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A systematic review of associations between emotion regulation characteristics and inflammation

Daniel P. Moriarity[a,*], **Mora M. Grehl**[b], **Rachel F.L. Walsh**[b], **Lydia G. Roos**[a], **George M. Slavich**[a], **Lauren B. Alloy**[b]

[a]Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, USA

[b]Department of Psychology & Neuroscience, Temple University, USA

Abstract

Elevated inflammation is a risk factor for many psychiatric (e.g., depression) and somatic conditions (e.g., rheumatoid arthritis). Inflammation is influenced by psychosocial processes such as emotion regulation. Characterization of which emotion regulation characteristics impact inflammation could help refine psychosocial interventions aimed at normalizing health-harming inflammatory activity for individuals with psychiatric and somatic illnesses. To investigate this issue, we systematically reviewed the literature on associations between a variety of emotion regulation traits and inflammation. Out of 2816 articles identified, 38 were included in the final review. 28 (74%) found that (a) poor emotion regulation is associated with higher inflammation and/or (b) strong emotion regulation skills are associated with lower inflammation. Consistency of results differed as a function of the emotion regulation construct investigated and methodological characteristics. Results were most consistent for studies testing positive coping/social support seeking or broadly defined emotion regulation/dysregulation. Methodologically, studies testing reactivity to a stressor, adopting a vulnerability-stress framework, or using longitudinal data were most consistent. Implications for integrated, transdiagnostic psychoimmunological theories are discussed, as well as recommendations for clinical research.

Keywords

Emotion regulation; Inflammation; Stress; Immunology; Health

1. Introduction

Inflammation is a transdiagnostic correlate of many medical and psychiatric conditions (Dantzer et al., 2008; Michopoulos et al., 2016; Pearson et al., 2003; Saccaro et al., 2021; Sattar et al., 2003). Further, evidence suggests that inflammation has a causal

*Corresponding author. dmoriarity@mednet.ucla.edu (D.P. Moriarity).

Declaration of Competing Interest

None.

Appendix A. Supporting information

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effect on some of these health outcomes including depression (Capuron and Miller, 2004; Knight et al., 2022; Kuhlman et al., 2018; Moriarity, Kautz et al., 2020), ulcerative colitis (Ek et al., 2021), and osteoarthritis (Ek et al., 2021), positioning it to be a potentially important treatment target for a variety of disorders. Although inflammation-modulating biological treatments such as non-steroidal anti-inflammatory drugs, interferon-α therapy, and minocycline generally are considered primary interventions for inflammation-mediated conditions, psychosocial interventions such as cognitive-behavior therapy (CBT) and mindfulness meditation also have been shown to influence inflammatory biology (Black and Slavich, 2016; Shields et al., 2020). Inflammatory malleability to these biological and psychological interventions affords patients who suffer from inflammation-mediated disorders flexibility in treatment options. For example, biological interventions might be a useful adjunctive when individuals with both depression and elevated inflammation are struggling with the cognitive demands required to engage in evidence-based psychotherapy. Conversely, individuals for whom anti-inflammatory medications are contraindicated—or who refuse medication for other reasons—may benefit from psychosocial interventions (Shields et al., 2020).

Yet, the mere understanding that psychosocial interventions (e.g., cognitive-behavioral therapies) influence inflammation is insufficient to maximize therapeutic impact. It is necessary to explore which treatment targets of extant psychosocial interventions actually affect inflammatory biology. A nuanced understanding of which specific characteristics of psychosocial treatments reduce inflammation would have direct implications for treating inflammation-mediated mental and physical health problems and could help advance precision medicine approaches aimed at reducing risk for these conditions. Further, this work would integrate inflammatory mechanisms into existing, psychosocially oriented theories of psychiatric risk and resilience, which would guide theory development (Moriarity, 2021) and advance understanding of many complex, multifactorial health conditions.

Increasing the quantity and quality of emotion regulation skills, and decreasing emotional reactivity, is a shared goal of many psychotherapies (e.g., CBT, dialectical behavioral therapy, acceptance and commitment therapy), as strengthening emotion regulation aptitude can reduce distress in various areas of psychosocial functioning (Beatty et al., 2016; Ma and Fang, 2019). Indeed, skillful emotion regulation is associated with improved communication and social relationship functioning overall (Vater and Schröder, Abé, 2015). Additionally, individuals with advanced emotion regulation also are better able to select strategies that best align with their goals within the situational context (English et al., 2017). Given that inflammatory biology is reactive to increases in negative affect such as anger or anxiety (Carroll et al., 2011), it is plausible that improved emotion regulation also could influence inflammatory biology.

In fact, there are several extant theories/models implicating emotion regulation as a modulator of inflammation. The perseverative cognitions hypothesis is not specific to inflammation, but describes how perseverative (e.g., rumination, worry) reactions to unpleasant situations or emotions can simultaneously amplify the magnitude and duration of the physiological stress response-exacerbating downstream consequences for basal stress

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biology (Brosschot et al., 2006). Our team has extended this work to include cognitive vulnerabilities more generally in an immunocognitive model of psychopathology (Moriarity et al., 2018)-attempting to clarify discrepant results in stress/arousal→inflammation research by including emotion-modulating cognitive vulnerabilities as a moderator of this association. Others have described emotion regulation traits/abilities as a mediator of the negative emotionality→inflammation pathway (Renna, 2021) and suggested the possibility of bidirectional feedback loops between negative emotions, inflammation, and health outcomes. Although comprehensive tests of bidirectional relationships are lacking in this area, there is evidence from studies involving experimentally-administered endotoxin that inflammatory activity might increase negative reactivity (Dooley et al., 2018) and that certain health sequelae of inflammation (e.g., depression) are also predictive of future increases in inflammation (Moriarity, Kautz et al., 2020).

A few reviews have explored the association between emotion regulation and inflammation for specific emotion regulation constructs (e.g., see Szabo et al., 2022 for a scoping review on rumination and inflammation), but there have been no attempts to systematically review how a wide variety of emotion regulation characteristics are related to inflammatory biology. Given the range of both emotion regulation characteristics and inflammatory proteins, a systematic review of the associations between these two constructs is an important contribution to the field insofar as it would point to the therapeutic processes that are most relevant for reducing inflammation, a key health-damaging process. This is especially important given that the identification of cognitive targets that impact inflammatory biology could lead to the development of more precise psychological interventions for a variety of inflammation-mediated health outcomes (Moriarity, 2021).

We addressed this need by systematically reviewing for the first time all of the available evidence for associations between various emotion regulation characteristics and circulating inflammatory proteins in clinical (i.e., medical and psychiatric) and nonclinical samples. In addition to identifying which emotion regulation characteristics are associated with inflammatory biology, we assessed contextual factors that might influence the presence or absence of theoretically consistent associations to the extent possible (e.g., emotion regulation tested as a moderator of arousal-related characteristics and inflammation, emotion regulation as a trait vs. in the context of acute stress). Then, we used the reviewed evidence to formulate recommendations for clinical practice, and the integration of inflammation into theories of emotion regulation and psychopathology.

2. Method

2.1. Transparency and openness

This study was pre-registered (PROSPERO study protocol: CRD42021253574; link: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=253574) and conducted in accordance with PRISMA 2020 guidelines for systematic reviews (Page et al., 2021).

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2.2. Search strategy and selection criteria

Several steps were used to identify and assess relevant articles for inclusion in this systematic review. First, PubMed and PsycInfo were searched for articles written in English and published until June 16th, 2022. Specific search terms are reported in Supplemental Table 1 and were filtered for human samples and articles available in English. One notable term that we did not include was “mindfulness”, given that the goal of mindfulness is to *notice* emotional states (among other things) rather than directly regulate them. Relatedly, broad-based immune terminology (e.g., “immune”, “immune response”, “immune activation”) were not included to ensure a focused review on inflammatory biology–streamlining attempts to connect the results of this review to specific clinical processes. Duplicate articles were removed. Then, abstracts and titles were screened for exclusion criteria. Studies passing this step had their full texts reviewed for inclusion criteria. To be included, studies had to be (1) empirical (i.e., no reviews), (2) based on human samples, (3) specifically test the association between a facet of emotion regulation and levels of inflammatory proteins (e.g., no gene expression or LPS-stimulated proteins), (4) not retracted, (5) devoid of critical analytic flaws (in the case that only some tests in a study were critically flawed, the appropriately conducted analyses are reported), and (6) published in a peer-reviewed academic journal (e.g., no pre-prints or unpublished theses/dissertations). If additional relevant articles were identified during the full-text review process, these steps were repeated to determine if the article should be included in the review.

Given the small number of studies testing the associations between identical emotion regulation measures + biomarkers, as well as a variety of other methodological disparities between studies (e.g., duration of assessment lags in longitudinal or experimental research, sample health characteristics, sample developmental stage, whether inflammatory proteins were measured in blood or saliva), it was determined that a quantitative meta-analysis would be inappropriate and risk contributing to growing concerns about lack of meta-analytic replicability (Sotola, 2022). To illustrate, the most popular protein in this review is CRP assayed in blood (23 studies) and the most common temporal design with CRP was cross-sectional (13 studies). Of these 13, the most popular emotion regulation construct was cognitive reappraisal (4 studies). Of these 4 studies only 3 used the same measure and all three featured fundamentally different samples (community adult, community adolescent, trauma-exposed veterans). Meta-analysis is an important tool for scientific advancement and we would rather stick to a narrative review that provides space for a detailed look into potential drivers of differing results (e.g., emotion regulation construct, longitudinal vs. cross-sectional designs) instead of potentially collapsing studies where different effect sizes are plausible. Hopefully this systematic review inspires more research on this topic so that the literature grows to a point that a meta-analysis would be more methodologically sound.

