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Understanding Associations Between Rumination and Inflammation: A Scoping Review

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Abstract

A growing body of evidence suggests that rumination, or focused attention on mental representations of negative events, may have physiological consequences that adversely affect long term health. We conducted a scoping review on quantitative studies of humans examining associations between rumination and inflammation, which included 13 studies representing 14 samples and 1,102 unique participants. The review included 8 biomarkers measured in plasma, serum and saliva (C reactive protein, and C-C motif chemokine 11, interleukin (IL)-1β, IL-4, IL-6, IL-8, IL-10 and tumor necrosis factor alpha). More consistent findings of an association between greater rumination and increased inflammation were found in studies that used experimental designs and manipulated rumination. Emerging research suggests rumination may interact with other factors (e.g., socioeconomic status, anxiety) to predict inflammation. This review offers an up to date synthesis of the emerging research focused on rumination and inflammation. The relationship between inflammation and rumination may be contingent on how rumination is conceptualized and measured, as well as the measure of inflammation (i.e., at rest/ in response to stress).

Keywords

rumination; repetitive thought; perseverative thought; cytokines; CRP; IL-6; TNF-α

1. Introduction

Rumination is an emotion regulation strategy broadly characterized by repetitive reflection on negative thoughts, emotions, and past events, as well as the causes and consequences of those events and emotions (Smith & Alloy, 2009). Overall, evidence suggests rumination is a transdiagnostic factor. The effects of rumination can contribute to emotional vulnerability

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(e.g. being unable to consider more helpful, alternative outcomes to a distressing situation) that increase susceptibility to a number of negative mental health outcomes, such as depression, anxiety, PTSD, and comorbid conditions (Nolen-Hoeksema, 2000; McLaughlin & Nolen-Hoeksema, 2011; Szabo et al., 2017; Watkins & Roberts, 2020). There are several types of rumination which capture different dimensions of this psychological construct and may be uniquely relevant for health outcomes (i.e., brooding, depressive, stress reactive, angry and reflective rumination). However, differences in measurement may cause challenges in determining a consistent definition across studies (Smith & Alloy, 2009), and contribute to difficulties identifying ways in which rumination impacts overall health. For example, brooding is characterized by persistent reflection on one's negative mood and depressive symptoms and has been associated with suicidal ideation, substance abuse, as well as the onset and maintenance of depression (Watkins & Roberts, 2020), whereas angry rumination is the reflection on feelings of anger or an anger inducing event and has been associated with trait hostility and increases in blood pressure (Gerin et al., 2006).

There is also a growing body of evidence that the effects of rumination are a transdiagnostic vulnerability factor with implications for cognitive and physical health. Previous studies have found rumination to be associated with higher self-reported pain and somatic symptoms (Sansone & Sansone, 2012). Additionally, cognitive dysfunction, such as difficulty concentrating, impaired executive functioning and subjective cognitive complaints have been associated with rumination (Szabo et al., 2020; Watkins & Roberts, 2020). In fact, the transdiagnostic nature of rumination and associated cognitive deficits has been identified in one recent study, finding that negative, repetitive thinking was predictive of Alzheimer's disease(Marchant et al., 2020). Results of neuroimaging studies have linked self-referential processing and rumination to hyperactivation of the Default Mode Network (DMN), and the dorsomedial prefrontal cortex (dmPFC) node of this network in particular (Zhou et al., 2020). Abnormal activation of the DMN has been linked to numerous neuropsychiatric conditions (Mohan et al., 2016) and systemic inflammation (Marsland et al., 2017), perhaps via a rumination mechanism. Resting state data in depression has found lower connectivity within the DMN to be associated with rumination (Jacob et al., 2020; Zhou et al., 2020). Recruitment of dmPFC and limbic regions have also been associated with rumination in task-based fMRI. Some such studies include rumination-induction and comparison of ruminative self-focus and distraction conditions in depressed individuals (Cooney et al., 2010), and those with remitted depression and healthy controls (Burkhouse et al., 2017) with results indicating ruminative self-focus conditions to be associated with enhanced recruitment of limbic regions as well as dmPFC and dorsolateral prefrontal cortex (DLPFC).

The associations of rumination with myriad psychological and physiological diagnoses and symptoms leads to the intriguing question of how rumination may be fueling transdiagnostic issues. Theories of the relationship between cognition and rumination generally indicate deficits in attention and executive functioning exist in those who have a ruminative cognitive style. Rumination is theorized to contribute to deficits in executive functioning due to impaired disengagement from negative thoughts (Koster et al., 2011; Mor & Daches, 2015) and inability to switch efficiently from negative to more neutral aspects of stimuli (Malooly et al., 2013). More basic attentional mechanisms of inhibition may be related to rumination as proposed by Linville (Linville, 1996), who theorized that rumination increases

the likelihood that internal thoughts become repetitive by facilitating the retrieval of no longer relevant information, making it more difficult for the ruminator to remove these thoughts from memory.

When attentional and executive functioning/cognitive resources are depleted by rumination, and an individual is immersed in negative, perseverative thinking, an acute distress response may be expected that contributes to somatic symptoms. An emerging body of evidence suggests the psychological stress induced by rumination may chronically activate a physiological stress response, which could adversely affect long term health. Specifically, the perseverative cognition theory suggests that repetitive negative patterns of thinking can increase or amplify physiological reactions to psychological stress in ways that place individuals at an increased risk for immune dysfunction and cardiovascular disease (Brosschot et al., 2006). Support for the perseverative cognition hypothesis has been synthesized in a recent systematic review and meta-analysis, which found associations between perseverative cognitions and greater systolic blood pressure, diastolic blood pressure, cortisol and lower heart rate variability (Ottaviani et al., 2016). Moderator analyses revealed that “triggering” state rumination, or worry, was significantly associated with perseverative cognition and increased heart rate or diminished variability, rather than having a trait perseverative style (Ottaviani et al., 2016). Rumination associations have also been found with neuroendocrine and immune system function (Thomsen et al., 2004; Zoccola et al., 2008). Rumination has recently been examined in regards to inflammation, with some studies showing an association (Zoccola et al., 2014), while others do not (e.g., Ysseldyk et al., 2018). Better understanding the nature of the relationship between rumination and inflammation might inform an immunocognitive model of health and propose new intervention pathways.

Inflammation is a tightly regulated system of markers that orchestrate a response to injury or infection and promote healing. Markers of inflammation include pro-inflammatory cytokines, anti-inflammatory cytokines and acute phase proteins, among others. These markers are detectable in several bodily fluids, including blood, urine, and saliva. Inflammation has been associated with the development of several health conditions, including diabetes, and cardiovascular disease (Golia et al., 2014; Tsalamandris et al., 2019). More recently, inflammation has been recognized as a correlate of mental health disorders, including major depressive disorder, anxiety and posttraumatic stress disorder (Howren et al., 2009; Michopoulos et al., 2017). Stress is one transdiagnostic vulnerability factor, which may contribute to prolonged activation of the immune response and, in turn, result in elevated inflammation that increases risk for negative health outcomes (Miller et al., 2002; Slavich, 2015). Additionally, the persistent experience of negative mood states such as anger, fear, and sadness can alter cardiac functioning as well as stress and immune responses, impacting inflammation and overall health (DeSteno et al., 2013). The study of how emotions may impact health has resulted in further understanding of the importance of not just the type of emotions that are experienced, but also how these emotions are modulated or regulated (DeSteno et al., 2013; Gross, 2014). The goal of this work is to examine associations between rumination, an emotion regulation strategy that may have physiological consequences, and markers of inflammation, with the aim to advance integrated models of health from a psychoneuroimmunology perspective.

Specifically, the purpose of the scoping review was to identify studies that examined associations between rumination and inflammation to summarize what is known about the relationship between these two constructs. A scoping review was chosen because the goal of our approach was to identify the types of available evidence for an association between rumination and inflammation and identify knowledge gaps that can be addressed in future research on this topic (Munn et al., 2018). Our second goal was to review and discuss themes across different methodologies to guide future research by reporting on study design, recruitment, and measurement of rumination and inflammation.

2. Methods

The review was conducted using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for scoping reviews (Tricco et al., 2018). The PRISMA-ScR checklist can be found in supplementary materials (Supplementary Table 1). Due to the nascency of this topic and the differing methodologies, the authors did not preregister this review, but clearly note *a priori* versus post hoc decisions. Unless otherwise noted, post hoc decisions were made prior to any reviewing of the articles included in the search, but after the initial search had been conducted. Articles were collected using an *a priori* combination of electronic database searches and reference treeing. Electronic database searches of PsycINFO, PubMed and Google Scholar using the following key words: rumination, repetitive thought, cytokine, chemokine, inflammation, acute phase protein, C reactive protein, and fibrinogen (see Supplemental Table 1 for full search criteria). Full-text searching was used whenever possible. The time frame for searches was 1977, when the seminal article on rumination was published (Rippere, 1977), through February 2021. Because Google Scholar sorts results by relevance, the first 50 results were retained *a priori*. We also updated the literature search on December 13, 2021, limiting searches to 2021 and retaining only the first 10 results from Google Scholar. For all full text articles meeting eligibility for inclusion in the review, the reference sections were reviewed for additional possible articles. Further, we decided post-hoc to conduct a search to see if published papers were available for each of the dissertations that were found in the search.

Only quantitative, peer reviewed studies were eligible for inclusion. Each study was *a priori* required to examine the relationship between rumination and a marker of inflammation in humans. No restrictions were made on the participants being studied (i.e., age or health status) or on the medium of inflammatory measure (i.e., urine, serum, saliva) or type of sample (i.e., circulating or stimulated).

2.1 Data charting process and items

Titles, abstracts and citation information obtained through the database search were exported to Mendeley where duplicates were removed, then one coder (YZS) screened abstracts and titles: quantitative study, humans, measure of rumination and measure of inflammation. For articles that met these criteria, full-text documents were obtained. Then, 3 criteria were used to screen articles: quantitative study of humans, measure of rumination, and measure of rumination correlated with inflammation. After training on 3 articles, the remaining articles were screened independently by two coders (YZS and CMB; 90% agreement, $\kappa = .79$).

Studies that met inclusion criteria were independently coded for the following information: country of data collection, population, study design, biomarkers, sample type, measure of rumination, and results of each eligible study. The data-charting form was jointly developed by both coded to determine which variables to extract. The two coders independently coded the data, discussed the results and continuously updated the data-charting form in an iterative process. All articles were double coded for inclusion into the table (i.e., independently coded and reviewed for any missed or discrepant information before adding to a master table). Any discrepancies were resolved by discussion. Some articles used non-validated measures of rumination. These were eligible for inclusion as long as the authors conceptualized this as rumination, and the items did not better assess another construct (i.e., worry or intrusions). The Perseverative Cognitions Questionnaire has been conceptualized to measure both worry and rumination, but the items do not anchor to the future (i.e., worry) and thus decided post hoc that studies using this measure could be included. While definitions of rumination broadly describe reactions to negative events and emotions, one study included a measure of rumination on positive affect. Given we had not *a priori* incorporated this into our exclusion criteria, this study was included in the review. Finally, our search revealed some non-independence of samples (i.e., 4 papers derived from 2 datasets). We opted post hoc to include these papers as they report on different analyses, but clearly note them as non-independent in the review and table.

2.2 Synthesis of results

The results of the studies are reported in 3 ways: 1) descriptive information and narrative results are presented in Table 1; 2) When reported in the study, effect sizes and statistical significance are included in Table 1; When not reported, but able to be calculated, the authors calculated the effect size, 3) Narratively report on all studies meeting criteria, organizing the results by study design. In interpreting the findings of each study, we consider measure of rumination and inflammation, study design and recruitment of participants. Given that the purpose of scoping reviews is to examine evidence without critical quality of assessment (Peters et al., 2015), we did not rate each study using an established quality measure. To inform future research, we also included a brief description on the literature as a whole in the areas of reporting of inclusion/exclusion criteria, precision of the assays used, adjusting for relevant confounds and using validated measures of psychosocial constructs.

3. Results

3.1 Overview of Studies

A flow chart of the screening process is available in Supplementary Figure S1. The database search returned 157 citations. One additional study was included after reference treeing and 3 articles were obtained by the search for published versions of the excluded dissertations. Removal of duplicates yielded 98 abstracts and titles. Of these, 23 articles were determined to be eligible for full-text screening. Authors excluded 10 articles through the full text screening process. A total of 13 articles representing 14 studies were determined to meet full eligibility and were included, with a total of 1,221 participants (n = 1,102 unique). All samples but two recruited from the United States of America. Across the 14 eligible studies, eight biomarkers were assessed in serum, plasma or saliva, with interleukin 6 (IL-6)

measured the most frequently (k = 10; 5 plasma, 3 saliva, 2 serum), followed by tumor necrosis factor alpha (TNF-α) (k = 6, 3 plasma, 2 saliva, 1 serum), interleukin 1 beta (IL-1β) (k = 6; 4 saliva, 1 plasma and 1 serum), C reactive protein (CRP) (k = 5; 4 plasma, 1 whole blood), interleukin 8 (IL-8) (k = 3, plasma), interleukin 10 (IL-10) (k = 3, 1 saliva, 1 serum, 1 plasma), interleukin 4 (IL-4) (k = 1, serum), and C-C motif chemokine 11 (CCL11) (k = 1, serum). One study measured CRP, IL-6, IL-8 and TNF-α as a composite, one study measured IL-6, IL-8, IL-10 and TNF-α as a composite and one study also examined the ratio of IL-1β/ IL-10. All studies reported circulating markers, though one also reported lipopolysaccharide (LPS) stimulated markers.

3.2 Individual study results and synthesis

3.2.1 Correlational analyses between rumination and inflammation.—

Six studies reported cross-sectional analyses. Across these studies, CRP, IL-1β, IL-6, IL-8, TNF-α, IL-10 were assessed, with one study measuring these markers as a composite only. Three longitudinal studies report baseline associations between rumination and inflammation. Moriarity and colleagues (2018) reported on a sample of 140 adolescents that were part of a longitudinal study examining vulnerability to depression (ACE). Participants completed the rumination subscale of the Children's Response Styles Questionnaire (CRSQ) at baseline and gave blood samples for assay of plasma IL-6 and CRP at both baseline (T1) and approximately 13.5 months later (T2). Sample sizes differed by analyses, but associations were not significant and primarily negligible, though the correlation with T1 CRP was negative and small (IL-6; T1 r = −.02 & T2 r = −.08; CRP; T1 r = −.13 & T2 r = .05, all p > .05; Moriarity et al., 2018).

In contrast, Moriarity and colleagues (2020a) report on a sample of 103 adolescents who were part of a different longitudinal study focused on vulnerability to bipolar spectrum disorders (TEAM) and therefore had been screened to report moderate to high levels of reward sensitivity, or the degree to which an individual derives pleasure from positive stimuli. Participants completed the Rumination on Positive Affect Scale (RPAS) to measure self-focused rumination, and the brooding subscale of the Ruminative Responses Scale (RRS). Blood samples were collected and assayed for plasma IL-6, IL-8, CRP and TNF-α. Baseline correlations between self-focused rumination and each of the biomarkers were not significant and negligible (IL-6, IL-8, TNF-α; rs < |.04|) to small (CRP; r = .10), with the association with CRP in the positive direction. All associations with brooding were in the positive direction and ranged from negligible (IL-8; r = .06), small (TNF-α; r = .14), to medium (IL-6; r = .25, p < .05) and CRP; r = .33, p < .05), with the last two reaching statistical significance (Moriarity, Ng, Titone, et al., 2020).

Both studies described above excluded for severe psychiatric, developmental, or learning disorders and both were longitudinal studies assessing vulnerability to different mood disorders. Though these studies were similar in design, one study found a significant positive correlation between both IL-6 and CRP and rumination (Moriarity, Ng, Titone, et al., 2020) while the other (Moriarity et al., 2018) did not. However, this could be explained by differences in measures of rumination and sample differences. It is also important to note

that the time of sample collection and pre-visit restrictions, which can impact levels of inflammatory markers, were not described for either study.

The third study examined circulating CRP and both circulating and LPS stimulated IL-1β, IL-6, IL-8, IL-10 and TNF-α, analyzed as a composite, among a sample of midlife adults and controlling for age and BMI (Knight et al., 2021). This study reported a significant interaction between rumination, measured using the Rumination and Reflection Questionnaire (RRQ) and gender in predicting the stimulated cytokine composite (B = −0.50, p = .002), whereby greater rumination was associated with greater inflammation in men (B = .31, p = .02), but less inflammation in women (B = −.19, p = .03). There were no significant gender dependent associations, or gender specific association with reflection, nor were there associations with basal cytokines or CRP with rumination or reflection.

The remaining three studies reporting cross-sectional analyses recruited undergraduate students. In one study, fifty-four female undergraduate students completed the RRS to assess reflective, brooding and depressive rumination, and gave blood samples for assay of plasma TNF-α and IL-10 in one afternoon session (Ysseldyk et al., 2018). Participants were instructed not eat or drink anything besides water or smoke for at least an hour prior to the visit and engaged in a 30-minute rest period prior to giving samples. None of the associations with rumination and inflammation were statistically significant, associations with each scale and TNF-α were positive and negligible for reflection (r = .01), small for depressive (r = .24) and brooding (r = .13, all ps > .05). Associations with IL-10 were negative, but negligible for brooding and depression (r = −.07 to −.08), but small and positive for reflection (r = .10, all ps > .05).

A study by Woody and colleagues (2016), reported baseline analyses among 30 female undergraduates prior to completing an experimental stressor. Participants completed a 2-hour afternoon session and refrained from non-steroidal anti-inflammatory medication (NSAID), alcohol, and exercise for 24 hours, caffeine for 4 hours, and food for 1 hour prior to the visit. Participants completed the RRQ, which has two subscales corresponding to rumination and reflection and gave blood for assay of plasma IL-6, TNF-α and CRP, after a 20-minute rest and questionnaire period. No significant correlations emerged for reflection, with negligible, positive correlations with IL-6 (r = .09) and TNF-α (r = .05), but a negative, small correlation with CRP (r = −.25; all ps > .05). There were no significant associations with rumination, correlations with IL-6 (r = .19) and TNF-α (r = .11) were small and positive, but CRP was small and negative (r = −.24, all ps > .05; Woody et al., 2016).

The final study recruited 84 undergraduate students and was only the second to consider potential covariates (Boren & Veksler, 2017). Participants completed the co-rumination questionnaire, a measure of engagement in excessive discussion about negative problems in dyadic relationships and gave blood for the assessment of CRP in whole capillary blood and saliva by passive drool for assay of IL-6. Bivariate correlations showed no significant associations, with a negligible correlation with CRP (r = .06), but a small, negative association with IL-6 (r = −.22, ps > .05). However, partial correlations that controlled for anxiety, perceived stress and the participants' temperature were statistically significant,

with a medium positive association for CRP (r = .42) and a small, negative association with IL-6 (r = −.28, ps < .05; Boren & Veksler, 2017).

Drawing conclusions across these studies is made difficult by multiple measures of rumination and several markers. While all studies recruited non-clinical samples, there were not clear patterns of associations. Associations with CRP seem to have the strongest support, with a positive, medium association observed in two studies that measured brooding and co-rumination. Of note, the association with CRP and co-rumination only emerged once considering potential covariates. Conversely, the third study found a negative, albeit not significant, correlation between CRP and rumination. Associations between rumination and IL-6 was also significant in two studies, but one in the positive direction and one negative. Little effect was observed for rumination and each IL-8, TNF-α and IL-10. Only one studied analyzed LPS-stimulated markers, and analyzed them as a composite. Thus, cross-sectional analyses show inconsistent support for an association between rumination and inflammation but focusing on CRP or IL-6, or stimulated markers, as well as adjusting for potential confounds may be fruitful areas of future inquiry.

3.2.2 Associations between inflammation and rumination.—Two studies examined associations between inflammation and rumination, one cross-sectional that used advanced statistical modeling and one longitudinal. Inflammation was measured using IL-1β, IL-4, IL-6, IL-10, TNF-α and CCL11 in serum. Silveira and colleagues (2020) used machine learning to understanding correlates of rumination, measured by the RRS, among 200 adults who met criteria for Anxiety Disorders, Obsessive Compulsive Disorder, Post-traumatic Stress Disorder, Major depressive, Bipolar, Schizoaffective disorders or schizophrenia who did not have a history of substance use disorders, pregnancy/breastfeeding, neurological illness or inflammatory conditions. They report no association between IL-1β, IL-6, IL-10, TNF-α and CCL11 and rumination, and including inflammation did not improve the prediction of rumination (Silveira et al., 2020). In a second study, Mitchell and Christian (2019) collected serum samples of IL-4 and IL-6 from 66 pregnant women at one study visit and measured repetitive perseverative thinking, including rumination, using the Perseverative Thinking Questionnaire approximately 30 days later. There was a small, negative association between rumination and IL-4 that was statistically significant (r = −.24, p < .05), but no significant association with IL-6 (r = .07). Of note, this study also included models with an interaction between SES and rumination as the predictor and inflammation as the outcome. These analyses suggested a significant positive association between higher IL-6 and greater rumination emerged among those with higher SES (Mitchell & Christian, 2019). Thus, one study suggested a relationship between IL-4 and rumination, but little evidence for the relationship of inflammation to rumination among IL-1β, IL-6, IL-10, TNF-α and CCL11.

3.2.3 Longitudinal studies of rumination predicting inflammation.—Three longitudinal studies examined rumination as a predictor of inflammation. Plasma levels of CRP, IL-6, IL-8, IL-10, IL-1β and TNF-α were assessed across the three studies. Moriarity and colleagues (2018), described above, assessed whether symptoms of anxiety and depression interacted with rumination to predict levels of IL-6 and CRP among 86

adolescents with complete data in the ACE study. Rumination was measured using the CRSQ at baseline (T1), and participants provided plasma samples at T1 and follow up (T2), and measures of anxiety and depression at T1, T2, and a second follow up (T3). The mean time between T1 and T2 was 13.5 months (SD = 5.9), and the mean time between T2 and T3 was 12.5 months (SD = 6.5). Analyses controlled for age, SES, sex, race, T1 biomarker levels, T1 depressive symptoms, T2 BMI, time of T2 blood draw, and time in study. The interaction between symptoms of anxiety and rumination was a significant predictor of T2 IL-6, with high rumination predicting greater IL-6 (b = .0004, SE= .0002, p = .0392, and lower rumination predicting lower levels of IL-6 (b = .0004, SE = .0002, p = .0420) at high levels of anxiety. Additionally, there was an indirect effect of T1 anxiety symptoms on T3 depression symptoms which was mediated by log IL-6 at low levels of rumination only (−1 SD below the mean: b = −.0178, SE = .0121; Moriarity et al., 2018).

One of the above longitudinal studies using a sample of 109 TEAM participants also assessed whether interactions between two types of rumination and reward responsiveness were associated with inflammation (Moriarity, Ng, Titone, et al., 2020). The RPAS, the brooding subscale of the RRS, and the Behavioral Activation System Scale (BAS) were administered at baseline, and plasma samples of CRP, IL-6, IL-8, and TNF-α were collected several years later. These analyses controlled for gender, race, age at blood draw, BMI at blood draw, birth control use, use of anti-inflammatory medications, and time of day of the blood draw. Greater global inflammation, measured by a composite score of inflammatory markers, was associated with combined high reward responsiveness and high rumination on positive affect (b = .134, SE = .067, t = 1.987, p = .050) as well as combined low reward responsiveness and low self-focused rumination (b = −.152, SE = .076, t = −1.987, p = .050). Follow up analyses suggest these findings were driven by significant associations with IL-8. However, there was no association between global inflammation and the interaction between reward responsiveness and brooding rumination (Moriarity, Ng, Titone, et al., 2020).

The final study, also described above, reported on circulating and LPS-stimulated levels of IL-1β, IL-6, IL-8, IL-10 and TNF-α analyzed as a composite (Knight et al., 2021). Longitudinal analyses (multilevel coupling analyses) over three waves of data collection approximately 1 year apart examined interactions between gender and each rumination and reflection predicting the circulating CRP and cytokines as well as stimulated cytokines as a composite. Similar to the cross-sectional findings, rumination was positively associated with stimulated cytokines for men, and negatively coupled with stimulated cytokines in women, however the confidence interval for men included zero. There were no association with rumination and CRP or circulating markers, or for reflection and any of the circulating or stimulated measures.

Together, these show that rumination seems to interact with other psychological risk factors, including anxiety and reward responsiveness, and gender. Notably, this was observed across measures of self-focused rumination and brooding. In terms of study design, these three studies used longitudinal designs and examined vulnerability to different mood disorders and healthy aging. Other studies using data from the same study as Moriarity et al., 2018 reported up to 40% of the ACE sample had been diagnoses with a mood, anxiety, or externalizing disorder (Alloy et al., 2012). Moriarity, Ng, Titone, et al., 2020 report that

in their total sample of 109 TEAM participants that 72 had high BAS scores, 37 were moderate, and 32 had a history of bipolar spectrum disorders. Therefore, these studies differ from others reviewed thus far with their inclusion of individuals with persistent mental health symptoms or including the spectrum of non-clinical and clinical participants. This may suggest that rumination is a particularly potent vulnerability factor for changes in inflammation among those with other vulnerabilities to poor mental health or those at midlife, which is a critical timepoint for the development of health conditions.

3.2.4 Experimental studies or laboratory studies—Seven studies examined associations between rumination and inflammatory responses to a laboratory stressor. Across these studies, 6 biomarkers were assessed including CRP, IL-6, IL-8, IL-1β, IL-10, and TNF-α. In a seminal experimental study by Zoccola and colleagues (2014), 34 female undergraduates completed self-report measures including the RRQ, completed a 5 minute speech in front of two evaluators and a video camera, and then were randomly assigned to either complete a 5-minute guided rumination or distraction task. This study excluded individuals who reported any chronic health condition, smoking, or the use of anti-inflammatory medication, antidepressants, beta blockers, or hormonal contraceptive. All visits took place in the afternoon and pre-visit restrictions included no strenuous exercise, alcohol, or NSAIDs for 24 hours, caffeine for 4 hours, and food for 1 hour. Participants provided blood samples prior to, as well as 20, 43, and 62 minutes after beginning the speech, which were assayed for plasma levels of IL-6, TNF-α, and CRP. After controlling for BMI and baseline levels of inflammatory markers, significant group differences were found with the rumination group showing greater increases in CRP than the distraction group 62 minutes after stressor onset. However, there were no significant group differences in TNF-α or IL-6 over the course of the session (Zoccola et al., 2014). Secondary analysis of this sample (n = 30) combined the two experimental conditions and examined associations between trait reflection, a neutral type of repetitive thought using the Rumination-Reflection Scale, and change in IL-6, TNF- α, and CRP from baseline to the 62 minute post-stressor time point. Trait reflection was a significant predictor of changes in IL-6 only, with increased reflection predicting smaller increases in IL-6 (b = −.43, $t(28)$ = −2.50, p = .019). After controlling for BMI, personality traits (e.g. openness to experience, neuroticism), trait rumination, experimental condition, and SES, trait reflection remained a significant predictor of IL-6 (b = −70, p = .007), but no association was observed between trait rumination and changes in CRP, IL-6, or TNF-a (Woody et al., 2016).

Though these studies used the same sample, the authors used different analytic approaches and conceptualizations of rumination which could explain the differences in their findings. Zoccola and colleagues (2014) assessed group differences in inflammatory markers over time, while controlling for baseline levels between experimental rumination, which could be conceptualized as state rumination, and distraction, whereas Woody and colleagues (2016) examined trait reflection as a predictor of pre to post-stress changes in inflammatory markers while controlling for trait rumination and experimental condition. Neither study found a significant association between rumination and IL-6 or TNF- α, but the two studies differed in their findings for CRP. The first found that those who completed a 5-minute guided rumination had higher levels of CRP 62 minutes after a 5-minute speech stressor

among compared to those who completed a distraction task. However, secondary analysis controlling for experimental condition did not find rumination to be associated with changes in CRP from baseline to 62 minutes post-stress. This may suggest that active rumination may influence stress reactivity of certain cytokines rather than an individual's tendency to engage in ruminative thinking and that reflection may be protective.

Two studies asked participants to recall upsetting events and measured markers of inflammation in saliva. In a study by Futterman Collier and colleagues (2016), 46 women with textile making experience and who did not have a history of psychiatric disorders in the past year, a major chronic health condition, or an acute infection, recalled an upsetting or traumatic event for 8 minutes and were randomly assigned to one of three conditions: textile making, ruminative expressive writing, or relaxation meditation. Sessions took place between 7:00 am and 12:00 pm and participants were asked not to drink alcohol, tea, or coffee, or engage in strenuous exercise before the morning of the visit. Salivary IL-1β samples were taken after the recall and again after 15 minutes of the assigned activity, approximately 25 minutes later. Salivary IL-1β significantly increased for those in the ruminative writing condition ($t(11) = -2.37$, $p = .039$), but did not change significantly in the other two conditions (Futterman Collier et al., 2016). The second study was reported in Newton and colleagues (2017), which included 68 young adults who were recruited from the local university community. Participants attended two study visits with the first being used to determine eligibility, those who were pregnant, nursing, or using prescription medications other than oral contraceptive were excluded, and participants completed a reaction time ignoring/forgetting task to measure interference control, conceptualized as an objective measure of rumination mechanisms. The visits took place between 12:00 pm and 4:00 pm approximately 4 days apart, and pre-visit restrictions for visit 2 were discussed at visit 1, which were no surgery, dental work, or acute medical condition in the previous week, no alcohol for 12 hours, and no major meal, sugary food or drinks, dairy products, caffeine, or tooth brushing for 1 hour before the visit. At the second study visit participants completed self-report measures, including the stress reactive rumination scale, and provided saliva samples via passive drool assayed for IL-1β, IL-6, and TNF-α and adjusted for flow rate, 10 minutes prior to, and 40 minutes after a 10 minute angry memory retrieval task. Participants were also randomized into a post-stressor rest condition, meant to maximize the opportunity for rumination, or a distraction condition. There was a significant difference in post-retrieval levels of IL-1β between the groups, with the rest condition showing greater increases in this cytokine than the distraction condition. No significant correlations emerged between stress-reactive rumination and the reactivity of IL-6, IL-1β, TNF-α. There were no significant correlations between cytokine reactivity and the objective measures of rumination - ignoring or forgetting (Newton et al., 2017). Taken together findings from each of these studies suggest IL-1β measured in saliva may be sensitive to rumination on personally upsetting events.

Several studies described results from modified versions of the Trier Social Stress Test (TSST), a standard psychosocial stressor. In a separate study described in Newton et al., 2017, 68 young adults completed a modified TSST (mTSST), in which participants prepared for and completed a mock interview with evaluators in a separate room who communicated with them through an intercom and were then directed to count backwards

in increments of 13 starting at 2011. The same recruitment methods and pre/post stressor procedures were used as in the study mentioned above. Notably, the samples were recruited to be free of mental or physical health conditions, however these were not exclusions, and some participants screened positive for one or more condition. In this study, there were no significant group differences in the stress reactivity of any inflammatory marker, but a significant correlation between stress reactive rumination and change in IL-6 in the overall sample was identified ($r = .26$, $p \leq .035$). No significant correlations emerged between rumination and the stress reactivity of IL-1β or TNF-α. There were no significant correlations between cytokine reactivity and ignoring or forgetting (Newton et al., 2017).

Similarly, Szabo and colleagues (2019) used the same mTSST in an independent sample of 71 female undergraduates, after excluding current smokers, individuals with chronic health conditions, those who used medication other than birth control, had an oral health condition, or screened positive for a probable psychiatric condition. Study sessions took place between 12:00 pm and 5:00 pm and participants were asked not to eat, brush their teeth, exercise, or drink anything besides water for one hour beforehand. Saliva samples were collected using passive drool for assay of IL-10 and IL-1β 10 minutes before and 35 minutes after beginning the 10-minute stressor and were adjusted for flow rate. After completing the stressor, participants sat quietly for 35 minutes and then reported what they thought about during the post-stress phase. This was coded as 0 = did not think about the stressor and 1 = thought about the stressor and was used as a measure of rumination. When controlling for BMI, age, hormonal birth control use, and baseline cytokine levels, positive associations were identified between rumination and post-stress IL-1β ($\beta = 0.16$, $p = .03$) as well as the IL-1β/IL-10 ratio ($\beta = 0.17$, $p = .01$). However, there were no significant associations between rumination and post-stress IL-10 (Szabo et al., 2019). Though the design of this study was similar to that of the mTSST study described in Newton et al., 2017, Szabo and colleagues 2019 measured momentary reports of rumination while Newton et al., 2017 used a measure of trait stress-reactive rumination. The former recruited for healthy men and women, while the latter recruited only women and screened out participants based on self-report of a range of medical and psychiatric conditions. Further, Szabo et al., 2019 predicted post-stress levels of cytokines, controlling for baseline levels and Newton et al., 2017 used change scores, which all could explain the differences in their findings.

Finally, one study reported on a subsample of 89 adolescent participants from the ACE study mentioned above, who completed a mTSST that was shortened and modified for adolescents (Moriarity, Ng, Curley, et al., 2020). The BAS and the rumination subscale of the CRSQ were collected at a separate visit prior to completing the mTSST. Plasma samples, which were assayed for IL-6, TNF-α, CRP, IL-10 and IL-8, were collected immediately before stressor onset and 60 minutes post-stressor. Only IL-6 and IL-8 showed stress reactivity, so hypotheses were tested on these cytokines only. High reward sensitivity interacted with high rumination to predict greater post-stress levels of IL-6 only when controlling for baseline levels, gender, income, age, and race ($b = 0.003$, $SE = 0.001$, $p = 0.044$; Moriarity, Ng, Curley, et al., 2020). Despite all using modifications of the TSST, these three samples studies varied in their recruitment of participants, measure of rumination, measure of inflammation and approach to data analysis. This variability makes drawing conclusions across studies difficult.

More generally, all seven studies using experimental designs varied in their inclusion criteria, measurement of rumination, choice of acute stressor and approach to data analysis. First, all but two studies recruited female subjects only, with the two studies from Newton et al., (2017) representing a primarily female sample (72%) and Moriarity et al., (2020b) study more evenly split (i.e., 50.6% female). Additionally, these samples were predominately healthy, though inclusion/exclusion varied by study. The studies also varied in inflammatory markers included in analysis, with five studies including analysis of IL-6, four including IL-1β, four including TNF-a, two including CRP, and IL-8 and IL-10 were each included in one study. Significant associations between rumination and each IL-1β and IL-6 were observed in three and two studies, respectively. None of the studies found significant associations between rumination and TNF-α, IL-10, or IL-8.

In sum, there were more consistent findings for an association between rumination and inflammation among those that included a rumination manipulation. Zoccola et al., 2014 and Futterman et al., 2016 both included rumination conditions (5-minute guided rumination; 15- minute ruminative writing task) and both found group differences in cytokine reactivity, with rumination conditions being associated with greater reactivity of CRP in one study and IL-1β in the other. Additionally, when opportunity of rumination was maximized with a post-stressor rest period as in Szabo et al., 2019 or a randomized rest condition as in the memory retrieval study by Newton et al., 2017, differences in IL-1β measured in saliva were observed. However, this was not observed in the mTSST also described in Newton et al., 2017, though this may be explained by a lower level of post-stress rumination and little difference in rumination between the two post-stress conditions (i.e., those in the distraction condition and the opportunity of rumination condition).

Study Quality: The majority of the included studies (92.9%) reported clear inclusion and exclusion criteria. While measures of rumination varied, 78.6% used at least one validated measure, and 14.3% used a manipulation as their primary measure. For inflammation, 57.1% of studies reported pre-visit restrictions for things that could impact inflammation levels, such as eating, drinking or exercise. In terms of assays, only 42.8% clearly reported coefficient of variation (CVs) that were below the recommended level of 10% for intra-assay variability and 15% for inter-assay variability. Another 35.7% reported one or more measure that was above suggested threshold or it was unable to be determined if a value above 10% referred to inter-assay or intra-assay. Missing data was an issue, as only 35.7% of studies clearly mentioned missing data, particularly for the detection of inflammatory markers. Finally, 64.3% of studies presented analyses adjusting for potentially relevant covariates, though an additional 21.4% either included strict inclusion criteria or adjusted for psychosocial but not health related covariates.

4. Discussion

Inflammation is a transdiagnostic process implicated in mental and physical health problems. Critically, inflammation is multifactorial with both psychosocial and physiological correlates. Perseveration involves a thinking style that is repetitive and can be harmful due to repeated reflection on stressors, negative mood states, and anger inducing events (Brosschot et al., 2006) and has been implicated in reduced treatment efficacy

for psychotherapy (Kertz et al., 2015). