating the effects of CM on depressive symptoms in adulthood, highlighting components of the SST.

Findings from the present study conflict with the findings of Runsten et al. (2014), who also found an association between broadly defined childhood adversity and perceptions of SS but found an inverse association between SS and CRP. Although, the present study differed in that CRP was positively associated with depressive symptoms despite there being no significant indirect effect from CM to depressive symptoms via

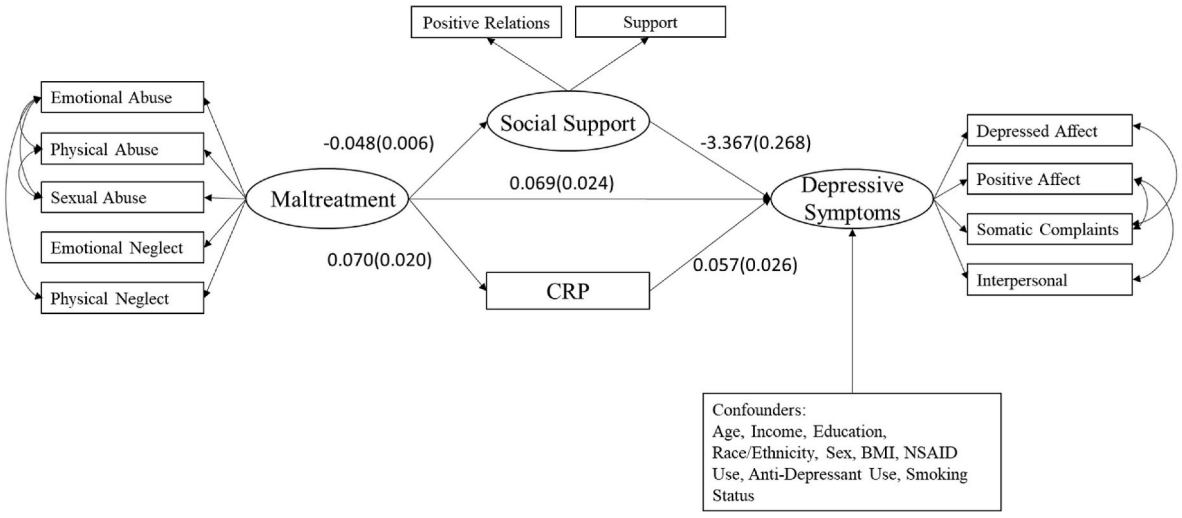

Fig. 1. Path model depicting significant associations after adjustment by covariates
Path diagram of structural equation models, presenting significant betas and standard errors for Maltreatment, Social Support, CRP, and Depressive Symptoms. Presented associations are based on the multivariate model adjusted for covariates. All depicted associations are significant. Further review of associations should be reviewed in Table 5.

Table 6
Indirect and cumulative effect of mediation paths.

	Main Model Adjusted for Covariates	Sensitivity Analysis
	z(SE)	z(SE)
Indirect Effects		
Maltreatment → Social Support → CRP	−1.095 (0.009)	−0.495(0.024)
Social Support → CRP → Depressive Symptoms	0.987 (0.012)	0.409 (0.004)
Maltreatment → CRP → Depressive symptoms	1.857 (0.002)	0.696 (0.001)
Maltreatment → Social Support → Depressive Symptoms	6.748 (0.023)***	6.991 (0.023)***
Maltreatment → Social Support → CRP → Depressive Symptoms	−0.980 (0.0005)	−0.409 (0.001)
Cumulative Effect	6.861 (0.024)***	7.018 (0.023)***

Significance testing conducted via Sobel test.
CRP: C-reactive protein.
*P < 0.05.
**P < 0.01.
***P < 0.001.

CRP; however, CRP was no longer associated when individuals with CRP levels greater than 10 μg/mL were included. Notably, Runsten et al.'s (2014) study reports on 116 Finnish women, while the present study reports on a large sample of both men and women in the United States. Further, because of this increased samples size we were able to conduct additional statistical testing such as mediation analysis and improved statistical control. Thus, the present study extends our current understanding of the effects of CM on SS, CRP, and depressive symptoms.

With that said, the finding of a non-significant association between SS and inflammation in the present study should be considered carefully. Analyses utilized a similar method to measuring SS as Elliot et al. (2018) who also did not identify a significant association between inflammation and SS in the MIDUS data set. Our study differed by using two wings of the MIDUS study (Refresher and Wave 2) to double our sample size and combining SS measures into a composite. Still, results remain the same and contrast with a meta-analysis of 73,037 individuals across 41 studies which found that greater perceptions of SS and integration were associated with lower inflammation across several inflammatory molecules, including CRP (Uchino et al., 2018). One potential reason for this lack of association is the way in which SS is framed and the context in which the sample is drawn. Indeed, a study comparing several inflammatory molecules and their associations between social integration (such as cohabitation, religious service attendance) and SS in samples drawn from the United States and Taiwan found that greater SS associated with higher CRP in the American sample but lower in the Taiwanese sample (Glei et al., 2012). These results were then partially replicated in a sample of 963 Americans, finding social integration to be associated with higher CRP in an American sample (Elliot et al., 2018).

Despite this, SST proposes that relationships that are inclusive and foster feelings of belonging and connection are the most consequential for health (Slavich, 2020). One potential explanation for the discrepancy between our results and theoretical expectations is the relevance of caregiving in socially supportive relationships. Jiang et al.'s (2022) study of 1054 adults identified that SS was associated with lower levels of IL-6, but this relationship was significant only for those engaged in giving support. Similarly, a study of 94 spousal dyads found perceived SS was related to lower CRP levels in their spouse (Landvatter et al., 2022). Thus, results from the present study support that social safety as measured by perceived SS may be protective for health and behavior in the context of depressive symptoms. However, engagement in relationships that are focused on reciprocal caregiving needs further consideration.

Notably, the present study did find support for how early threats can affect human health and behavior. The experience of CM has been associated with the disruption of neural circuits recruited for emotion regulation when exposed to neutral or negative images, mediating the association between CM and general risk for psychopathology (Jenness et al., 2021). A bias towards negative interpretations in neural stimuli may help explain why the present study identified a negative association between experiences of CM and positive relationships. Further, a bias towards negative interpretation may also be associated with a greater likelihood for activation of the same stress response that would bias towards an increased pro-inflammatory state. Future studies aiming to model the SST may benefit from exploring how emotion regulation may mediate the path between CM and SS, inflammation, and depressive symptoms.

With respect to the development of treatment and prevention of depressive symptoms, results seem to indicate SS may be effective at relieving depressive symptoms, even for nearly 30% of individuals with MD and chronic inflammation. However, a focus on SS in addition to reciprocal social engagement focused on mutual support may be critical

for modifying the inflammatory component. This helps explain why meta-analytic results of 56 RCT's identified CBT, which often has a social engagement component, as being particularly effective among psychosocial interventions for improving immune related health (Shields et al., 2020; Chien et al., 2020). Although, while psychosocial interventions seem to have the greatest effect for those experiencing psychological distress, individuals who are more likely to engage with support may also be more likely to spend less time engaged with CBT and at increased risk for treatment drop out when delivered in an online format (O'Toole et al., 2018; Chien et al., 2020). Worryingly, a 192% increase in community health centers and corresponding 65% decrease in accessibility across three Southern states from 2008 to 2016 has not improved treatment engagement (Evans et al., 2019). A major focus for improving treatment outcomes for individuals who experience depressive symptoms seems to require the continued elimination of barriers to effective treatments.

4.1. Limitations

While the present study offers important strengths, several limitations should be considered. First, SS data was collected during the main survey while measures of CM, depressive symptoms, and CRP were collected during the biomarker subproject. Current evidence does not suggest that recall of CM is altered by current psychological states; however, some questions within the CTQ are related to experiences of CM in which a family member may be a perpetrator (Paivio, 2001). Recent experiences with family members could influence a participant's recall of CM with that family member. Second, early life social safety and adulthood social threats are not accounted for in the present model. There is evidence that high enrichment environments early in life can be protective for mental health, and social strain is an inherently different property from SS (Sheridan et al., 2012). Third, the MIDUS data set has poor racial/ethnic representation. While the present study expands on Runsten et al.'s (2014) work through a greater sample size, more complex multivariate analyses, and using a sample outside of the Finnish population, the United States has a complex history social inequities and epidemiological paradoxes known to affect inflammation and depressive symptoms (Mezuk et al., 2013; Uchino et al., 2016). Fourth, important sex differences may be at play between CM, depressive symptoms, inflammation, and SS. Evidence for a sexual dimorphism in the occurrence of depressive symptoms has developed over the past few decades, and differences exist between the associations between depressive symptoms, CM, and inflammatory markers in men and women (Slavich and Sacher, 2019; O'Shields et al., 2023). Further, some evidence suggests that men and women may have differences in how they form, maintain, and enact social networks, which may help explain differences in men and women's experiences of depressive symptoms (Hyde et al., 2008). Last, the present study utilized MLR estimation, allowing for analyses that do not require the transformation of the main variables tested; however, the testing of indirect effects via bootstrapping is not currently available for MLR estimation. Therefore, indirect effects were tested via a Sobel test; however, this may underestimate the indirect effect leading to false negative results (Abu-Bader and Jones, 2021). Future studies that aim to test mediational effects may benefit from alternative modeling strategies (Alfons et al., 2021).

5. Conclusions

The present study sought to test aspects of SST to better understand how social relationships may serve as critical venues for improving depressive symptoms. CM was found to have lasting effects on SS, CRP, and depressive symptoms; however, significance of indirect effects were mixed. Results indicated that perceptions of SS, but not inflammation, mediated the association between CM and depressive symptoms, underscoring the potential for targeting perceptions of SS for the reduction depressive symptoms among those with a history of experiencing CM. Contrary to expected findings, perceptions of SS was not associated with inflammation, nor was there a serial mediating effect of perceptions of SS mediating the effects of CM on depressive symptoms through inflammation. Findings point towards partial support of the SST and highlight the relevance of SS to mitigate depressive symptoms, but not CRP.

CRediT authorship contribution statement

Jay O'Shields: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Orion Mowbray:** Methodology, Supervision, Writing - review & editing. **Zach Cooper:** Formal analysis, Writing - original draft.

Data availability

Data for the MIDUS study are publicly available through the University of Michigan Inter-university Consortium for Political and Social Research

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