2.3. Data extraction

Study characteristics were independently extracted from the reviewed articles by three authors, and discrepancies were resolved by consensus discussion including all authors. The information extracted was sample size, sample characteristics (e.g., community, clinical), study design (e.g., cross-sectional, longitudinal, acute laboratory stressor), emotion regulation constructs, inflammatory proteins, inflammatory protein measurement method

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(i.e., blood, saliva, or sweat), results, test statistics and standardized effect sizes (when available), and covariates.

3. Results

The literature search identified 2816 articles. After exclusion of duplicates and irrelevant articles based on screening titles and abstracts, 67 full-text articles were screened, resulting in 38 studies included in the systematic review (see Fig. 1 for PRISMA flowchart outlining the study selection process). All included studies are systematically summarized in Table 1. Results are organized in the following subsections: emotion regulation (broadly defined), negative affectivity/emotional reactivity, emotional expression/suppression, perseverative cognitions and distraction/disengagement, cognitive reappraisal, and positive coping and support-seeking. Studies that tested several relevant emotion regulation constructs are described in multiple sections. For ease-of-reading, only significant associations (other than studies that only had null results) are highlighted below, but all relevant significant and null results are reported (with standardized effect sizes and metrics of significance, to the extent available) in Table 1.

3.1. Study characteristics

Of the studies included in this review, 19 included cross-sectional data, 13 included longitudinal data, 8 included acute stressors, and 4 qualified as experimental designs. Twenty-six featured community samples, whereas the remaining 12 featured clinical samples (6 medical, 5 psychiatric, 1 combined medical and psychiatric). Regarding the assessment of inflammatory proteins, 34 studies used blood, 3 used saliva, and 1 used sweat. Only 6 studies featured nonadult samples (5 adolescent, 1 preschool-aged).

To provide structure for this review, seven emotion regulation categories were created. First, “Emotion Regulation/Dysregulation” describes results using measures that claimed to broadly capture the ability, or inability, to adaptively regulate emotions. The rest of the categories pertain to more specific emotion regulation skills/traits/strategies. Second, “Negative Affectivity/Emotional Reactivity”, includes studies evaluating (often through the use of mood-induction tasks) individual differences in the magnitude of emotional responses. Although these characteristics are theoretically different from regulation, we believe they are important to include in this review both because (a) they illustrate the inflammatory correlates of the emotional reactions that regulation traits modulate and (b) they are a marker of how successful an individual is at regulating their emotions. Third, “Expressive Suppression vs. Emotional Expression” describes studies investigating the tendency to keep emotions bottled up and away from others vs. openly communicating them. Fourth, “Cognitive Reappraisal” includes studies evaluating individuals’ ability or tendency to attempt to reframe stressful situations and/or negative emotions in a more neutral or positive light. Fifth, “Perseverance vs. Distraction/Disengagement” describes studies testing tendencies to ruminate or worry about stressful situations/emotions or, the inverse, to seek opportunities for disengagement from negative situations and emotions. Sixth, “Psychological Flexibility” covers research on either “psychological flexibility”—the ability to live in the present and change or persist behaviors aligned with values instead

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of emotions)—or its subcomponents such as acceptance of positive and negative aspects of life. Finally, "Positive Coping/Social Support Seeking" includes several studies of emotion regulation strategies commonly seen as adaptive (although this is influenced by the context of the stressor in question, discussed in further detail in the Discussion section).

3.2. Emotion regulation/dysregulation

Five studies investigated emotion regulation broadly. Difficulties with global emotion regulation were consistently associated with higher CRP in a mixed sample of adults with and without ADHD (Yang et al., 2020). When emotion regulation subscales were probed in this study, CRP was related specifically to limited access to effective emotion regulation strategies. A similar positive association between emotional dysregulation and CRP was observed in a small sample of Black American women with diabetes (Powers et al., 2016). Two studies from the New England Family Study corroborate this finding with a related construct called "inappropriate self-regulation" (reflecting emotional functioning in children whose behavior was unrestrained and impulsive) in childhood predicting adult inflammatory outcomes. Children with higher inappropriate self-regulation had higher CRP as adults (Appleton et al., 2011) and this association was stronger for participants who grew up in families with lower income (Appleton et al., 2012). Counter to hypotheses, a study of low-income preschoolers found that stronger parent-reported emotion regulation skills were associated with higher TNF-α cross-sectionally (Miller et al., 2013). It is worth noting that this study was the smallest (n = 34) and it is possible that such young participants may not have experienced enough cumulative emotionally-triggered inflammatory responses to shift their inflammatory baseline. Further, this also was the only study on this topic to not include covariates; therefore, it is possible that untested confounds drove this unexpected result. Finally, if socioeconomic status is an important moderator of the relation between emotion regulation and inflammatory proteins in children, restricting this sample to low-income children might have reduced the variability in the variables analyzed, influencing results via Berkson's bias (i.e., conditioning sample recruitment based on levels of an analyzed variable).

3.3. Negative affectivity/emotional reactivity

Ten of the studies reviewed analyzed the associations between intensity of negative emotional responses and inflammatory proteins. The above-referenced investigations from the New England Family Study also evaluated emotional reactivity in the form of temperamental "distress proneness" (i.e., the tendency to be emotionally labile and easy to frustrate) in children significantly predicting adult CRP concentrations (Appleton et al., 2011), which was stronger for children in low- and middle-income families relative to their high-income peers (Appleton et al., 2012). Further, parallel to the results with perceived emotion regulation broadly, the above-referenced study of pre-school aged children found that higher negative lability predicted elevated TNF-α cross-sectionally (Miller et al., 2013). Negative affectivity also was associated with higher TNF-α in a study of the immunological correlates of "Type D personality" (defined as a combination of negative affectivity and tendency to inhibit emotional expression in social situations) in men with congestive heart failure (Denollet et al., 2003). Elevated emotional reactivity also was associated with higher levels of CRP in euthymic patients with bipolar disorder using

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both continuous methods (Dargél et al., 2017) and clinical cut-offs (Dargél et al., 2020) of emotional reactivity. However, two of the cross-sectional studies with clinical samples found null associations. One case-control study of posttraumatic stress disorder (PTSD)—in which all participants, regardless of whether they had PTSD, had mechanical injuries to extremities—found no association between emotional reactivity and five inflammatory proteins (Gierlotka et al., 2015). Similarly, a study of patients with rheumatoid arthritis found no association between emotional orientation (described as attending to, valuing, and experiencing emotions intensely) and IL-6 (van Middendorp et al., 2005).

Two of the studies reviewed tested associations between acute emotional reactivity and inflammatory proteins. The first, a case-control study of females with major depressive disorder (MDD) found that increased sadness reactivity during a sadness induction predicted greater IL-18 increases in controls but not participants with MDD (Prossin et al., 2011). The lack of association in participants with MDD might have been due to ceiling effects because individuals with MDD had higher IL-18 and negative affect compared to controls at baseline and the sample was small (n = 12 per group). Another study found negative affect post-Trier Social Stress Test was associated with greater IL-6, IL-1β, and TNF-α, but emotional reactivity to an angry autobiographical memory recall was not associated with any of these three proteins (Newton et al., 2017). Importantly, both studies randomized participants to a distraction group or a resting group to create the opportunity for rumination.

3.4. Expressive suppression vs. emotional expression

Twelve articles evaluated the association between tendencies to either express or suppress emotions and inflammatory biology. A cross-sectional study using data from the New England Family Study found that adults reporting higher levels of expressive suppression had higher levels of CRP (Appleton et al., 2013). Similarly, expressive suppression was positively associated with CRP and fibrinogen in trauma-exposed veterans (Khan et al., 2020), IFN-γ and TNF-α in recently bereaved spouses (Lopez et al., 2020), and TNF-α in men with congestive heart failure (contextualized as “Type D” personality, as described in the study above; Denollet et al., 2003). Two studies evaluated expressive suppression as a moderator of childhood adversity. The first observed null main effects of expressive suppression on changes in CRP and IL-6 but found that expressive suppression interacted with childhood abuse such that expressive suppression amplified the positive association between child abuse and increases in CRP and IL-6 (Jones et al., 2022). The second explored whether expressive suppression also interacted with chronic family stress, which was not supported in a separate cross-sectional dataset (Jones et al., 2018). The rheumatoid arthritis study described above also did not find associations between IL-6 and subcategories of emotion regulation related to ambivalence or resistance to expressing emotions (van Middendorp et al., 2005).

Consistent with evidence that suppressing emotions might elevate inflammatory profiles, several studies indicated that processing and expressing emotions is associated with lower levels of circulating inflammatory proteins. For example, a small longitudinal study of men who had undergone radical prostatectomy or radiation therapy for prostate cancer in the previous two years found that higher emotional processing predicted lower IL-6 four

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months later (Hoyt et al., 2013). One study randomized dyads of married men and women to "conflict" or "no conflict" discussion with their partner and assessed changes in IL-6 and TNF-α over 24 h. Higher cognitive processing word use, an indicator of emotion regulation, during conflictual conversation was associated with less steep IL-6 increases 24-hours post-discussion (Graham et al., 2009). However, another acute stressor study found no associations between a related construct, trait "emotion approach coping" (described as a combination of purposeful emotional processing and emotional expression), and changes in salivary IL-6 (Master et al., 2009). It is important to note that this study was small ($n = 22$) and that emotional approach coping was measured at a different study visit than the stressor and inflammation measurements (the study provided no information on the average length of time between these visits), which may play a role in the lack of association observed. Interestingly, two studies from the same sample suggested that the association between some emotional regulation characteristics and inflammatory biology might be sex-specific and might also differ between cross-sectional and longitudinal modeling approaches. A cross-sectional analysis for the INTERHEART study found null gender-stratified associations for a variety of emotion regulation-CRP associations (including emotional expression; Shimanoe et al., 2014); however, a later longitudinal analysis using the same data found that higher emotional expression was associated with less CRP over time in women (Shimanoe et al., 2018).

3.5. Cognitive reappraisal

Nine studies tested whether positive cognitive reappraisal, the technique of reinterpreting emotionally arousing situations to reduce negative emotions, is associated with inflammatory biology. The cross-sectional New England Family study that found that expressive suppression was associated with higher CRP also found that the tendency to positively reappraise negative scenarios was associated with lower CRP (Appleton et al., 2013). A longitudinal sample observed consistent findings, with higher cognitive reappraisal being associated with decreases in IL-6, but not CRP, over time (Jones et al., 2022). A related construct, "shift-and-persist" (a combination of reappraisal and hopefulness/purpose), was associated with lower CRP and IL-6 (modeled as a composite) in adolescents but not parents (Chen et al., 2015). Conversely, no evidence of a direct association between cognitive reappraisal and inflammatory proteins (including CRP) was found in a study of recently bereaved spouses (Lopez et al., 2020), a large community sample (Shimanoe et al., 2014), or a sample of trauma exposed veterans (Khan et al., 2020), all of which were cross-sectional.

Five studies evaluated cognitive reappraisal as a moderator to buffer stress or stress-generative characteristics. Similar to the pattern of results for emotional expression in the INKHEART study described above, cognitive reappraisal did not interact with stress to predict CRP in cross-sectional data (Shimanoe et al., 2014), but this interaction was significant when predicting change in CRP over time (Shimanoe et al., 2018). Specifically, cognitive reappraisal buffered the risk that elevated stress in the past year had on longitudinal changes in CRP for men. Cognitive reappraisal also buffered the association between childhood neglect on change in IL-6 and CRP as well as the relation between childhood abuse and trauma on IL-6 (Jones et al., 2022). Lower cognitive reappraisal

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(focused on health-related cognitions) also interacted with an inability to disengage from unattainable goals (but not the capacity to re-engage with goals) to be associated with elevated CRP in female breast cancer survivors (Castonguay et al., 2014). Finally, cognitive reappraisal was not a moderator of the cross-sectional relation between chronic family stress and CRP in a community sample (Jones et al., 2018).

3.6. Perseverance vs. distraction/disengagement

The most commonly assessed emotion regulation characteristics were related to perseverative cognitive styles. Interestingly, all four studies that tested main effects between perseverative cognitive styles and inflammatory biology in observational data (cross-sectional or gender-stratified analyses in longitudinal data) found null results (Gierlotka et al., 2015; Knight et al., 2022; Ysseldyk et al., 2018) and one study found associations in the opposite direction than hypothesized (Segerstrom et al., 2017). With respect to the latter, this study also found a significant interaction between repetitive thoughts and verbal IQ predicting IL-6 in an unexpected direction. Specifically, IL-6 was relatively stable for those with higher IQs, regardless of repetitive thought, but was negatively associated with repetitive thought at lower IQ levels. Notably, the average IQ of the sample was almost 1 standard deviation higher than would be expected (IQ tests are normed to have a mean of 100 and SD of 15). Additionally, as part of an exploratory analysis, a quadratic relation between rumination and IQ was found such that the inverse association between repetitive thought and IL-6 was strongest at lower levels of repetitive thought.

Three studies that measured acute inflammatory reactivity to acute laboratory stressors found results more consistent with theory that perseverative thoughts about negative situations and emotions would increase levels of inflammatory proteins. One study of female college undergraduates who completed a social stress task found that random assignment to an instructed rumination condition led to steeper increases in CRP compared to an instructed distraction condition (Zoccola et al., 2014). A different study using a social stressor that randomized some participants to a rest condition to make the opportunity for rumination or a distraction condition found that although no group difference was observed, higher trait rumination was associated with increases in salivary IL-6 after a social stressor (Newton et al., 2017). The total number of people in the rest condition who reported ruminating in post-stressor assessments was low (8 out of 45 people), which might have attenuated observable group-level effects relative to studies that instructed participants to ruminate. This publication also featured a second study with an angry autobiographical memory stressor and randomization to the same conditions and found that the rest/rumination group experienced steeper increases in IL-1β relative to the distraction condition. The final experiment randomly assigned textile handcrafters to: (a) a writing exercise designed to induce rumination, (b) a neutral ego contemplation, or (c) textile art making (hypothesized to be a positive emotional experience) after instructed recall of an upsetting memory (Collier et al., 2016). Significant increases in IL-1β only were observed in the rumination condition.

Several of the studies by the authors of this review investigated perseverative thinking styles as moderators of the relation between arousal-modulating characteristics and inflammatory biology in a vulnerability-stress conceptualization. For example, a more perseverative

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cognitive response style ratio (quantified as rumination/[distraction + problem-solving]) amplified the relation between reward drive (the domain of reward functioning related to intensity and arousal in the pursuit of rewards) and increases in IL-6 (but not IL-8) to a social stress task (Moriarity et al., 2020b). When this interaction was followed-up with an investigation of individual cognitive styles, all 3 subscales interacted with reward drive to predict change in IL-6. Specifically, high rumination amplified the association between reward drive and increases in IL-6 (the other subscale results are described in thematically appropriate sections, below). Another study in a community sample of adults selected for high or moderate reward sensitivity found that self-focused rumination aimed to promote positive affect interacted with high reward sensitivity to predict IL-8 (Moriarity et al., 2020a). Conversely, higher levels of perseverative thought aimed at dampening positive affect interacted with low reward sensitivity to predict higher CRP. Finally, in the same sample of adolescents as the first study of this paragraph, higher rumination amplified the association between baseline anxiety symptoms and increases in IL-6 (but not CRP) over time (Moriarity et al., 2018). Further, data supported a moderated mediation in which changes in IL-6 partially mediated the association between baseline anxiety and changes in depression and this indirect effect was amplified in adolescents who tend to ruminate on negative affect. Another study from a different research team found that low levels of repetitive negative thinking interacted with higher socioeconomic status (SES) to predict less IL-6 in a longitudinal sample of pregnant women (Mitchell & Christian, 2019).

Finally, some studies evaluated tendencies to disengage from perseverative cognitions as a protective factor against elevated inflammation. For example, a small study of adult women featuring a social stress task followed by either 5 min of directed rumination or distraction found that trait reflection, a characteristic of “intellectual self-attentiveness” described as an emotionally-neutral cognition compared to the negative focus of rumination, was negatively associated with change in IL-6 post stressor (Woody et al., 2016). A study in the same sample (referenced above; Zoccola et al., 2014) found that participants in the distraction group had shorter inflammatory spikes that started to return to baseline by the end of the visit (roughly 50 min post-stressor), unlike the rumination group whose IL-6 did not decrease in the timeframe assessed. A separate study pairing an acute stressor (an angry autobiographical memory) with a resting/rumination and distraction condition found that participants in the distraction condition had less steep increases in IL-1β post-stressor (Newton et al., 2017). Further, the tendency to cognitively respond to negative emotion with distraction buffered the positive association between reward drive and increases in IL-6 post-social stressor in adolescents (Moriarity et al., 2020b). The above-referenced cross-sectional study in the INTERHEART cohort found that the tendency to disengage from stressful situations and negative emotions was associated with lower CRP concentrations in men, but not women (Shimanoe et al., 2014). Conversely, a daily diary study in adolescents did not support a hypothesized buffering interaction between various negative life events and disengagement predicting CRP (Low et al., 2013).

3.7. Psychological flexibility

Two studies tested either psychological flexibility or acceptance (a skill that helps foster psychological flexibility). One cross-sectional analysis examining acceptance in a case-

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control study of high-stress caregivers of children with Autism and non-high stress caregivers of neurotypical children did not find significant associations between acceptance and either CRP or IL-6 (Crosswell et al., 2022). Interactions between acceptance and parental stress predicting these proteins were also null. A separate study of overweight or obese, high-stress individuals tested post-Acceptance and Commitment Therapy levels of psychological flexibility (both general and specific to weight-related difficulties) predicting levels of CRP, IL-1 receptor agonist, and adiponectin 6 months later also found null results (Järvelä-Reijonen et al., 2020).

3.8. Positive coping/social support seeking

Several other studies investigated emotion regulation characteristics hypothesized to be negatively associated with inflammatory proteins. For example, the daily diary study described above found that, unlike disengagement, positive engagement coping (the tendency to change focus to positive qualities of life, keep a sense of humor, strategize how to handle the situation, focus on self-improvement) buffered the positive association between (a) conflictual life events, (b) daily interpersonal conflicts/tension, and (c) total negative life events and CRP (Low et al., 2013). Further, one study found that reward drive predicted greater increases in IL-6 post stressor for adolescents with low trait problem solving when feeling negative emotions relative to adolescents with greater proclivities to problem solve (Moriarity et al., 2020). Additionally, adults low in coping self-efficacy (confidence in one's ability to navigate difficult situations through emotion regulation, problem-solving, and social support) had higher TNF-α and IL-10 (Hladek et al., 2020). Finally, high tendency to seek emotional support socially was associated with lower CRP in adults with high levels of perceived stress (Shimanoe et al., 2014).

4. Discussion

This systematic review summarizes the findings of 38 studies that investigated associations between emotion regulation and inflammatory proteins. Broadly, there was support for the hypothesis that emotion regulation abilities are related to differences in inflammatory activity. Specifically, 74% of studies found results consistent with the hypothesis that difficulty regulating emotion was associated with elevated inflammatory biology whereas skillful emotion regulation was associated with lower inflammation. However, the consistency of empirical support differed as a function of the specific aspects of emotion regulation examined and study methodology (Table 2), supporting the decision to not aggregate these studies in a quantitative, meta-analytic review.

Relations between broadly defined emotion regulation/dysregulation and inflammatory proteins were observed in all five articles reviewed, although one of these studies found an association in the direction opposite to hypotheses and results from the other four studies (i.e., better emotion regulation was associated with higher concentrations of inflammatory proteins). Higher negative affectivity and emotional reactivity were associated with elevated levels of inflammatory proteins in eight of 10 studies reviewed. Of the articles testing associations between tendencies to suppress vs. express emotions and inflammatory proteins, five of seven supported the hypothesis that suppressing emotions

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would be related to elevated inflammatory biology; whereas a less convincing proportion (three of five) found that emotional expression was associated with lower concentrations of inflammatory proteins. It is possible that “expressing emotions” is not a specific enough construct to reliably associate with inflammatory outcomes. For example, “expressing emotions” could equally take the form of collaborative, healthy discussion in a productive manner with friends or expressing emotions in a hostile, confrontational manner. Slightly above half (five of nine) of the studies that examined cognitive reappraisal supported an association between reappraisal of negative situations and emotions as a protective factor against higher inflammation. The most common emotion regulation category reviewed was perseverative cognition vs. distraction/disengagement. Of the 14 studies reviewed, ten found evidence for a relation between these emotion regulation characteristics and inflammatory biology, three found null results, and one found results opposite of the hypothesized direction (e.g., more repetitive thought led to lower concentrations of inflammation in individuals with lower verbal IQ scores; Segerstrom et al., 2017). Neither of the two studies testing psychological flexibility (either generally or the subcomponent of acceptance) found significant associations with inflammatory biology. Plausibly, this might be due to psychological flexibility/acceptance being skills that open up the ability to engage with alternate responses to emotion; thus, they could facilitate inflammatory modulation emotion regulation but themselves are not sufficient. But, with only two published studies in this category, more work is needed. The remaining emotion characteristics were grouped into a “positive coping/social support-seeking” category. All four included studies supported that these traits predicted lower concentrations of inflammatory proteins. In sum, the evidence from this systematic review supports that emotion regulation is a modulator of inflammatory biology.

4.1. Integration of inflammation into emotion regulation models of risk

Given the breadth of physical and psychological health outcomes associated with emotion regulation and inflammation, it is critical for future work to consider integrated, multi-level frameworks of risk to develop theory. Establishment of etiological theories integrating malleable psychological (e.g., emotion regulation) and biological (e.g., inflammatory biology) constructs are critical for maximally comprehensive, and maximally flexible, healthcare (Moriarity, 2021). One such model tested by three studies in this review is an immunocognitive model of psychopathology (Moriarity et al., 2018, 2020b, 2020a), in which cognitive vulnerabilities (e.g., emotion regulation) amplify the impact of stress or stress-modulating characteristics (e.g., anxiety) on inflammation in ways that increase risk for psychopathology (e.g., depression). However, it is plausible to consider that this mechanistic pathway also might be relevant for many, if not all, inflammation-mediated disease processes (e.g., rheumatoid arthritis).

Clinically, identifying both psychosocial and biological treatment targets better facilitates comprehensive health care and coordination among medical and psychological members of a treatment team. Fully characterizing a risk pathway provides flexibility for idiosyncratic needs of patients. For example, if dysphoria or fatigue are obstacles to treatment adherence targeting emotion regulation (e.g., cognitive-behavioral therapies), understanding that reducing inflammation might improve these symptoms (Moriarity et al., 2022; Moriarity,

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Kautz et al., 2020) could warrant consideration of anti-inflammatory adjunctive medications. Conversely, some clients are unable, or unwilling, to take anti-inflammatory medications for an immune-mediated disease (e.g., arthritis, HIV/AIDS). Targeting inflammation using emotion regulation skills in a psychosocial intervention (e.g., cognitive behavioral therapies) might be an effective means of symptom reduction. Reduced inflammation might even be a biological mediator of some of the beneficial outcomes of psychosocial interventions (Shields et al., 2020).

In addition to treatment implications, it is critical to consider how these findings might facilitate fostering resiliency. This perspective helps health providers reduce illness recurrence and can inform organizational strategy (e.g., first year college orientation activities and resources) and policy change (e.g., educational materials provided to public schools). This review covers several emotion regulation skills (e. g., cognitive reappraisal, problem solving, distraction, social support-seeking) that might buffer the impacts of stress on inflammatory biology and inflammation-related outcomes. Although all of these skills plausibly could reduce the negative emotional impact of an event/stressor, social support-seeking (only evaluated in one reviewed study) might be a particularly promising emotion regulation skill for future research given empirical work suggesting that social stressors are particularly strongly associated with inflammatory stress responses (Dickerson et al., 2009; Slavich et al., 2020). Social Safety Theory argues that social safety schemas (socially-specific schemas about social safety or threat) are of particular importance for biological and psychological health (Slavich, 2020, 2022, Slavich et al., 2023).

4.2. Methodological implications

Across different emotion regulation traits, several methodological characteristics seemed to be associated with results in the hypothesized directions (i.e., difficulty with emotion regulation relating to higher concentrations of inflammatory proteins).

4.3. Longitudinal data

Longitudinal datasets investigating change in inflammatory proteins as a function of emotion regulation traits resulted in a greater proportion of results in the direction hypothesized relative to cross-sectional studies (77% vs. 63%), especially for studies testing perseverative thinking. For studies with repeated measures, this could be partially due to the benefit of being able to account for baseline levels of inflammatory proteins and focus on within-person change. Given the necessity of longitudinal data for analyses to have the potential causal relevance necessary to build and evaluate models of risk and resilience, this finding highlights the importance of collecting multiple timepoints of emotion regulation and inflammatory data in future research. Importantly, this distinction also suggests temporal specificity (Moriarity and Alloy, 2021)—, namely the possibility of the strength of the association between emotion regulation and inflammatory biology to change over time. This physiometric information is critical to design future research studies testing the extent to which emotion regulation characteristics influence trajectories of inflammation, in both observational and intervention studies.

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4.4. Acute stressor designs

Testing emotion regulation as a predictor of inflammatory reactivity to an acute stressor also provided a higher proportion of theory-consistent results relative to naturalistic, cross-sectional studies (88% vs. 63%). Similar to longitudinal data, this may be due to the ability to account for baseline levels of inflammatory proteins and quantify within-person change. Acute stressors also provide the opportunity to evaluate specific contexts (e.g., social stressors) that might be most impactful to train emotion regulation skills and mitigate impact on inflammatory outcomes. Further, randomization to various conditions with instructed engagement in particular emotion regulation strategies (e.g., rumination vs. distraction; Woody et al., 2016; Zoccola et al., 2014)) can facilitate direct comparison of different emotion regulation options people use in response to a common stressor. Acute stressors also provide an important opportunity to test state emotion regulation/dysregulation as a predictor of inflammatory reactivity, whereas other designs typically rely on self-report of trait emotion regulation/reactivity. Given recent research on how individuals transition between using various emotion regulation strategies (Daniel et al., 2022), one important future direction that might be testable in an acute stressor design would be to evaluate how individual differences in emotion regulation transitions relate to inflammatory outcomes. Additionally, given evidence that different affective reactions have different inflammatory correlates (Carroll et al., 2011), future acute stressor studies should collect data on specific affective responses in addition to generalized distress.

4.5. Vulnerability-stress framework

Another factor that was associated with high theoretical consistency of results was the evaluation of emotion regulation characteristics (especially perseverative thinking) in the context of either stress (e.g., perceived stress, childhood trauma) or a variable that modulates stress responses or exposure (e.g., anxiety symptoms). Specifically, 81% of such studies found theoretically consistent results relative to 69% of the remaining studies. Given that the use of emotion regulation characteristics is contingent on emotional responses/exposure to emotionally-salient events, moderation studies might be particularly relevant for advancing theory on the association between emotion regulation, inflammation, and related health outcomes. It is important to note that by “moderation” studies we both refer to statistical moderation, as well as study designs that allow for tests of emotion regulation in the context of experienced emotion that can be regulated (e.g., acute stressor designs).

4.6. Context matters: actionable stressors

One critical detail that is not included in any of the reviewed articles, and thus could not be evaluated in this systematic review, is how specific contextual details of a stressor influence which emotion regulation skills/traits might be adaptive. Specifically, the ability of an individual to successfully intervene on a stressor by taking action might influence the long-term usefulness of a given emotion regulation strategy (Ford and Troy, 2019), a distinction taught as a foundational perspective in several psychotherapeutic frameworks (e.g., dialectical behavioral therapy). For example, problem-solving and/or emotional expression might be most adaptive in situations where an individual’s actions can change the situation (e.g., discussing boundaries and separating household responsibilities with

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a roommate). On the other hand, emotion-focused strategies like cognitive reappraisal, acceptance, and social support seeking might be best suited for stressors out of an individual's realm of influence (e.g., the loss of a loved one). Future research and theory development should be careful to consider the limits of agency in emotionally-arousing situations to ensure maximum clinical-translatability. Two strategies for incorporating this nuance in future research are (a) comparing the interaction between different types of stressors and different emotion regulation traits and/or (b) using "common stressor" designs in which all participants experience the same, naturally occurring stressor.

4.7. Clinical research

Finally, much information could be gained from intervention research targeting emotion regulation characteristics. It is worth noting that several intervention studies that plausibly target emotion regulation were found during the initial literature search and excluded because they did not specifically test whether reductions in dysfunctional emotion regulation covaried with reductions in inflammatory biology. Given that the behavioral foci of many psychosocial interventions could have impacts on inflammatory biology (e.g., changes to appetite, substance use, or diet), there are many opportunities for confounds in psychosocial intervention studies unless specifically analyzed to test whether reductions in maladaptive emotion regulation are associated with inflammation. Therefore, we look forward to secondary data analysis on this topic in the future that, if results support this line of inquiry, can inform the design of intervention studies specifically created to test these research questions. To the extent that sample size might be a concern for readers with access to relevant data, we refer them to integrative data analysis (which facilitates the combination of different datasets) as a potential resource (Curran and Hussong, 2009) to aggregate multiple relevant datasets.

5. Conclusion

This systematic review of 2816 studies broadly found support for an association between a variety of emotion regulation constructs and inflammatory biology. We propose that integrated, multi-level theories of disease risk incorporating emotion regulation and inflammation as inter-related risk factors might result in more comprehensive treatment plans that provide flexibility for client needs and preferences. Across emotion regulation domains, theory-consistent results (i.e., difficulties with emotion regulation being associated with higher concentrations of inflammatory proteins) seemed to be more likely with longitudinal data, studies leveraging acute stressors, and/or studies testing vulnerability-stress models of risk for elevated inflammation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

No data were used for the research described in the article.

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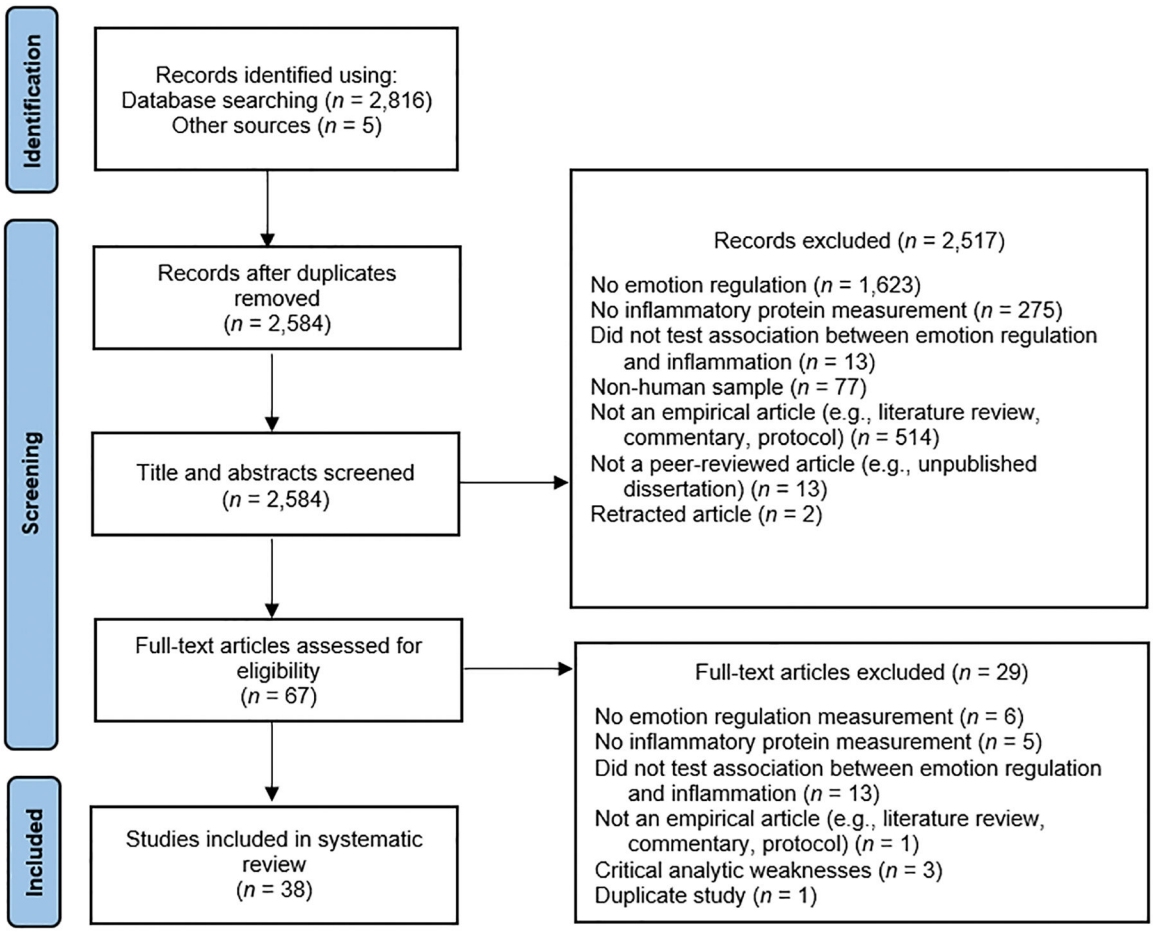

Fig. 1.
Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Diagram.

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Table 1.

Summary of Studies Reviewed

Authors (Year)	Sample Size	Sample Type & Age	Study Design	Inflammatory Proteins	Inflammatory Measurement Method	Emotion Regulation Variables	Emotion Regulation Category for Narrative Summary	Covariates	Results
Appleton et al. (2011)[a]	379–400 (depending on model)	Community M_{age} 42.2 years, SD 1.8 years	Longitudinal	CRP	Blood	Inappropriate self-regulation, distress proneness	Emotion Regulation/ Dysregulation Negative Affectivity/ Emotional Reactivity	Age, sex, race, study site, smoking status, depression, education, BMI, gestational age, WISC score, childhood SES, childhood health.	↑ Childhood inappropriate self-regulation → ↑ Adult CRP (p = .002) ↑ Childhood distress proneness → ↑ Adult CRP (p = .03)
Appleton et al. (2013)[a]	379	Community M_{age} 42.2 years, SD 1.7 years	Cross-sectional	CRP	Blood	Emotional suppression, Cognitive reappraisal	Emotional Suppression Cognitive Reappraisal	Age, race, gender, study site	↑ Cognitive reappraisal →↓ CRP (p < .01) ↑ Suppression → ↑ CRP (p < .001).
Appleton et al. (2012)[a]	388	Community M_{age} 42.1 years, SD 1.7 years	Longitudinal	CRP	Blood	Childhood distress proneness, inappropriate self-regulation	Emotion Regulation/ Dysregulation Negative Affectivity/ Emotional Reactivity	Age, race, gender, study site, physical health, WISC score, BMI, depression, education, smoking status, gestational age	↑ Childhood inappropriate self-regulation * ↓ income→ ↑ adult CRP (p < .05) ↑ Childhood distress proneness * ↓ income→ ↑ adult CRP (p < .05) ↑ Childhood distress proneness * middle income→ ↑ adult CRP (p < .05)
Castonguay et al. (2014)	121 women	Clinical (breast cancer survivors) M_{age} 55.5 years, SD 11.0 years	Cross-sectional	CRP	Blood	Health-related self-protection positive reappraisal	Cognitive Reappraisal	Age, education, smoking status, BMI, cancer stage, time since cancer diagnosis	↓ Positive reappraisal * ↓ Capacity to disengage from unattainable goals→ ↑ CRP (β = .22, p = .01) Null: Positive reappraisal * Capacity to re-engagement with goals→ CRP (β = -.06, p=.55)
Chen et al. (2015)	122 adolescents, 122 parents (tested separately)	Community Adolescent M_{age} 16.0 years, SD 1.2 years Parents M_{age} 46.7 years, SD 6.9 years	Cross-sectional	Composite of CRP, IL-6	Blood	Shift (positive reappraisal/ reframing and cognitive restructuring), persist (developing purpose in life, holding onto	Cognitive Reappraisal	Age, sex, ethnicity, waist circumference	↑ Shift + persist * ↓ SES→ ↓ Composite (β = .18, p = .044) in adolescents but not parents (p = .72)

