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Inflammation and emotion regulation: Findings from the MIDUS II study

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ABSTRACT

Emotion regulation (ER) strategies are thought to contribute to mental as well as physical health outcomes. Two common ER strategies include expressive suppression, or inhibition of emotional expression, and cognitive reappraisal, which involves changing how to think about an emotion-eliciting event in order to change its emotional impact. Recent reports have hypothesized that one potential way in which ER may be linked to health outcomes is via the immune system. However, information on this putative link is scarce. The present study aims to explore whether peripheral inflammatory biomarkers are associated with individual differences in ER-strategy use. Participants (n = 117) from the Midlife in the United States II (MIDUS II) study completed the Emotion Regulation Questionnaire (ERQ), and provided a blood sample for immune biomarker extraction including interleukin (IL)-6, IL-8, IL-10, tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), E-selectin, Intercellular Adhesion Molecule-1 (ICAM-1), and fibrinogen. Results showed higher levels of expressive suppression were associated with decreased IL-10, TNF-α, and ICAM-1 levels (controlling for age, sex, BMI, total prescribed medications, and depressive symptoms). Consistent with these findings, hierarchical regression results identified TNF-α as a significant predictor of expressive suppression use. In contrast, no inflammatory markers were associated with predicted use of cognitive reappraisal. Our findings suggest a link between inflammation and specific ER-strategy use. Future research should consider the effects of pro-vs. anti-inflammatory cytokines on adaptive ER and subsequent mental and physical health.

1. Introduction

Emotion regulation (ER) is a crucial determinant of mental and physical health (Appleton et al., 2014; Hu et al., 2014; Williams et al., 2015). Importantly, it is becoming clear that different ER strategies have quite different profiles of consequences (Gross, 2015). Two commonly used ER strategies that have received particular research attention are: 1) expressive suppression, a response-focused strategy which acts late in the emotion-generative process and inhibits emotional expression in response to an emotion-eliciting event; and 2) cognitive reappraisal, an antecedent-focused strategy which acts early in the emotion-generative process and involves changing how to think about an emotion-eliciting event in order to change its emotional impact (Gross, 1998).

Expressive suppression is considered to be cognitively and physiologically burdensome, having been linked with increased experience of negative emotions and depressive symptomatology (Gross and John, 2003), heightened sympathetic nervous system (Gross and Levenson, 1997) and neuroendocrine activation (Otto et al., 2018), and worsened physical health and mortality (Appleton et al., 2014; Chapman et al., 2013). In contrast, cognitive reappraisal use has been associated with increased experience of positive emotions and fewer depressive symptoms (Gross and John, 2003), more beneficial patterns of sympathetic nervous system response (Mauss et al., 2007), and decreased cardiovascular risk (Appleton et al., 2014).

Given its relation to physiological activity, recent research has linked ER with inflammation. Among healthy adults, use of cognitive reappraisal has been shown to correlate with lower levels of C-reactive protein (CRP) (Appleton et al., 2013) and interleukin-6 (IL-6) (Brown et al., 2020). Conversely, increased inflammation, specifically CRP, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), has been linked with routine expressive suppression use (Appleton et al., 2013; Ellis et al., 2019; Lopez et al., 2020). Similar associations have also been

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evident in various psychiatric groups, linking inflammatory biomarkers with expressive suppression (Khan et al., 2020; Ospina et al., 2021; Powers et al., 2016). However, previous studies linking inflammation and ER have been limited by focusing on specific populations (e.g., bereaved spouses, psychiatric groups) and/or measurement of a narrow range of cytokines and abbreviated ER assessments. The present study builds on prior literature and more broadly investigates whether individual differences in levels of inflammatory cytokines are associated with expressive suppression and cognitive reappraisal in a national sample of middle-aged adults. In particular, we hypothesized that expressive suppression would be associated with higher inflammation, while cognitive reappraisal would correlate with lower inflammation.

