Childhood Adversity, Stress in Adulthood, Emotion Regulation Strategies and Inflammation: a Replication and Extension Study

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Abstract

Inflammation has important implications in the field of medicine and overall health. Research related to its relationship with socioemotional factors, such as emotional regulation, is still unclear. Moreover, the connection between childhood adversity and inflammation in adulthood is rather ambiguous. The present study aims to replicate the findings of a paper by Ospina et al. (2022), examining the relationship between inflammation and emotion regulation (ER) strategies. Participants (N = 117) from the Midlife in the United States (MIDUS II) database completed the Emotion Regulation Questionnaire (ERQ), measuring levels of expressive suppression (ES), which involves the inhibition of emotional expressions, and cognitive reappraisal (CR), which involves making changes in thought processes to reframe stressors. The subsequent extension examines childhood adversity subscores based on the Childhood Trauma Questionnaire (CTQ) for emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect, and their relationship to various inflammatory biomarkers. The present study successfully replicated the results from Ospina et al. (2022) and identified a significant negative association between ES and IL-10, TNF-α, ICAM-1, and Fibrinogen. In contrast, CR was not significantly associated with inflammatory variables. These findings suggest a relationship between ES use and inflammation. There was also a significant positive association between physical abuse, sexual abuse, and physical neglect experienced in childhood with IL-6, E-Selectin, and ICAM-1 levels. This suggests that childhood adversity is associated with increased inflammation in adulthood, which can potentially cause worse health outcomes. Overall, the present study suggests a relationship between early life stressors, inflammation, and emotional regulation.

Introduction

Emotion Regulation Strategies: Expressive Suppression and Cognitive Reappraisal

Emotion regulation (ER) is one of the most important aspects of our overall health and is a critical indicator of our well-being. Maladaptive ER strategies are a transdiagnostic process that has been linked to various psychiatric disorders like borderline personality disorder, PTSD, depression, anxiety, and eating disorders (Sörman, 2021) and is furthermore associated with variations in prefrontal cognitive control (Vanderhasselt, 2013). Two prominent emotion regulation strategies are expressive suppression (ES) and cognitive reappraisal (CR). These terms have been defined by various researchers and stand in opposition to each other. ES is a strategy that involves inhibiting the expression of their emotions; cognitive reappraisal (CR) is an adaptive behavior that allows individuals to cope with environmental stressors through changes in cognition to better regulate their emotions (Gross & John, 2003). For example, this includes reframing emotional stimuli through a less unpleasant lens (Gross, 2015 & Kivity, 2021).

Inflammatory Markers

The immune response is a complex process composed of several biomarkers working concertedly across the body. For our research, we focused on the effects of interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), E-selectin, Intercellular Adhesion Molecule 1 (ICAM-1), and fibrinogen. Previous studies have found these biomarkers to be associated with depressive symptoms (Marsland, 2022), impaired mood regulation (Harrison et. al, 2009), higher perceived stress levels (Marsland, 2022), and increased cardiovascular disease risk (Chiang et. al, 2020). This demonstrates how inflammatory markers can have effects beyond the immune system, demonstrating a need to understand the implications of inflammation in our daily lives.

Inflammation and Emotion Regulation

Stress is a psychophysiological phenomenon. Research on emotional regulation strategies is important for understanding how interventions on psychological faculties could improve physiological stress responses and downstream health outcomes. For example, ES has been linked with worse health outcomes and increased depressive symptomatology, sympathetic nervous system activation, and neuroendocrine activity (Appleton et al., 2013). CR, on the other hand, is associated with increased positive emotions, fewer depressive symptoms (Gross and John, 2003), improved patterns of sympathetic nervous system response (Mauss et al., 2007), and decreased cardiovascular risk (Appleton et al., 2014).

Childhood Adversity, Adult Stress, and Inflammation

Remarkably, current and past stressors have been found to alter our body's inflammatory response. Childhood adversity refers to the experiences children have that are potentially harmful to their physical or psychological health, development, or well-being (Bartlett & Sacks, 2019); adult-perceived stress is an individual's subjective perception and evaluation of stress in their adulthood (Fliege et al., 2005). Maltreatment, socioeconomic disadvantages, domestic violence, parent separation, natural disasters, and parental mental illness have the potential to develop into physical and mental health problems later in life when experienced in childhood (Chiang et al., 2022). For example, a study found childhood adversity to be associated with higher odds of later-life depressive symptoms, particularly among those with poor perceived social support (Cheong et al., 2017). Additionally, childhood adversity was associated with increased stress perception following stress vulnerability (LoPilato et al., 2020). Importantly, childhood adversity may result in severe developmental consequences which extend into impaired stress regulation responses in adulthood, such as increased risk-taking, aggressive behavior, involvement in

violence, relationship difficulties, and even PTSD (post-traumatic stress disorder) (Afifi et al., 2020; El-Khodary et al., 2019). Given the consensus in the current literature that stress during adolescence has lasting effects on adulthood, it is crucial to understand how these effects may be mediated by inflammation across a lifespan.

Limitations in the current literature

The original paper by Ospina et al. (2022) used a small convenience sample for this observational study, so the results are preliminary and causality cannot be inferred. Future research must use larger samples with a wider range of biomarkers and evaluate the effect of mediators on ER (emotion regulation). There also needs to be more clarity in the actual demographic breakdown of race and education. Out of the 117 participants, only 78 reported their race and educational status (Ospina et al., 2022). Previous studies have identified education level (Friedman and Herd, 2010) and race (Stepanikova et al., 2017) as important factors in inflammation levels, so these socioeconomic factors could be potential confounders. Further, ER measures were not recorded on the same day as the blood draw, which adds a degree of ambiguity when studying the relationship between ER and inflammation. Future research should collect repeated and timely assessments of ER during various emotion-evoking stimuli to examine how ER strategies impact changes in inflammation. The sample was also skewed toward older women, of whom 18 out of 44 were in menopause, potentially increasing pro-inflammatory biomarkers related to estrogen deprivation (Gameiro et al., 2010). The participant's menstrual status could also be considered in future studies.

The Present Study

The replication portion of the present study replicates the effects of different ER strategies on various inflammatory variables from the original study by Ospina et al. (2022). Due

to differences in exclusionary criteria, our analytical sample deviated slightly from the original study. We base the success of our replication on whether or not we achieved the same directionality of effect as the original paper. Based on the original research as well as relevant literature, we expect ES to be associated with higher levels of inflammation, and CR to be associated with lower levels of inflammation.

The extension in the present study aims to understand how stress experienced in childhood and adulthood impacts inflammation. This extension will analyze how different facets of childhood adversity and current levels of perceived stress in adulthood relate to inflammatory biomarker levels in adults. Given the current literature on the effects of stress and inflammation, we predict that higher levels of childhood stress and current perceived stress levels are associated with higher levels of inflammation.

Methods

Participants

This study analyzes data from the Midlife in the United States (MIDUS) study which collected sociodemographic and psychosocial data on the mental and physical health of US adults aged 25-74 years in the United States (Ryff et al., 2010). Out of the 7,108 initial MIDUS participants that were interviewed by phone, 4,963 individuals participated in the second wave of the study (MIDUS II). An additional assessment of MIDUS II, the Biomarkers project, collected detailed medical histories and biological samples from participants to investigate biological mechanisms of behavioral and psychosocial factors (N = 1255) (Ryff et al., 2021). A subset of these individuals further participated in the Neuroscience Project which collected assessments of neural circuitry, EMG, and EEG data stimulated by affective imagery (N = 331) (Ryff et al., 2010). Of the participants in the Neuroscience Project, ER measures and inflammatory

biomarkers were obtained from a smaller subset of individuals (N = 117), which determined the analytic sample of the present study. Participants in this analytic sample were between the ages of 37-84 years (M = 49.29, SD = 10.2), and 53.8% were female.

Measures

Inflammatory Biomarkers

The Biomarker Project assessed various inflammatory biomarkers, including IL-6, IL-8, IL-10, TNF-α, CRP, E-selectin, ICAM-1, and fibrinogen. On the second day of their hospital stay, participants provided blood samples which were stored at -65°C and later assayed. Different techniques such as ELISA, nephelometer, and immuno-electrochemiluminescence were used to measure the biomarkers, with re-analysis done for samples that were below the assay range.

Emotion Regulation Measures

The Emotion Regulation Questionnaire (ERQ) was used to measure the use of specific ER strategies (Gross and John, 2003). The questionnaire consists of 10 items (CR: 6 items, ES: 4 items) and is scored on a 7-point scale, with higher scores indicating higher use of a specific strategy. The ERQ has demonstrated good reliability and validity, with alpha scores of 0.79 for CR, 0.73 for ES, and 0.69 for both in good test-retest reliability (Gross and John, 2003). Averages are reported in Table 1 for other participant characteristics known to affect ER and inflammation, including the number of medications taken, BMI, and CESD depression scores.

Childhood Adversity and Adult Stress Measures

The history and severity of childhood trauma were measured using a recall-based questionnaire, the Childhood Trauma Questionnaire (CTQ). The CTQ includes five subtypes of childhood trauma under two broader categories, including childhood abuse (Emotional Abuse, Physical Abuse, and Sexual Abuse) and experiences of childhood neglect (Emotional Neglect

and Physical Neglect). The CTQ was scored on a scale of 25-125. Participants answered five questions regarding their experiences of abuse or neglect in each subcategory, with participant values between 1 and 5 for each question (1 = "never" experienced, 5 = "very often" experienced); a total subscore of 5 from these five questions refers to "no trauma exposure", and a total subscore of 25 from these five questions refers to "extreme trauma exposure".

Current everyday stress levels were measured using the Perceived Stress Scale (PSS). Participants answered 40 questions with a value between 0 and 4 (0 = "never", 4 = "very often"). PSS scores range from 0-40, with higher values indicating higher levels of stress.

Statistical Analysis

Replication

The replication of the present study focused on the relationship between ER strategies, CR and ES, and various inflammatory variables. First, we calculated Pearson correlations between inflammatory biomarkers and ER strategies. Second, we assessed the association between ER strategies and various inflammatory biomarkers by conducting a hierarchical linear regression, using demographic and clinical covariates (age, sex, total prescribed medications, depression scores) in block 1, and inflammatory biomarkers in block 2. All analyses were conducted using R Studio.

Extension

The extension aimed to understand how stress and adversity experienced in childhood and adulthood affect inflammation. Similar to the replication, we calculated Pearson correlations between CTQ and PSS scores and inflammatory biomarkers. We next assessed the association between CTQ, PSS scores, and various inflammatory biomarkers using hierarchical linear regression. To study their effect on each inflammatory marker, demographic and clinical

covariates (age, sex, total prescribed medications, depression scores) were analyzed in block 1, PSS in block 2, and CTQ in block 3. All analyses were also conducted using R Studio.

Results

Table 1. Demographic, Clinical, Independent, and Dependent Variables Summary (N=117)

	M(SD)
Sociodemographic Characteristics	
Age	49.29(10.20)
Sex	63 females (53.8% female)
Health Indicators	
BMI	30.35(6.21)
Current Depression Ratings	8.15(6.30)
Total # of prescription medications/person	5.72(4.68)
Emotion Regulation	
Expressive Suppression	3.45(1.22)
Cognitive Reappraisal	4.99(0.92)
Inflammation Levels	
IL-6 (pg/mL)	1.28(4.48)
IL-8 (pg/mL)	14.44(15.62)
IL-10 (pg/mL)	0.37(1.55)
TNF-a (pg/mL)	2.22(0.95)
CRP (ug/mL)	3.02(4.78)
E-Selectin (ng/mL)	43.39(22.72)
ICAM-1 (ng/mL)	288.55(115.61)
Fibrinogen (mg/dL)	348.92(87.85)
Childhood Adversity & Adult Stress Variables	
Perceived Stress (adult)	22.79(6.16)
Emotional Abuse (childhood)	7.55(3.80)
Physical Abuse (childhood)	6.84(2.80)
Sexual Abuse (childhood)	6.58(3.84)
Emotional Neglect (childhood)	9.36(4.47)
Physical Neglect (childhood)	7.13(2.86)
Overall CTQ Score	37.46(13.40)

Note: N = 117. IL: interleukin; TNF-α: tumor necrosis factor-α; CRP: C-reactive protein; ICAM-1: Intercellular Adhesion Molecule-1. The perceived stress scale measures stress in adulthood using the Perceived Stress Scale (PSS). The Childhood Trauma Questionnaire (CTQ) measures 5 subscales of childhood adversity: Emotional, physical, and sexual abuse, as well as emotional and physical neglect

Table 1 presents the summary statistics for the present study's analytic sample (N=117), inflammatory markers, emotion regulation measures, childhood adversity levels from the CTQ,

and current perceived stress levels in adulthood with the PSS. Inflammatory biomarker statistics reflect average inflammatory levels before log-scaling.

Data for the mean Overall CTQ Score was right-skewed, with an average score of 35 obtained (the full-scale ranges from 25-125); this indicates that most participants did not experience extreme levels of childhood adversity. The PSS by comparison, shows a more central distribution, with an average value of 22.79 (the full-scale ranges from 0-40).

Table 2. Pearson Correlation Coefficients (N=117)

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.
1. ER-CR	-														
2. ER-ES	-0.01	-													
3. IL-6	-0.07	-0.07	-												
4. IL-8	0.06	-0.11	0.15	-											
5. IL-10	0.02	-0.19*	0.05	0.32***	-										
6. TNF-α	0.08	-0.25**	0.38***	0.28**	0.37***	-									
7. CRP	0.01	0.00	0.51***	0.12	0.02	0.21*	-								
8. E-Selectin	-0.04	-0.10	0.13	0.27**	0.13	0.00	0.16	-							
9. ICAM-1	0.07	-0.21*	0.08	0.18**	0.18	0.43***	0.07	0.25**	-						
10. Fibrinogen	-0.09	-0.12	0.43***	0.16	0.05	0.21*	0.56***	0.16	0.18*	-					
11. Perceived Stress (adult)	-0.09	0.12	-0.03	-0.15	0.06	0.01	0.07	0.06	-0.11	0.08	-				
12. Emotional Abuse (childhood)	-0.01	-0.16	0.08	0.11	0.01	0.08	0.06	0.14	0.17	0.02	0.14	-			
13. Physical Abuse (childhood)	0.06	-0.12	0.19*	0.15	0.02	0.12	0.08	0.21*	0.19*	0.06	0.10	0.73***	-		
14. Sexual Abuse (childhood)	-0.04	-0.22*	0.20*	-0.11	0.02	0.15	0.06	0.00	0.08	0.06	0.08	0.49***	0.49***	-	
15. Emotional Neglect (childhood)	0.06	0.06	-0.04	0.04	-0.12	-0.05	0.06	0.00	0.09	0.05	0.18*	0.53***	0.38***	0.08	-
16. Physical Neglect (childhood)	-0.05	-0.01	0.08	0.08	-0.05	-0.08	0.19*	0.00	0.02	0.01	0.19*	0.61***	0.56***	0.19*	0.67***

Note: *p<0.05, **p<0.01, ***p<0.001. IL: interleukin; TNF-α: tumor necrosis factor-α; CRP: C-reactive protein; ICAM-1: Intercellular Adhesion Molecule-1. The perceived stress scale measures stress in adulthood using the Perceived Stress Scale (PSS). The Childhood Trauma Questionnaire (CTQ) measures 5 subscales of childhood adversity: Emotional, physical, and sexual abuse, as well as emotional and physical neglect

Table 2 presents the Pearson Correlation Coefficients between ER strategies, CTQ and PSS scores, and inflammatory biomarkers. There were no significant correlations between ER-CR and inflammatory biomarkers. However, there were significant negative associations between ER-ES and IL-10 ($r = -0.19$, $p < 0.05$), TNF-α ($r = -0.25$, $p < 0.01$), and ICAM-1 ($r =$

-0.21, $p < 0.05$). These results successfully replicate the findings of the original study (Ospina et al., 2022). These correlations indicate that greater levels of IL-10, TNF-α, and ICAM-1 are associated with lower ES use, supporting evidence for a relationship between inflammation levels and the ER-strategy use of ER-ES.

Different subscores of childhood trauma appear to be significantly associated with each other. In particular, emotional abuse had a significant positive association with such as physical abuse ($r = 0.73$, $p < 0.001$), sexual abuse ($r = 0.49$, $p<0.001$), emotional neglect ($r = 0.53$, $p < 0.001$), and physical neglect ($r = 0.56$, $p < 0.001$), suggesting that these subtypes of childhood trauma tend to be experienced concertedly. There was also a significant negative correlation between sexual abuse during childhood and ES use in adulthood ($r = -0.22$, $p < 0.05$). This means that people who experienced greater levels of sexual abuse in childhood are less likely to use ES strategies, demonstrating a potential link between childhood stressors and current emotion regulation strategies. Interestingly, subscores of childhood trauma that were more physical in nature (physical abuse, sexual abuse, and physical neglect) seem to have a significant association with various inflammatory markers. There is a positive, significant correlation between physical abuse in childhood and IL-6 ($r = 0.19$, $p < 0.05$), E-Selectin ($r = 0.21$, $p < 0.05$), and ICAM-1 ($r = 0.19$, $p < 0.05$). Sexual abuse is also positively correlated with IL-6 ($r = 0.20$, $p < 0.05$), and physical neglect is also positively correlated with CRP ($r = 0.19$, $p < 0.05$). This suggests that individuals who experienced higher levels of abuse that was more physical in nature as a child exhibit higher levels of inflammation in adulthood. Additionally, there was a significant positive association between some forms of childhood trauma and perceived stress in adulthood. Individuals who experienced higher levels of both emotional ($r = 0.18$, $p < 0.05$) and physical ($r = 0.19$, $p < 0.05$) neglect as children experience higher levels of perceived stress in

adulthood, demonstrating the lasting impact of childhood trauma on adult mental wellbeing.

Adult perceived stress levels are not significantly associated with any inflammatory biomarkers.

Table 3. Hierarchical Linear Regression for Inflammatory Biomarkers on Emotion Regulation Strategies

Predictors	**ERQ - Expressive Suppression**		**ERQ - Cognitive Reappraisal**	
	B(SE)	**β**	**B(SE)**	**β**
Age	0.03(0.01)	0.03	0.00(0.01)	-0.02
Sex	-0.41(0.23)	-0.41	0.29(0.19)	0.16
BMI	0.03(0.02)	0.03	0.00(0.02)	-0.00
Total # Prescribed Meds	-0.05(0.03)	-0.05	-0.01(0.03)	-0.05
Depressive Symptoms	0.04(0.02)	0.04*	0.00(0.01)	-0.01
IL-6	-0.05(0.22)	-0.06	-0.14(0.18)	-0.10
IL-8	0.17(0.29)	0.17	0.16(0.24)	0.07
IL-10	-0.19(0.21)	-0.19	-0.04(0.17)	-0.03
TNF-α	-1.06(0.43)	-1.06*	0.20(0.36)	0.07
CRP	0.19(0.14)	0.19	0.03(0.12)	0.04
E-Selectin	-0.35(0.27)	-0.35	-0.08(0.22)	-0.04
ICAM-1	-0.14(0.28)	-0.14	0.12(0.23)	0.06
Fibrinogen	-1.10(0.71)	-1.10*	-0.67(0.59)	-0.15
F	2.15*	-	0.43	-
R2	0.22	-	0.06	-

Note: Hierarchical linear regression results for ERQ strategies as predicted by demographic variables and clinical covariates in block 1, and inflammatory biomarkers in block 2. *p < 0.05

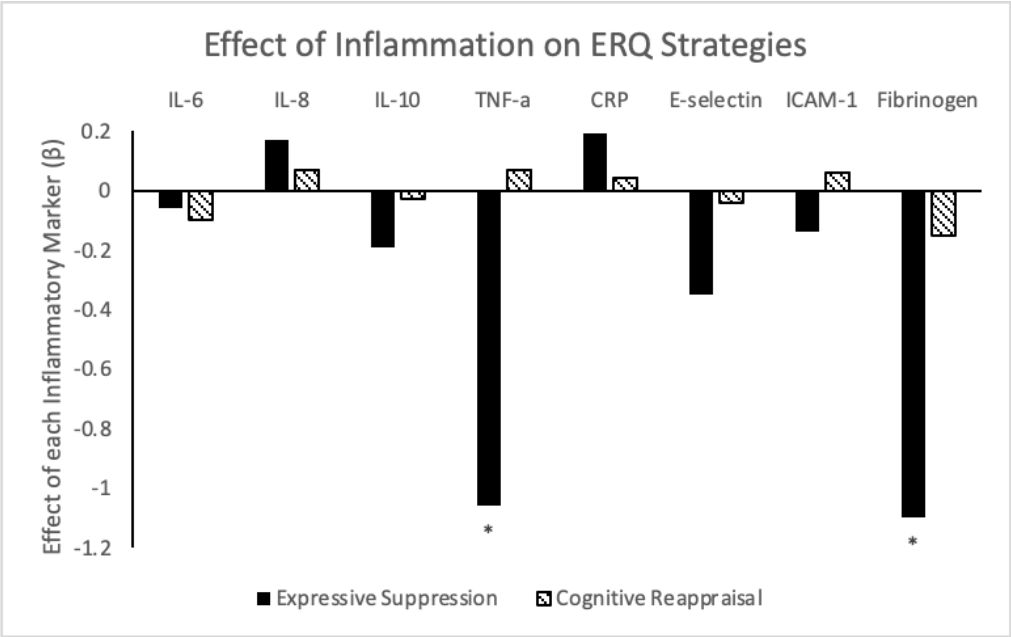

Fig. 1. Effect of Inflammation on ERQ Strategies

This data is based on results from the hierarchical linear regression (Table 3). Significant results are indicated by the * ($p<0.05$). The model was adjusted for age, sex, BMI, total number of prescribed medications, and depression scores.

The hierarchical linear regression results for the replication portion of the present study are displayed in Table 3 and Figure 1. In general, our model successfully replicated the data from the original study (Ospina et al., 2022). Our model for ES found that depressive symptoms significantly predict ES use ($\beta = 0.04$, $p < 0.05$), suggesting that individuals with more severe depressive symptoms typically use ES to regulate emotions more often. Significant inflammatory predictors included TNF-α ($\beta = -1.06$, $p < 0.05$) and Fibrinogen ($\beta = -1.10$, $p < 0.05$). And similar to the original study, the model including covariates and inflammatory biomarkers was significant, accounting for 22% of the variance ($F(13, 117) = 2.15$, $p < 0.05$). The model for CRl did not yield significant predictors.

Table 4a. Hierarchical Linear Regression for Childhood Adversity and Adult Stress on Inflammation

Predictors	**IL-6**		**IL-8**		**IL-10)**		**TNF-a**	
	B(SE)	**β**	**B(SE)**	**β**	**B(SE)**	**β**	**B(SE)**	**β**
Age	0.02(0.01)	0.24 *	0.00(0.01)	0.1	0.00(0.00)	-0.04	0.01(0.00)	0.23*
Sex	0.15(0.11)	0.11	0.12(0.08)	0.14	0.07(0.12)	0.06	0.05(0.07)	0.07
BMI	0.05(0.01)	0.43 ***	0.00(0.01)	0.02	0.00(0.01)	0.00	0.01(0.01)	0.18
Total # Prescribed Meds	0.00(0.02)	0.00	0.02(0.01)	0.18	0.03(0.02)	0.20	0.00(0.01)	-0.03
Depressive Symptoms	0.01(0.12)	0.11	0.00(0.01)	-0.03	0.02(0.01)	0.20	0.00(0.01)	0.03
Perceived Stress (Adult)	-0.02(0.02)	-0.13	-0.01(0.01)	-0.12	0.00(0.01)	-0.04	0.00(0.01)	0.01
Emotional Abuse (Childhood)	-0.01(0.02)	-0.07	0.02(0.02)	0.16	0.01(0.03)	0.04	0.01(0.01)	0.13
Physical Abuse (Childhood)	0.04(0.03)	0.19	0.04(0.02)	0.29	0.03(0.03)	0.12	0.02(0.02)	0.16
Sexual Abuse (Childhood)	(0.01)(0.02)	0.08	-0.04(0.01)	-0.38 **	-0.01(0.02)	-0.08	0.00(0.01)	0.04
Emotional Neglect (Childhood)	(-0.02)(0.02)	-0.12	-0.01(0.01)	-0.10	-0.03(0.02)	-0.20	0.00(0.01)	-0.02
Physical Neglect (Childhood)	0.01(0.03)	0.04	-0.01(0.02)	-0.04	-0.01(0.03)	-0.07	-0.03(0.02)	-0.26
F	1.14	-	2.87*	-	0.86	-	1.51	-
R2	0.33	-	0.19	-	0.08	-	0.14	-

Table 4b. Hierarchical Linear Regression for Childhood Adversity and Adult Stress on Inflammation (cont.)

Predictors	CRP		E-Selectin		ICAM-1		Fibrinogen	
	B(SE)	β	B(SE)	β	B(SE)	β	B(SE)	β
Age	0.01(0.01)	-0.05	0.00(0.00)	-0.10	0.00(0.01)	-0.02	0.01(0.00)	0.36***
Sex	0.55(0.18)	0.25**	0.04(0.09)	0.04	0.16(0.09)	0.17	0.09(0.04)	0.21*
BMI	0.09(0.01)	0.52***	0.01(0.01)	0.20*	0.01(0.01)	0.08	0.01(0.00)	0.32***
Total # Prescribed Meds	0.01(0.03)	0.04	0.00(0.01)	0.02	0.00(0.01)	0.01	0.00(0.00)	-0.05
Depressive Symptoms	0.01(0.02)	0.04	0.02(0.01)	0.25	0.02(0.01)	0.25	0.00(0.00)	0.13
Perceived Stress (Adult)	-0.01(0.02)	-0.03	-0.01(0.01)	-0.10	-0.02(0.01)	-0.29*	0.00(0.00)	-0.01
Emotional Abuse (Childhood)	-0.01(0.04)	-0.04	0.01(0.02)	0.07	-0.01(0.02)	0.09	0.00(0.01)	-0.01
Physical Abuse (Childhood)	-0.02(0.05)	-0.04	0.06(0.02)	0.36*	0.05(0.03)	0.29	0.01(0.01)	0.15
Sexual Abuse (Childhood)	-0.03(0.03)	-0.09	-0.02(0.01)	-0.20	-0.01(0.01)	-0.08	0.00(0.01)	-0.03
Emotional Neglect (Childhood)	-0.02(0.03)	-0.08	0.00(0.01)	-0.02	0.01(0.01)	0.13	0.00(0.01)	0.07
Physical Neglect (Childhood)	0.09(0.05)	0.23	-0.04(0.02)	-0.27	-0.05(0.02)	-0.30*	-0.01(0.01)	-0.16
F	5.68	-	1.9	-	1.76	-	0.40	-
R2	0.37	-	0.17	-	0.13	-	0.28	-

Note: Hierarchical linear regression results for inflammatory biomarkers as predicted by participant characteristics in block 1, perceived stress in block 2, and childhood trauma in block 3. *p < 0.05, ** p < 0.01, *** p < 0.001.

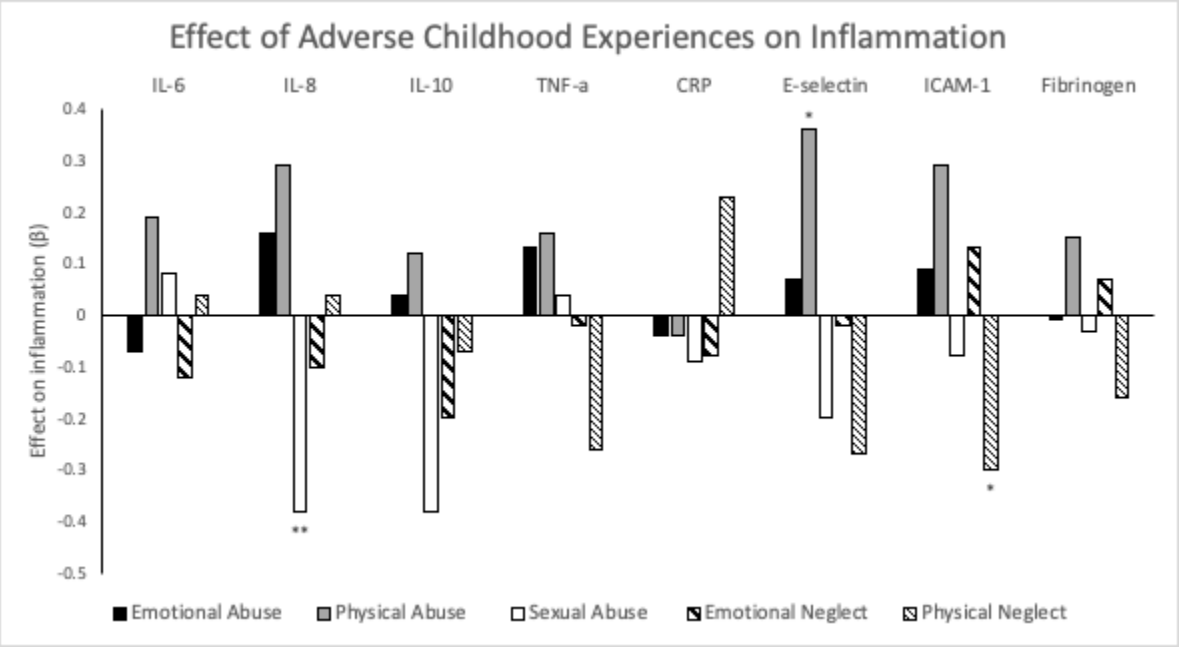

Fig. 2. Effect of Childhood Adversity and Perceived Stress in Adulthood on Inflammation
This data is based on results from the hierarchical linear regression (Tables 4a and 4b). Significant results are indicated by the * ($p<0.05$), ** ($p<0.01$). The model was adjusted for age, sex, BMI, total number of prescribed medications, and depression scores.

The hierarchical linear regression results for the extension of the present study are displayed in Tables 4a and 4b, as well as in Figure 2. Similar to our extension results in Table 2, our model identified physical forms of childhood adversity to be significant predictors of certain inflammatory markers. In particular, sexual abuse is a significant predictor for IL-8 levels ($\beta = -0.38$, $p < 0.01$), physical abuse is a significant predictor for E-Selectin levels ($\beta = 0.36$, $p < 0.05$) and physical neglect is a significant predictor for ICAM-1 levels ($\beta = -0.30$, $p < 0.05$). Perceived stress during adulthood was not a significant predictor of any inflammatory biomarker levels, demonstrating that childhood adversity had a greater effect on inflammation than stress in adulthood in our sample. The model for IL-8 including covariates, PSS, and CTQ data was the only significant model compared to models examining other inflammatory markers. The model for IL-8 accounts for 19% of the variance ($F(1, 5) = 1.90$, $p < 0.05$).

Discussion

Inflammation is a crucial component underlying several aspects of physical and psychological health. It is interlinked with many socioemotional factors of daily life and creates lasting impacts across the lifespan. Given its importance on overall well-being, the present study examines its relationship with emotion regulation strategies, childhood adversity, and perceived stress.

Our findings successfully replicated the original paper and found significant, negative associations between ES and IL-10 (Table 2), TNF-α (Table 2; Table 3; Fig. 1), ICAM-1 (Table 2), and Fibrinogen (Table 3; Fig. 1). This indicates that higher levels of ES are associated with

lower levels of IL-10, TNF-α, ICAM-1 and Fibrinogen. Contrastingly, CR was not significantly associated with any inflammatory biomarkers. To relate our findings to the known functions of our most significant inflammatory markers, IL-10, TNF-α, ICAM-1, and Fibrinogen levels tend to increase during stressors in both animals and humans (Curtin et al., 2009; Liu et al., 2015; Bhowmick et al., 2021; Lazzarino et al., 2015). However, our findings contrast with previous reports of TNF-α, ICAM-1, and Fibrinogen and ES use. TNF-α, ICAM-1, and Fibrinogen are pro-inflammatory agents, so higher levels of stress are *positively* associated with higher levels of these inflammatory markers. Moreover, a biobehavioral model proposes that maladaptive ER strategies like ES are linked to higher levels, resulting in increased inflammation (Renna, 2021). Our contradictory findings thus suggest a need to further investigate the mechanisms underlying TNF-α, ICAM-1, Fibrinogen, and ER.

On the other hand, our findings for IL-10 align with Renna's (2021) biobehavioral model and its known function. IL-10 is an anti-inflammatory agent that prevents excessive inflammation. Considered within Renna's (2021) model, this supports our findings in that maladaptive ES use is associated with lower IL-10 levels which reduce the regulation of inflammation, resulting in increased inflammation and worse health outcomes overall.

Our extension results suggest a link between PSS, childhood adversity, and inflammation. Most notably, childhood adversity that is more physical in nature (physical abuse, sexual abuse, physical neglect) is positively associated with IL-6, E-Selectin, and ICAM-1 levels. These findings align with each protein's proinflammatory effects (Popko et al., 2010; Ruchaud‐Sparagano, 1998; Lee, 2000), in which greater levels of stress experienced in childhood result in greater inflammation in adulthood and worse health outcomes. Moreover, other studies have found similar positive associations between experiences of childhood trauma

and proinflammatory proteins like CRP (Danese et al., 2007) and TNF-α (Baumeister et. al., 2016). While the specific inflammatory markers may differ between samples, this suggests a general trend in which stressors experienced during childhood are associated with inflammation and worse health outcomes.

The significance between physical forms of childhood trauma and inflammation may be explained by the known function of inflammatory markers: inflammatory cytokines are produced in response to physical stressors like injury, so chronic exposure to such stressors throughout childhood can result in a dysregulated immune response and chronic inflammation in adulthood (Seiler et al., 2020). Recognizing childhood adversity as a stressor and contributor to chronic inflammation is vital in understanding the cause and treatments of future health outcomes. One study found that elevated levels of IL-6 and CRP were predecessors in the development of depressive disorders (Valkanova & Ebmeier, 2013). Other studies found that individuals with higher inflammation rates were unlikely to respond to customary antidepressant medicine (Cattaneo et. al., 2013), and were instead, more responsive to anti-inflammatory treatments (Raison & Rutherford, 2013). Understanding the roles and presence of these biomarkers can aid in developing adequate treatment as well as preventing diseases for individuals suffering from physical and psychiatric conditions caused by chronic inflammation associated with adverse childhood experiences.

There are a few limitations in the present study to consider. For one, the original researchers did not set a clear benchmark for each inflammatory variable for determining which participants to exclude from our analytic sample, so we did not remove any outliers from our data results and did not conduct a partial Pearson's Correlation test.

Additionally, more than half of our final participant pool were females over the age of 37; as previously mentioned in the discussion of the original paper's limitations, pro-inflammatory responses conferred by menopause could be a confounder in our data collection. Without menstrual status taken into account, researchers may unknowingly be tracking *post-menopausal* changes in inflammatory profiles in tandem with the original series of inflammatory responses recorded that were uninfluenced by any pre or post-menopausal changes.

Educational status, race, and income are among many socioeconomic status (SES) factors that may also have been confounding factors to our study. SES is especially important to consider since the present study evaluates the effects of various stressors on inflammation, which often covaries with SES. Relatedly, it may be beneficial to consider additional factors that relate to health outcomes. For example, while participants' current BMI was considered, previous BMI patterns may also be a significant predictor of health outcomes and inflammation. In a meta-analysis on CRP, TNF-a, and IL-6, researchers discuss how early-life stress tends to have a "programming effect" on the function of one's future inflammatory immune system by making changes to their epigenetic regulation of gene expression (Baumeister, et. al 2016). Studies have also found that higher BMIs in childhood are strong predictors of cardiometabolic risks (Arisaka et al., 2020). This provides a compelling reason to consider additional variables related to a participant's health history.

Future studies may consider conducting a cross-sectional design instead of a longitudinal one using samples of participants who experienced different histories of trauma and perceived stress. This could potentially mean taking samples from more disadvantaged communities who are like more-exposed to childhood stressors and comparing them to a sample from a more privileged community. Implementing a stress-inducing behavioral paradigm may also be a more

accurate measure of current stressors, and allow researchers to collect inflammatory markers in a timely manner.

Conclusion

The present study examines the relationship between childhood adversity, current life stressors, emotion regulation, and health. While this was only a correlational study, our findings suggest that certain types of childhood stressors and current life stressors are associated with increases in inflammation and that there is a relationship between ES and inflammation.

The mechanistic properties of emotion regulation strategies and inflammatory responses are yet to be discerned. However, ES was observed to have a significant relationship with inflammation and can potentially lead to worse health outcomes, while no such relationship was found for CR. This finding has potential therapeutic applications, as CR could be operationally employed more widely as a tool for overcoming stressors, conflict, and anxiety, while also minimizing the negative health outcomes evidenced by inflammatory profiles.

This research also demonstrates the lasting impact of stress on the human body. Early life experiences can potentially rewire the body and can increase an individual's risk for chronic inflammation, cardiovascular disease, mental illnesses like depression, and even cancer (Deeks et al., 2013). Research on this topic can be used to target populations who have experienced greater levels of childhood adversity as people who now have a higher risk of health problems, and may need therapeutic or medical interventions. This also has major implications in child development, emphasizing the importance of minimizing physical and emotional stressors throughout childhood and adolescence.

Inflammation has important implications in the fields of medicine, psychology, and public health. Understanding its relationship with emotional regulation as well as past and

present life stressors brings us one step closer to comprehending the biopsychosocial components of overall health.

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