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Authors (Year)	Sample Size	Sample Type & Age	Study Design	Inflammatory Proteins	Inflammatory Measurement Method	Emotion Regulation Variables	Emotion Regulation Category for Narrative Summary	Covariates	Results
						hope future might be better)			
Collier et al. (2016)	47 textile handcrafters	Community M_{age} 53.5 years, SD 14.0 years	Experimental acute stressor- After recalling an upsetting situation randomized to a) writing exercise (rumination), b) quiet ego contemplation (neutral), c) textile art making	IL-1β	Saliva	Rumination	Perseverance vs. Distraction/ Disengagement	None	↑ IL-1B after negative mood induction only in rumination condition (p = .039)
Crosswell et al. (2022)	182	High risk community (92 high-stress caregivers of a child with autism, 91 controls without high stress who are caregivers of a neurotypical child) M_{age} 44.0 years	Cross-sectional	CRP, IL-6	Blood	Acceptance	Psychological Flexibility	Age, BMI	Null: Acceptance → CRP (β = .012, p = .806) Null: Acceptance → IL-6 (β = -.015, p = .552) Null: Acceptance * Parental stress → CRP (p > .05) Null: Acceptance * Parental stress → IL-6 (p > .05)
Dargél et al. (2017)[b]	613	Clinical- Bipolar disorder (type I, II, or Not Otherwise Specified) not in acute mood episode not in acute mood episode Mage 41.2 years, SD 12.4 years	Cross-sectional	CRP	Blood	Emotional reactivity	Negative Affectivity/ Emotional Reactivity	None	↑ Emotion reactivity→ ↑ CRP (p < .001)
Dargél, et al. (2020)[b]	1072	Clinical- Bipolar disorder (type I, II, or Not Otherwise Specified) not in acute mood	Cross-sectional	CRP	Blood	Emotional reactivity	Negative Affectivity/ Emotional Reactivity	None	CRP higher in those with (M = 3.87, SD = 1.98) vs. without (M = 2.17, SD = 2.63) emotion hyper-reactivity (p < .001)

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Authors (Year)	Sample Size	Sample Type & Age	Study Design	Inflammatory Proteins	Inflammatory Measurement Method	Emotion Regulation Variables	Emotion Regulation Category for Narrative Summary	Covariates	Results
		episode not in acute mood episode M_{age} 41.2 years, SD 12.4 years							
Denollet et al. (2003)	42 males	Clinical-congestive heart failure M_{age} 57.9 years, SD 10.5 years	Cross-sectional	TNF-α	Blood	"Type D personality" (negative affectivity and tendency to inhibit emotional expression in social situations)	Negative Affectivity/ Emotional Reactivity Emotional Suppression	None	↑ Type D personality→ ↑TNF-α (d = .90, p = .003)
Gierlotka et al. (2015)	65	Clinical (33 PTSD, 32 control, all with mechanical injuries to extremities) PTSD M_{age} 37.7 years Control M_{age} 34.9 years	Cross-sectional	IFN-γ, IL-6, IL-10, sIL-2, TNF-α	Blood	Perseverance, emotion reactivity	Negative Affectivity/ Emotional Reactivity Perseverance vs. Distraction/ Disengagement	None	Null: All
Graham et al. (2009)	84	Community (married men and women) M_{age} 37.0 years, SD 13.1 years	Longitudinal + experimental acute stressor—randomized to conflict or no-conflict	IL-6, TNF-α	Blood	Cognitive processing word use (underlying mechanism of emotion expression and disclosure)	Emotional Suppression	Gender, age, BMI, education, baseline inflammatory level, hostile interactions, positive interactions, marital quality, depression, hostility.	↑ Cognitive word use during conflict → ↓ IL-6 24 hours later (β = -.26, p < .05) Null: Cognitive word use during conflict → TNF-a 24 hours later (β = -.18, p = .09)
Hladek et al. (2020)	49	Community M_{age} 50.9 years, SD 25.9 years	Cross-sectional	IL-6, IL-10, TNF-α	Sweat patch	Coping self-efficacy (problem-solving, emotion regulation, social support)	Positive Coping/Social Support-Seeking	Age, sex, race, BMI, chronic diseases	↓ Coping self-efficacy→ ↑ TNF-α (β = −.03, p = .028) ↓ Coping self-efficacy→ ↑ IL-10 (β = −.017, p = .007) Null: Coping self-efficacy→ ↑ IL-6 (β = −.22, p = .054)

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Authors (Year)	Sample Size	Sample Type & Age	Study Design	Inflammatory Proteins	Inflammatory Measurement Method	Emotion Regulation Variables	Emotion Regulation Category for Narrative Summary	Covariates	Results
Hoyt et al. (2013)	41 men	Clinical-Prostate cancer M_{age} 66.6 years, SD 9.6 years	Longitudinal	CRP, IL-6	Blood	Emotion processing, emotion expression	Emotional Suppression	Age, ethnicity, BMI, # of months since completing primary cancer treatment	↑ Emotional processing → ↓ IL-6 (β = -.66, .05 < p < .01) Null: Emotional processing → CRP (β = -.43, .05 < p < .10) Null: Emotional expression → IL-6 (β = .38, .05 < p < .10) Null: Emotional expression → CRP (β = .44, .05 < p < .10)
Järvelä-Reijonen et al. (2020)	169	Clinical (84 face-to-face treatment, 85 mobile treatment) Face-to-face M_{age} 51.0 years, SD 6.5 years Mobile M_{age} 48.8 years, SD 7.7 years	Longitudinal	CRP, IL-1Ra, adiponectin	Blood	Psychological Flexibility (both general and weight-related)	Psychological Flexibility	Age, sex	Null: General acceptance → CRP (β = -.03, p = .772) Null: Weight-related acceptance → CRP (β = .16, p = .099) Null: General acceptance → IL-1Ra (β = .01, p = .888) Null: Weight-related acceptance → IL-1Ra (β = .00, p = .807) Null: General acceptance → adiponectin (β = .01, p = .946) Null: Weight-related acceptance → adiponectin (β = .02, p = .812)
Jones et al. (2022)	279	Community M_{age} 40.2 years, SD 6.2 years	Longitudinal	CRP, IL-6	Blood	Cognitive reappraisal, Expressive suppression	Emotional Suppression Cognitive Reappraisal	Age, sex assigned at birth, racial/ ethnic identity, time between assessments, inflammatory protein at baseline	↑ Cognitive reappraisal→ ↓ IL-6 (β = -.155, p = .006) ↓ Cognitive reappraisal * ↑ Childhood trauma→ ↑ IL-6 (β = -.001, p = .012) ↓ Cognitive reappraisal * ↑ Childhood abuse→ ↑ IL-6 (β = -.001, p = .043) ↑ Expressive suppression * ↑ Childhood abuse→ ↑ IL-6 (β = .002, p = .011) ↑ Expressive suppression * ↑ Childhood abuse→ ↑ CRP (β = .001, p = .033) ↓ Cognitive reappraisal * ↑ Childhood neglect→ ↑ IL-6 (β = -.001, p = .009) ↓ Cognitive reappraisal * ↑ Childhood neglect→ ↑ CRP (β = -.002, p = .036) Null: Expressive suppression→ IL-6 (β =

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Authors (Year)	Sample Size	Sample Type & Age	Study Design	Inflammatory Proteins	Inflammatory Measurement Method	Emotion Regulation Variables	Emotion Regulation Category for Narrative Summary	Covariates	Results
									-.062, p = .294) Null: Expressive suppression * Childhood trauma → IL-6 (β = .001, p = .074) Null: Cognitive reappraisal→ CRP (β = -.056, p = .253) Null: Expressive suppression→ CRP (β = -.046, p = .362) Null: Cognitive reappraisal * Childhood trauma → CRP (β = -.005, p = .362) Null: Expressive suppression * Childhood trauma → CRP (β = .001, p = .117) Null: Cognitive reappraisal * Childhood abuse→ CRP (β = .001, p = .518) Null: Expressive suppression * Childhood neglect → CRP (β = .0003, p = .636) Null: Cognitive reappraisal * Childhood neglect→ IL-6 (β = -.0002, p = .472)
Jones et al. (2018)	261 adolescents	Community M_{age} 14.6 years, SD 1.1 years	Cross-sectional	CRP, IL-6	Blood	Cognitive reappraisal, expressive suppression	Emotional Suppression Cognitive Reappraisal	Age, sex, ethnicity, income, and BMI	Null: Chronic family stress * cognitive reappraisal→ CRP (β = -.079, p = .194) Null: Chronic family stress * suppression→ CRP (β = -.044, p = .472) Null: Chronic family stress * cognitive reappraisal→ IL-6 (β = .068, p = .256) Null: Chronic family stress * suppression→ IL-6 (β = -.005, p = .993)
Khan et al. (2020)	606	Clinical (trauma exposed veterans) M_{age} 58.0 years, SD 11.2 years	Cross-sectional	Fibrinogen, CRP	Blood	Cognitive reappraisal, Expressive suppression	Emotional Suppression Cognitive Reappraisal	Sex, age, race, education, income, creatinine, PTSD	↑ Emotional suppression→ ↑ CRP (β = .11, p = .01) ↑ Emotional suppression→ ↑ Fibrinogen (β = 0.10, p = 0.02) Null: Cognitive reappraisal→ CRP (β = .03, p >.05) Null: Cognitive reappraisal → Fibrinogen (β = 0.01, p >.05)
Knight et al. (2022)	162	Community M_{age} 44.4	Cross-sectional, longitudinal	CRP + Cytokine composite	Blood	Rumination	Perseverance vs. Distraction/ Disengagement	Age, BMI	Null-No gender-stratified relationships between rumination and CRP, the

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Authors (Year)	Sample Size	Sample Type & Age	Study Design	Inflammatory Proteins	Inflammatory Measurement Method	Emotion Regulation Variables	Emotion Regulation Category for Narrative Summary	Covariates	Results
		years, SD 11.2 years		(IL-1β, IL-6, IL-8, IL-10, TNF-α)					inflammatory composite, or individual cytokines
Lopez, et al. (2020)	99 recently bereaved spouses	Community M_{age} 68.6 years, SD 10.7 years	Cross-sectional	IL-2, IL-6, IL-17A, IFN-γ, TNF-α	Blood	Expressive suppression, cognitive reappraisal	Emotional Suppression Cognitive Reappraisal	Age, sex, BMI, education, income, sleep, depression, medication, smoking status, Clinical conditions, physical activity, time since spouse passed away	↑ Expressive suppression → ↑ IFN-γ (corrected $p = .015$) ↑ Expressive suppression → ↑ TNF-α (corrected $p = .015$) Null: Expressive suppression → IL-2, IL6, IL-17A Null: Cognitive reappraisal with all proteins.
Low et al. (2013)	245 adolescents	Community M_{age} 15.7 years, SD 1.3 years	Longitudinal-Daily diary	CRP	Blood	Positive engagement coping, disengagement coping	Perseverance vs. Distraction/ Disengagement Positive Coping/Social Support-Seeking	Age, race, sex. BMI, smoking status, income	↑ Positive engagement coping * ↑ negative life events→ ↓ CRP ($\beta = -.14$, $p = .013$) ↑ Positive engagement coping * ↑ conflict life events→ ↓ CRP ($\beta = -.12$, $p = .039$) ↑ Positive engagement coping * ↑ daily interpersonal conflict/tension→ ↓ CRP ($\beta = -.13$, $p = .039$) Null: Disengagement coping * negative life events→ CRP Null: Disengagement coping * conflict life events→ CRP Null: Disengagement coping * daily interpersonal conflict/ tension→ CRP
Master et al. (2009)	22	Community M_{age} 20.1 years, SD 1.5 years	Acute stressor	IL-6	Saliva	Emotion approach coping	Emotional Suppression	Baseline IL-6	Null: Emotion approach coping → baseline IL-6 Null: Emotion approach coping → 25-minutes post stressor IL-6 Null: Emotion approach coping → 55-minutes post stressor IL-6
Miller et al. (2013)	34 preschoolers	Community M_{age} 4.1 years, SD 0.6 years	Cross-sectional	IL-6, TNF-α	Blood	Emotion regulation, negative liability	Emotion Regulation/ Dysregulation Negative Affectivity/ Emotional Reactivity	Age	↑ Emotion regulation → ↑ TNF-α ($p < .05$) ↑ Negative lability → ↓ TNF-α ($p < .05$) Null: Emotion regulation → IL-6

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Authors (Year)	Sample Size	Sample Type & Age	Study Design	Inflammatory Proteins	Inflammatory Measurement Method	Emotion Regulation Variables	Emotion Regulation Category for Narrative Summary	Covariates	Results
									Null: Negative lability → IL-6
Mitchell & Christian (2019)	67	Clinical (pregnant) M_{age} 29.8 years, SD 5.3 years	Longitudinal	IL-4, IL-6	Blood	Perseverative thinking	Perseverance vs. Distraction/ Disengagement	Race, BMI, gestational age, Clinical conditions	↓ Repetitive thinking * ↑ SES→ ↓ IL-6 (ΔR^2 = .07, p = .03) Null: Repetitive thinking * SES→ IL-4 (p = .35)
Moriarity et al. (2018)[c]	140 adolescents	Community M_{age} 16.5 years, SD 1.2 years	Longitudinal	CRP, IL-6	Blood	Rumination	Perseverance vs. Distraction/ Disengagement	Age, BMI, timing of blood draw, SES, sex, race, time in study, baseline IL-6/CRP, baseline depression symptoms (when predicting depression)	↑ Anxiety * ↑ Rumination→ ↑ IL-6 (p = .042) ↑ Anxiety * ↑ Rumination→ ↑ IL-6→ ↑ Depression (95% CI: .001-.004) Null: Anxiety * Rumination→ CRP (p = .745) Null: Anxiety * Rumination→ CRP→ Depression (95% CI: -.003-.002)
Moriarity et al. (2020a)	109	Community M_{age} 21.5 years, SD 2.1 years	Longitudinal	Composite + individual proteins- CRP, IL-6, IL-8, TNF-α	Blood	Rumination on positive and negative affect	Perseverance vs. Distraction/ Disengagement	Gender, race, age, BMI, birth control use, medication, time of day of blood draw	*only individual biomarkers (not the tested composite) are reported in this systematic review because no information was provided regarding the factor reliability/model fit of the inflammatory composite. Each of the interactions below was a follow-up of a significant interaction predicting the inflammatory composite ↑ Dampening of positive affect * ↓ reward responsiveness→ ↑ CRP (p = .022) ↑ Self-focused rumination on positive affect * ↑ reward responsiveness→ ↑ IL-8 (p = .013) Null: Dampening of positive affect * reward responsiveness→ IL-6 Null: Dampening of positive affect * reward responsiveness→ IL-8 Null: Dampening of positive affect * reward

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Authors (Year)	Sample Size	Sample Type & Age	Study Design	Inflammatory Proteins	Inflammatory Measurement Method	Emotion Regulation Variables	Emotion Regulation Category for Narrative Summary	Covariates	Results
									responsiveness→ TNF-α Null: Self-focused rumination on positive affect * reward responsiveness→ CRP Null: Self-focused rumination on positive affect * reward responsiveness→ IL-6 Null: Self-focused rumination on positive affect * reward responsiveness→ TNF-α
Moriarity et al. (2020b)[c]	89 adolescents	Community M_{age} 18.3 years, SD 1.4 years	Acute stressor	IL-6, IL-8	Blood	Rumination, problem solving, distraction	Perseverance vs. Distraction/ Disengagement Positive Coping/Social Support-Seeking	Baseline protein levels, time, gender, income, race, age	↑ Cognitive response ratio * ↑ Reward drive→ ↑ IL-6 (p = .002) Followed up with individual cognitive response styles ↑ Rumination * ↑ Reward drive→ ↑ IL-6 (p = .044) ↓ Problem solving * ↑ Reward drive→ ↑ IL-6 (p = .036) ↓ Distraction * ↑ Reward drive→ ↑ IL-6 (p = .008) Null: Cognitive response ratio * Reward drive→ IL-8
Newton et al. (2017)	Study 1: 68 (45 rest group, 23 distraction group) Study 2: 68 (46 rest group, 22 distraction group)	Community Study 1 M_{age} 20.8 years, SD 3.6 years Study 2 M_{age} 21.3 years, SD 3.8 years	Experimental acute stressor- Study 1: Social stressor—randomized to rest or distraction Study 2: Angry autobiographical memory recall—randomized to rest or distraction Rest group: sitting quietly for 40 minutes to create opportunity for rumination Distraction group: 29 emotionally neutral puzzles Note: Amount of participants who actively ruminated during the rest condition	IL-1β, IL-6, TNF-α	Saliva	Rumination, negative emotion reactivity	Negative Affectivity/ Emotional Reactivity Perseverance vs. Distraction/ Disengagement	None	**Study 1:** ↑ Rumination→ ↑ IL-6 (β = .22, $p \leq .035$) ↑ Negative emotion post-stressor→ ↑ IL-6 (β = .309, p = .012) ↑ Negative emotion post-stressor→ ↑ IL-1β (β = .288, p = .026) ↑ Negative emotion post-stressor → ↑ TNF-α (β = .255, p = .044) Null: Rumination → IL-1B (β = .011, p > .05) Null: Rumination → TNF-α (β = .064, p > .05). **Study 2:** Rest condition * ↑ Time→ ↑ IL-1B (p = .027) relative to distraction condition Null: Group * Time→ IL-6 (p = .434) Null: Group * Time→ TNF-α (p = .074) Null: Rumination → IL-6 (β = -.079, p > .05).

Authors (Year)	Sample Size	Sample Type & Age	Study Design	Inflammatory Proteins	Inflammatory Measurement Method	Emotion Regulation Variables	Emotion Regulation Category for Narrative Summary	Covariates	Results
			was low in both studies (15 and 8, respectively)						Null: Rumination → IL-1B (β =-.014, p > .05) Null: Rumination → TNF-α (β =-.03, p > .05). Null: Negative emotion post-stressor→ IL-6 (p > .18) Null: Negative emotion post-stressor→ IL-1β (p > .18) Null: Negative emotion post-stressor → TNF-α (p > .18)
Powers et al. (2016)	40 African American women	Clinical-Diabetes M_{age} 52.0 years, SD 7.6 years	Cross-sectional	CRP	Blood	Emotion dysregulation	Emotion Regulation/ Dysregulation	PTSD, depression, trauma, BMI	↑ Emotion dysregulation→ ↑ CRP (β = .58, p < .001)
Prossin et al. (2011)	28 females	Clinical (14 MDD, 14 controls) No age reported	Acute stressor	IL-18	Blood	Negative affective reactivity to sadness induction	Negative Affectivity/ Emotional Reactivity	None	↑ Negative affect post sadness induction → ↑ IL-18 (r_s = .60, p=.03) for controls but not MDD
Segerstrom et al. (2017)	120	Community M_{age} 74.2 years, SD 5.6 years	Longitudinal	IL-6	Blood	Repetitive thought (worry, rumination, self-reproach, reflection, emotion processing)	Cognitive Reappraisal Perseverance vs. Distraction/ Disengagement	BMI, age, medication	↑ Repetitive thought → ↓ IL-6 (p = .001) ↑ Repetitive thought * ↓ verbal IQ → ↓ IL-6 (p = .009) Quadratic effect of repetitive thought → IL-6 (p = .002), negative relationship between repetitive thought and IL-6 steepest at low levels of repetitive thought Null: Quadratic effect of repetitive thought * verbal IQ → IL-6
Shimanoe et al. (2014)[d]	7,873	Community Men M_{age} 55.6 years, SD 8.3 years Women M_{age} 54.3 years, SD 8.2 years	Cross-sectional	CRP	Blood	Emotion expression, emotion support seeking, positive reappraisal, problem solving, disengagement	Positive Coping/Social Support-Seeking Emotional Suppression Cognitive Reappraisal Perseverance vs. Distraction/ Disengagement	Age, BMI, body fat, alcohol consumption, smoking, physical activity level, sleeping, occupation, working hours, years of schooling, perceived stress, social support	↑ Disengagement → ↓ CRP in men but not women (partial η^2 = 0.002, p = .027 and partial η^2 < 0.001, p = .82, respectfully) ↑ Emotional support seeking→ ↓ CRP at high levels of stress in men only ($p_{interaction}$ = .021; p_{trend} = .028). Null: Other emotional regulation strategies → CRP (analyses ran separately for men and women)

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Authors (Year)	Sample Size	Sample Type & Age	Study Design	Inflammatory Proteins	Inflammatory Measurement Method	Emotion Regulation Variables	Emotion Regulation Category for Narrative Summary	Covariates	Results
									Null: Other emotional regulation strategies * perceived stress → CRP (analyses ran separately for men and women)
Shimanoe et al. (2018)[d]	7,256	Community Women M_{age} 55.0 years, SD 8.1 years Men M_{age} 56.0 years, SD 8.0 years	Longitudinal	CRP	Blood	Emotion expression, emotion support seeking, positive reappraisal, problem solving, disengagement	Emotional Suppression	Age, BMI, employment, alcohol consumption, smoking status, physical activity, sleep, medication, menopause status, HRT, social support, perceived stress	↑ Positive reappraisal * ↑ perceived stress →↓ CRP in men (p = .007) ↑ Emotional expression → ↓ CRP in women (p = .024) Null: Other emotional regulation strategies → CRP (analyses ran separately for men and women) Null: Other emotional regulation strategies * perceived stress → CRP (analyses ran separately for men and women)
van Middendorp et al. (2005)	60	Clinical-Rheumatoid Arthritis M_{age} 59.0 years, SD 11.2 years	Cross-sectional	IL-6	Blood	Ambiguity, control, orientation, and expression	Negative Affectivity/ Emotional Reactivity Emotional Suppression	None	Null: Emotional regulation subscales →IL-6 were null after Bonferroni corrections (uncorrected results not described)
Woody et al. (2016)[e]	34 women	Community M_{age} 20.7 years, SD 2.3 years	Experimental acute stressor-randomized to 5 minutes of rumination or distraction	CRP, IL-6, TNF-α	Blood	Reflection	Perseverance vs. Distraction/ Disengagement	Trait rumination, openness to experience, neuroticism, SES, BMI, condition	↑ Reflection→ ↓ IL-6 (β = -.70, p = .007) Null: Reflection→CRP (β = .22, p = .407) Null: Reflection→ TNF-α (β = -.05, p = .869)
Yang et al. (2020)	162	Clinical (105 ADHD, 57 control) ADHD Median Age = 36.0 years (25^{th}-75^{th}% = 29.0–43.0 years) Control Median Age = 38 years 25^{th}-75^{th}% = 34–43 years	Cross-sectional	CRP, SAA, sICAM-1, *s*VCAM-1	Blood	Emotion regulation	Emotion Regulation/ Dysregulation	Age, sex, BMI, ADHD medication, anti-inflammatory drugs, melatonin	↑ Total emotion regulation difficulty → ↑ CRP (adjustedR^2 = 0.25, p = 0.025) ↓ Effective emotion regulation strategies difficulty → ↑ CRP (adjustedR^2 = 0.27, p = 0.006) Null: Total emotion regulation difficulty→ SAA Null: Total emotion regulation difficulty→ sICAM-1 Null: Total emotion regulation difficulty→ *s*VCAM-1

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Authors (Year)	Sample Size	Sample Type & Age	Study Design	Inflammatory Proteins	Inflammatory Measurement Method	Emotion Regulation Variables	Emotion Regulation Category for Narrative Summary	Covariates	Results
Ysseldyk et al. (2018)	54 women	Community M_{age} 21.2 years, SD 6.0 years	Cross-sectional	IL-10, TNF-α	Blood	Rumination	Perseverance vs. Distraction/ Disengagement	None	Null: Depressive rumination→ TNF-α (r = .24, $p < .10$) Null: Brooding rumination→ TNF-α (r = -.13, $p > .05$) Null: Reflective rumination→ TNF-α (r = .01, $p > .05$) Null: Depressive rumination→IL-10 (r = -.08, $p > .05$) Null: Brooding rumination→IL-10 (r = -.07, $p > .05$) Null: Reflective rumination→IL-10 (r = .10, $p > .05$)
Zoccola et al. (2014)[e]	34 females	Community No age reported	Experimental acute stressor—randomized to rumination or distraction after stressor	CRP, IL-6, TNF-α	Blood	Distraction, rumination	Perseverance vs. Distraction/ Disengagement	BMI and baseline inflammatory protein values	Rumination group had linear increases in CRP (f^2 = .22, p < .001). Linear trajectory of CRP differed between rumination and distraction groups (f^2 = .18, p = .01). Distraction group had linear increases in CRP up to 43 minutes post stressor, after which they returned to baseline levels (f^2 = .14, p = .03). Null: Group → IL-6 Null: Group → TNF-a

Notes: Mage mean age, SD = standard deviation, BMI = body mass index, CRP = C-reactive protein, HRT = hormone replacement therapy, CRP = high-sensitivity C-reactive protein, IL = interleukin, IFN-γ = Interferon-gamma, IL-1Ra = interleukin-1 receptor antagonist, *MDD = Major depressive disorder,* PTSD *= Post-traumatic stress disorder, SAA* = Serum amyloid A, *SES = socioeconomic status,* sIL = soluble interleukin, sICAM-1 = soluble intercellular adhesion molecule 1, *s*VCAM-1 = soluble vascular cell adhesion molecule-1, *TNF-α = Tumor necrosis factor alpha, WISC* = Wechsler Intelligence Scale for Children

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Table 2

Percentage of Studies with Theoretically Consistent Results.

Category	% (Fraction)
Total Reviewed	74% (28/38)
Emotion Regulation Constructs	
Positive Coping/Social Support-Seeking	100% (4/4)
Emotion Regulation/Dysregulation	100% (5/5)
Negative Affectivity/Emotional Reactivity	80% (8/10)
Emotional Suppression	71% (5/7)
Perseverance vs. Distraction/Disengagement	71% (10/14)
Emotional Expression	60% (3/5)
Cognitive Reappraisal	56% (5/9)
Psychological Flexibility	0% (0/2)
Methodological Characteristics	
Acute Stressor	88% (7/8)
Vulnerability-Stress *	81% (17/21)
Longitudinal	77% (10/13)
Not Vulnerability-Stress	69% (15/22)
Cross-sectional	63% (12/19)

Note: *Vulnerability-Stress is defined as either (a) testing emotion regulation as a predictor of inflammatory reactivity to an acute stressor or (b) testing whether emotion regulation moderates the association between reported stress or a stress-modulating variable (e.g., anxiety symptoms) and inflammatory biology. Also, note that some individual studies fit into multiple categories.