2. Methods

We analyzed data from The Midlife in the United States (MIDUS) study, a longitudinal assessment of a national U.S. sample of adults developed to investigate how psychological, behavioral, and social factors relate to and influence mental and physical health (Brim et al., 2004). The first wave of the study (MIDUS I) collected sociodemographic and psychosocial data from 7108 English-speaking Americans, aged 25–74 years, living in the contiguous 48 states with access to at least one telephone (recruited by random digit dialing). Of the original MIDUS I participants, 4963 individuals were re-contacted and successfully completed the second wave (MIDUS II) of the study, which included a phone interview and completion of self-reports. As an additional assessment of MIDUS II, a subset of participants (n = 1255) completed the Biomarkers project between 2002 and 2006 to investigate biological mechanisms underlying behavioral and psychosocial factors, which included a detailed medical history and collection of biological samples (i.e., blood, urine, and saliva). A subset of participants (n = 331) who completed the Biomarker project also completed the Neuroscience Project between 2004 and 2009, which included assessment of the neural circuitry involved in affective style, regulation and reactivity via self-reports, EMG, EEG, and eyeblink startle magnitude at rest and in response to the presentation of affective imagery (Ryff and Davidson, 2010; Ryff et al., 2021).

2.1. Participants

Of the 331 participants who completed the MIDUS II Biomarker and Neuroscience projects, inflammatory biomarkers and the full ER measure were obtained from 117 participants; the following analyses focus on this subsample of participants. All procedures were approved by the Institutional Review Boards at the University of Wisconsin, the University of California – Los Angeles, Pennsylvania State University, and Georgetown University; all participants provided informed consent.

2.2. Measures

Inflammatory biomarkers assessed in the Biomarker Project included: CRP, Intercellular Adhesion Molecule-1 (ICAM-1), IL-6, fibrinogen, and E-selectin. Additional inflammatory biomarker data were extracted using stored MIDUS II samples and later added to the MIDUS Refresher Biomarker protocol, which included interleukin-8 (IL-8), interleukin-10 (IL-10) and TNF-α, as well as a re-analysis of CRP samples falling below the assay range. Assay procedures for all inflammatory markers have been described previously (Dienberg Love et al., 2010) and are available at the MIDUS website. In short, fasting blood samples were collected from each participant before breakfast on their second day of their hospital stay. Samples were subsequently stored in a −65 °C freezer until assay, where cytokines were assayed in the MIDUS Biocore Laboratory (University of Wisconsin, Madison, WI), and ICAM-1, E-selectin, fibrinogen and CRP assays were performed at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT). IL-8, IL-10 and TNF-α were assayed via immunoelectrochemiluminescence, which included using a V-plex Custom Human Cytokine Kit (catalog #K151A0H-2) manufactured by Meso Scale Diagnostics, Rockville, MD. IL-6 was measured using the Quantikine® High Sensitivity ELISA kit #HS600B manufactured by R&D Systems, Minneapolis, MN. ICAM-1 was assessed by an ELISA assay produced by Parameter Human sICAM-1 Immunoassay, R&D Systems, Minneapolis, MN. E-selectin was measured using a high-sensitivity ELISA assay (Parameter Human sE-Selectin Immunoassay, R&D Systems, Minneapolis, MN). Fibrinogen was evaluated used a BNII nephelometer (N Antiserum to Human Fibrinogen; Dade Behring Inc. Deerfield, IL). CRP was analyzed using the BNII nephelometer from Dade Behring utilizing a particle-enhanced immunoepholometric assay. Finally, samples falling below the assay range for CRP were re-assayed by immunoelectrochemiluminescence using a high-sensitivity assay kit (Meso Scale Diagnostics #K151STG).

The full 10-item version of the Emotion Regulation Questionnaire (ERQ) was utilized to assess use of specific ER strategies (Gross and John, 2003). The cognitive reappraisal and expressive suppression scales consist of six and four items, respectively. Participants were instructed to indicate using a 7-point scale (from (1) *strongly disagree* to (7) *strongly agree*) to what extent they agree with each item, with higher scores reflecting a higher endorsement of that strategy use. The ERQ has demonstrated adequate reliability, with alpha of 0.79 for cognitive reappraisal and 0.73 for expressive suppression, and good test-retest reliability (0.69 for both scales) (Gross and John, 2003).

Participant characteristics known to influence ER and inflammation were obtained during the biomarker collection and MIDUS II assessments, including sociodemographic factors (age and sex), total number of medications ingested (which includes prescription, over the counter, and alternative medications), body mass index (BMI), and depressive symptomatology total score indexed using the Center for Epidemiological Studies Depression Inventory (CESD; Radloff, 1997) (Appleton et al., 2013; Ellis et al., 2019).

2.3. Statistical analyses

Participant characteristics, including demographics, ER and inflammatory biomarker levels were computed for the sample. As inflammatory markers were skewed, we applied log-transformation to achieve normality, and removed any additional outliers via visual inspection. Next, we calculated Pearson's full and partial correlations between ER and inflammatory biomarkers, controlling for: age, sex, BMI, total number of prescribed medications, and total depression score. In order to evaluate whether inflammatory biomarkers predicted use of ER strategies, we conducted separate hierarchical linear regression models for expressive suppression and cognitive reappraisal with demographic and clinical covariates in block 1, and inflammatory biomarkers in block 2. All analyses were performed using SPSS version 24 (IBM Corp., Armonk, NY, USA). For all analyses, alpha was set at 0.05 and tests were two-tailed.

3. Results

In the study sample (N = 117), participants were aged 37–84 years (M = 53.84, SD = 9.99), and 52.1% were female. Only 78 participants disclosed racial and educational status, of which 96.15% self-reported as white, and 50% earned a bachelor's degree or higher. Follow-up analyses between responders and non-responders for racial and educational status revealed no difference between any ER strategies or inflammatory biomarkers. Full participant characteristics are presented in Table 1.

Full and partial Pearson's correlations between ER strategies and inflammatory biomarkers are presented in Table 2. Results for full correlations demonstrated significant negative relationships between expressive suppression and IL-10, TNF-α, and ICAM-1, with greater levels of IL-10, TNF-α, and ICAM-1 linked to lower expressive suppression. Results for partial correlations yielded similar results, with

Table 1
Participant characteristics – MIDUS subsample.

	M (SD)	N (%)
Sociodemographic characteristics		
Age	53.84 (9.99)	
Sex		61 (52.1% female)
Race[a]		75 (96.15% white)
Education[a]		39 (50.00% bachelor's degree or higher)
Health Indicators		
BMI	30.27 (6.21)	
Current depression ratings[b]	8.09 (6.32)	
Smoking status		9 (7.70% current smoker)
Total # of prescription medications per person	4.16 (3.84)	
# of people who take cardiovascular agents		41 (35.0%)
# of people who take psychotherapeutic agents		17 (14.5%)
# of people who take antihypertensive agents		13 (11.1%)
# of people who take antihistamine agents		7 (6.0%)
# of people who take anxiolytic and hypnotics		7 (6.0%)
# of people who take antidepressants		17 (14.5%)
# of people who take anti-inflammatories or NSAIDS		39 (33.3%)
Emotion Regulation		
Expressive Suppression	3.45 (1.24)	
Cognitive Reappraisal[b]	4.97 (0.90)	
Inflammation Levels		
IL-6 (pg/mL)	1.13 (1.17)	
IL-8 (pg/mL)	15.58 (8.77)	
IL-10 (pg/mL)	0.29 (0.25)	
TNF-α (pg/mL)	1.92 (0.53)	
CRP (ug/mL)	2.60 (2.63)	
E-selectin[c] (ng/mL)	62.03 (27.96)	
ICAM-1[c] (ng/mL)	214.36 (81.44)	
Fibrinogen (mg/dL)	357.21 (71.03)	

Note: N = 117. BMI: Body Mass Index; IL: interleukin; TNF-α: tumor necrosis factor-α; CRP: C-reactive protein; ICAM-1: Intercellular Adhesion Molecule-1.
[a] N = 78.
[b] N = 115.
[c] N = 116.

expressive suppression negatively correlating with TNF-α and ICAM-1, and at trend level for IL-10. Neither full nor partial correlations yielded significant associations between inflammatory biomarkers and cognitive reappraisal.

As indicated in Table 3, for the hierarchical regression model predicting expressive suppression, no significant covariates were found in block 1. However, significant covariates in block 2 included age ($\beta = 0.25$, $p = 0.04$), sex ($\beta = -0.20$, $p = 0.05$), and a trend for depressive symptomatology ($\beta = 0.16$, $p = 0.09$). Significant inflammatory predictors included TNF-α ($\beta = -0.24$, $p = 0.03$) and fibrinogen at trend-level ($\beta = -0.22$, $p = 0.07$). The model including inflammation markers was significant, accounting for 23% of the variance ($F(13, 113) = 2.32$, $p = 0.01$). Results for the hierarchical regression model predicting cognitive reappraisal yielded no significant predictors, neither covariates nor inflammatory biomarkers.

4. Discussion

Results from the present study expand upon previous literature investigating the link between inflammation and ER strategies in healthy adults. The most critical findings show that expressive suppression use is correlated with immune biomarkers, particularly IL-10, TNF-α, and ICAM-1, with increased inflammation relating to *lower* use of suppression.

These findings stand in contrast to previous reports suggesting a positive relationship between expressive suppression use and levels of CRP, IL-2, IL-6, and TNF-α (Appleton et al., 2013; Ellis et al., 2019; Lopez et al., 2020). Theoretically, one recent biobehavioral model (Renna, 2021) proposes that ER mediates the influence of negative affective experience on inflammation in a bi-directional manner, with continuous use of negative emotions increasing immune system dysregulation and promoting a cascade of maladaptive ER strategies (including suppression use) (Mennin et al., 2005), all of which subsequently increase risk for poor long-term health outcomes. Thus, our contradictory results invite speculation on the specific mechanistic properties of the investigated inflammatory biomarkers.

IL-10 is conceptualized as a major *anti*-inflammatory agent, and plays an important role in preventing inflammatory and autoimmune pathologies (Saraiva and O'garra, 2010). Therefore, lower levels of the anti-inflammatory IL-10 may promote subsequent increased levels of pro-inflammatory agents, which has previously been observed in association with higher expressive suppression use. Indeed, one prior study investigating the relationships between inflammation and emotional intelligence (including domains of emotion awareness and ER) discovered a positive relationship, with higher IL-10 levels linked to *better* emotional intelligence (Jung et al., 2019). IL-10 is often induced by inflammatory stimuli and has been observed to play a central role in limiting inflammatory response via multiple pathways (Saraiva and O'garra, 2010); as such, additional research is necessary to investigate the mechanistic effects of IL-10 on specific neuroanatomical regions implicated in ER use.

The other two significant biomarkers under investigation (TNF-α and ICAM-1), however, are considered pro-inflammatory (Rubel et al., 2001; Van de Stolpe and Van der Saag, 1996). Of these, TNF-α is considered the master immune regulator as its activation impacts related inflammatory responses such as vasodilation, leukocyte adhesion to epithelium through expression of adhesion molecules (such as ICAM-1), and blood coagulation (of which fibrinogen is an essential contributor) (Zelová and Hošek, 2013). Therefore, the significant and trend-level negative relationships of ICAM-1 and fibrinogen with expressive suppression (respectively) may be due to the primary significant negative relationship evident between TNF-α and expressive suppression. Prior studies assessing expressive suppression use and TNF-α have been limited and inconsistent, with one study demonstrating no association in a healthy sample (Jung et al., 2019), and another study showing higher TNF-α relating to greater expressive suppression use in bereaved spouses (Lopez et al., 2020). Still, these contradictory results conflict with our current results, suggesting that more research using similar demographic samples is necessary to more accurately assess the relationship between TNF-α and expressive suppression. Mechanistically, initial CNS research demonstrated neurodegenerative effects of increased TNF-α in the brain via neuronal apoptosis, leading to subsequent impairments in cognitive functioning and eventual pathogenesis of neurodegenerative diseases in various populations as a result of activation of TNF receptor 1 (McAfoose and Baune, 2009; Kogan et al., 2018,2019). Interestingly, TNF-α has also recently shown to exert *neuroprotective* effects, with increased synaptic plasticity via stimulation of TNF receptor 2 (Fischer & Maier, 2015). One model of cytokine function argues for consideration of the specific level of TNF-α as well as the sample population under investigation (McAfoose and Baune, 2009), as prior studies indicate that optimal levels of TNF-α in immunologically non-challenged individuals is essential for normal cognitive functioning

Table 2
Pearson's correlations between inflammation biomarkers and emotion regulation.

Full Pearson Correlation Coefficients										
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
1. ER-CR	–									
2. ER-ES	−0.00	–								
3. IL-6	−0.11	−0.06	–							
4. IL-8	−0.01	−0.13	0.14	–						
5. IL-10	0.01	−0.18*	0.01	0.34***	–					
6. TNF-α	0.00	−0.27**	0.32***	0.28**	0.33***	–				
7. CRP	−0.02	−0.00	−0.49***	0.11	−0.01	0.14	–			
8. E-Selectin	0.00	−0.14	0.18	0.32***	0.17	0.11	0.22*	–		
9. ICAM-1	0.03	−0.22*	0.03	0.14	0.14	0.33***	0.03	0.30***	–	
10. Fibrinogen	−0.12	−0.13	0.44***	0.15	0.05	0.23*	0.57***	0.18	0.17	–
Partial Pearson Correlation Coefficients (controlling for age, sex, BMI, total prescribed medications, depression rating)										
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
1. ER-CR	–									
2. ER-ES	0.03	–								
3. IL-6	−0.10	−0.07	–							
4. IL-8	−0.00	−0.09	0.08	–						
5. IL-10	0.02	−0.18	−0.08	0.33***	–					
6. TNF-α	0.04	−0.30**	0.15	0.22*	0.30**	–				
7. CRP	−0.04	0.04	0.38***	0.11	−0.05	0.11	–			
8. E-Selectin	0.01	−0.18	0.10	0.38***	0.17	0.11	0.11	–		
9. ICAM-1	0.03	−0.21*	−0.06	0.12	0.12	0.31***	−0.02	0.29**	–	
10. Fibrinogen	−0.11	−0.16	0.24*	0.08	−0.03	0.040	0.53***	0.13	0.13	–

Note: *<0.05, **<0.01, ***<0.001. Zero order/full correlations (N = 117) are presented first. Partial correlations (controlling for age, sex, BMI, total prescribed medications, depression rating; N = 113) are presented subsequently. ER-CR: Emotion Regulation-Cognitive Reappraisal; ER-S: Emotion Regulation-Expressive Suppression; IL: interleukin; TNF-α: tumor necrosis factor-α; CRP: C-reactive protein; ICAM-1: Intercellular Adhesion Molecule-1.

Table 3
Hierarchical linear regressions of inflammatory biomarkers on emotion regulation strategies.

Predictors	ERQ – Expressive Suppression		ERQ – Cognitive Reappraisal	
	N = 114		N = 113	
	B (SE)	**β (*p*)**	**B (SE)**	**β (*p*)**
Age	0.03 (0.02)	0.25 (0.04)*	−0.00 (0.01)	−0.03 (0.82)
Sex	−0.48 (0.24)	−0.20 (0.05)*	0.25 (0.20)	0.14 (0.21)
BMI	0.03 (0.02)	0.13 (0.24)	0.00 (0.02)	0.00 (0.99)
Total # prescribed meds	−0.05 (0.04)	−0.14 (0.20)	0.00 (0.03)	0.00 (0.99)
Depressive symptoms	0.03 (0.02)	0.16 (0.09)	−0.01 (0.02)	0.03 (0.74)
IL-6	−0.10 (0.51)	−0.02 (0.85)	−0.37 (0.42)	−0.11 (0.39)
IL-8	0.28 (0.71)	0.04 (0.70)	−0.06 (0.58)	−0.01 (0.92)
IL-10	−0.38 (0.49)	−0.08 (0.45)	−0.03 (0.41)	−0.01 (0.95)
TNF-α	−2.62 (1.18)	−0.24 (0.03)*	0.43 (0.98)	0.05 (0.66)
CRP	0.52 (0.34)	0.20 (0.13)	0.13 (0.29)	0.07 (0.650
E-Selectin	−0.81 (0.65)	−0.13 (0.22)	0.12 (0.53)	0.03 (0.82)
ICAM-1	−0.36 (0.64)	−0.06 (0.58)	0.09 (0.52)	0.02 (0.87)
Fibrinogen	−3.01 (1.65)	−0.22 (0.07)	−1.40 (1.38)	−0.14 (0.31)
F	2.32**		0.39	
R^2	0.23		0.05	

Note: *<0.05, **<0.01, ***<0.001. ER: Emotion Regulation; BMI: Body Mass Index; IL: interleukin; TNF-α: tumor necrosis factor-α; CRP: C-reactive protein; ICAM-1: Intercellular Adhesion Molecule-1.

(Baune et al., 2008). Overall, these observations may partly explain our current results, suggesting that an ideal level of activation of a particular TNF-α sub-type may correlate with optimal cognitive performance. Future research should investigate potential optimal levels of TNF-α in both immunologically impaired and unimpaired populations in relation to cognition, including adaptive ER use.

Our results showed no relationships between cognitive reappraisal use and inflammatory biomarker levels. Prior studies assessing this link have yielded inconsistent results. While greater cognitive reappraisal use has been associated with lower inflammatory biomarker levels (Appleton et al., 2013; Brown et al., 2020), other studies have shown no relationship (Ellis et al., 2019; Khan et al., 2020; Lopez et al., 2020). Possible explanations for this inconsistency may relate to sample size and characteristics, the manner in which inflammatory biomarkers are extracted (peripheral blood vs. nasal shedding), the specific inflammatory markers assessed, and lack of relevant covariates in statistical models. Future studies should aim to address these discrepancies.

Our results should be considered in light of a number of limitations in the present study. First, given the use of a small sample of convenience, our results should be considered exploratory. As this was a cross-sectional study, causality cannot be inferred. Given our and prior results of significant demographic covariates (e.g., age and sex), larger samples must be employed to assess the impact of mediators on ER, as well as assessing a broader range of inflammatory markers. Related to demographics, only 78 individuals of our subsample (N = 117) elected to report their race and educational status; therefore, the actual demographic breakdown of race and education remains unclear. While this explains why we did not include these variables as covariates in our correlation and regression analyses, future studies must account for these factors, given that previous literature suggests differential inflammation levels as a function of race (Stepanikova et al., 2017) and level of education (Friedman and Herd, 2010). There is also the possibility of reporting bias when using self-report assessments, such that participants' perceptions on how they generally regulate their emotions differs on their actual daily ER use. ER was not recorded on the same day as their blood draw for inflammatory assessment; future research should collect repeated assessments of ER during daily life and emotion-eliciting situations to examine whether specific ER-strategy use is linked to concurrent or subsequent changes in inflammation. Additionally, our sample skewed older, with 18 out of 44 women indicating

menopause as their current menstrual status. As menopause has been characterized by an increase in pro-inflammatory biomarkers attributed to estrogen deprivation (Gameiro et al., 2010), menstrual status must be considered in subsequent studies. Finally, given the current study's exploratory nature, corrections were not made for performing multiple statistical tests.

In summary, our results offer further evidence for a relationship between inflammation levels and ER, specifically between TNF-α and expressive suppression ER-strategy use. Understanding the underlying etiological mechanisms of adaptive ER is crucial for promoting improved physical and mental well-being. For example, chronic experience of negative emotions has been linked to a range of diseases such as cancer, infectious and autoimmune diseases, whose onset and course may be impacted by the immune system (Kiecolt-Glaser et al., 2002). Relatedly, maladaptive regulation of emotions, particularly persistent use of expressive suppression has been linked to a spectrum of disorders such as cardiovascular disease, chronic pain, arthritis and cancer (Panagopoulou et al., 2002), with one possible explanation for this relationship pointing towards altered immune response (Ellis et al., 2019). Indeed, the recent field of psychoneuroimmunology aims to discover the pathways through which negative emotionality and maladaptive ER influences physical health via altered immune functioning (Renna, 2021). Failure to adequately regulate ones' emotions perpetuates negative affective experience, which prolongs physiological activation and heightened immune levels, thereby increasing the risk of long-term health problems. Therefore, future research aiming to improve well-being may develop pharmacological and/or psychotherapeutic interventions that may dually target both enhanced immune response as well as effective ER.

Declaration of competing interest

All authors report no conflict of interests.

Data availability

Data will be made available on request.

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Appendix A. List of Abbreviations

Abbreviation	Definition
BMI	Body Mass Index
CESD	Center for Epidemiological Studies Depression Inventory
CNS	Central Nervous System
CRP	C-reactive protein
ER	Emotion Regulation
ERQ	Emotion Regulation Questionnaire
ICAM-1	Intercellular Adhesion Molecule-1
IL-2	Interleukin-2
IL-6	Interleukin-6
IL-8	Interleukin-8
IL-10	Interleukin-10
IFN-γ	Interferon-γ
MIDUS	Midlife in the United States
TNF-α	Tumor Necrosis Factor-α

References

Appleton, A.A., Buka, S.L., Loucks, E.B., Gilman, S.E., Kubzansky, L.D., 2013. Divergent associations of adaptive and maladaptive emotion regulation strategies with inflammation. Health Psychol. 32 (7), 748.

Appleton, A.A., Loucks, E.B., Buka, S.L., Kubzansky, L.D., 2014. Divergent associations of antecedent-and response-focused emotion regulation strategies with midlife cardiovascular disease risk. Ann. Behav. Med. 48 (2), 246–255.

Baune, B.T., Wiede, F., Braun, A., Golledge, J., Arolt, V., Koerner, H., 2008. Cognitive dysfunction in mice deficient for TNF-and its receptors. Am. J. Med. Genet. Part B: Neuropsychiatric Genetics 147 (7), 1056–1064.

Brown, R.L., Shahane, A.D., Chen, M.A., Fagundes, C.P., 2020. Cognitive reappraisal and nasal cytokine production following experimental rhinovirus infection. Brain, Behavior, & Immunity-Health 1, 100012.

Chapman, B.P., Fiscella, K., Kawachi, I., Duberstein, P., Muennig, P., 2013. Emotion suppression and mortality risk over a 12-year follow-up. J. Psychosom. Res. 75 (4), 381–385.

Ellis, E.M., Prather, A.A., Grenen, E.G., Ferrer, R.A., 2019. Direct and indirect associations of cognitive reappraisal and suppression with disease biomarkers. Psychol. Health 34 (3), 336–354.

Fischer, R., Maier, O., 2015. Interrelation of oxidative stress and inflammation in neurodegenerative disease: role of TNF. Oxid. Med. Cell. Longev. 2015, 1–18. https://doi.org/10.1155/2015/610813, 610813.

Friedman, E.M., Herd, P., 2010. Income, education, and inflammation: differential associations in a national probability sample (the MIDUS study). Psychosom. Med. 72 (3), 290.

Gameiro, C.M., Romão, F., Castelo-Branco, C., 2010. Menopause and aging: changes in the immune system—a review. Maturitas 67 (4), 316–320.

Gross, J.J., 1998. Antecedent-and response-focused emotion regulation: divergent consequences for experience, expression, and physiology. J. Pers. Soc. Psychol. 74 (1), 224.

Gross, J.J., 2015. Emotion regulation: current status and future prospects. Psychol. Inq. 26 (1), 1–26.

Gross, J.J., John, O.P., 2003. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. J. Pers. Soc. Psychol. 85 (2), 348.

Gross, J.J., Levenson, R.W., 1997. Hiding feelings: the acute effects of inhibiting negative and positive emotion. J. Abnorm. Psychol. 106 (1), 95.

Hu, T., Zhang, D., Wang, J., Mistry, R., Ran, G., Wang, X., 2014. Relation between emotion regulation and mental health: a meta-analysis review. Psychol. Rep. 114 (2), 341–362.

Jung, Y.H., Shin, N.Y., Jang, J.H., Lee, W.J., Lee, D., Choi, Y., Choi, S.H., Kang, D.H., 2019. Relationships among stress, emotional intelligence, cognitive intelligence, and cytokines. Medicine 98 (18).

Khan, A.J., O'Donovan, A., Neylan, T.C., Gross, J.J., Cohen, B.E., 2020. Suppression, but not reappraisal, is associated with inflammation in trauma-exposed veterans. Psychoneuroendocrinology 122, 104871.

Kiecolt-Glaser, J.K., McGuire, L., Robles, T.F., Glaser, R., 2002. Psychoneuroimmunology: psychological influences on immune function and health. J. Consult. Clin. Psychol. 70 (3), 537.
Kogan, S., Ospina, L.H., Kimhy, D., 2018. Inflammation in individuals with schizophrenia–Implications for neurocognition and daily function. Brain Behav. Immun. 74, 296–299.
Lopez, R.B., Brown, R.L., Wu, E.L.L., Murdock, K.W., Denny, B.T., Heijnen, C., Fagundes, C., 2020. Emotion regulation and immune functioning during grief: testing the role of expressive suppression and cognitive reappraisal in inflammation among recently bereaved spouses. Psychosom. Med. 82 (1), 2–9.
Love, G.D., Seeman, T.E., Weinstein, M., Ryff, C.D., 2010. Bioindicators in the MIDUS National Study: Protocol, Measures.
Mauss, I.B., Cook, C.L., Cheng, J.Y., Gross, J.J., 2007. Individual differences in cognitive reappraisal: experiential and physiological responses to an anger provocation. Int. J. Psychophysiol. 66 (2), 116–124.
McAfoose, J., Baune, B.T., 2009. Evidence for a cytokine model of cognitive function. Neurosci. Biobehav. Rev. 33 (3), 355–366.
Mennin, D.S., Heimberg, R.G., Turk, C.L., Fresco, D.M., 2005. Preliminary evidence for an emotion dysregulation model of generalized anxiety disorder. Behav. Res. Ther. 43 (10), 1281–1310.
Ospina, L.H., Beck-Felts, K., Ifrah, C., Shagalow, S., Lister, A., Russo, S.J., Gross, J.J., Kimhy, D., 2021. Relationships among inflammation, social cognition, and social functioning in schizophrenia. Schizophr. Res. S0920–S9964.
Otto, L.R., Sin, N.L., Almeida, D.M., Sloan, R.P., 2018. Trait emotion regulation strategies and diurnal cortisol profiles in healthy adults. Health Psychol. 37 (3), 301.
Panagopoulou, E., Kersbergen, B., Maes, S., 2002. The effects of emotional (non-) expression in (chronic) disease: a meta-analytic review. Psychol. Health 17 (5), 529–545.
Powers, A., Michopoulos, V., Conneely, K., Gluck, R., Dixon, H., Wilson, J., Jovanovic, T., Pace, T.W., Umpierrez, G.E., Ressler, K.J., Bradley, B., 2016. Emotion dysregulation and inflammation in African-American women with type 2 diabetes. Neural Plast. 2016.
Radloff, L.S., 1997. Scale: a self-report depression scale for research in the general population. J. Clin. Exp. Neuropsychol. 19, 340–356.
Renna, M.E., 2021. A review and novel theoretical model of how negative emotions influence inflammation: the critical role of emotion regulation. Brain, Behavior, & Immunity-Health 18, 100397.
Rubel, C., Fernández, G.C., Dran, G., Bompadre, M.B., Isturiz, M.A., Palermo, M.S., 2001. Fibrinogen promotes neutrophil activation and delays apoptosis. J. Immunol. 166 (3), 2002–2010.
Ryff, C.D., Davidson, R.J., 2010. Midlife in the United States (MIDUS 2): Neuroscience Project, 2004–2009 [Data file].
Ryff, C.D., Seeman, T., Weinstein, M., 2021. Midlife in the United States (MIDUS 2): Biomarker Project, 2004-2009 (ICPSR 29282).
Saraiva, M., O'garra, A., 2010. The regulation of IL-10 production by immune cells. Nat. Rev. Immunol. 10 (3), 170–181.
Stepanikova, I., Bateman, L.B., Oates, G.R., 2017. Systemic inflammation in midlife: race, socioeconomic status, and perceived discrimination. Am. J. Prev. Med. 52 (1), S63–S76.
Van de Stolpe, A., Van der Saag, P.T., 1996. Intercellular adhesion molecule-1. J. Mol. Med. 74 (1), 13–33.
Williams, D.P., Cash, C., Rankin, C., Bernardi, A., Koenig, J., Thayer, J.F., 2015. Resting heart rate variability predicts self-reported difficulties in emotion regulation: a focus on different facets of emotion regulation. Front. Psychol. 6, 261.
Zelová, H., Hošek, J., 2013. TNF-α signalling and inflammation: interactions between old acquaintances. Inflamm. Res. 62 (7), 641–651.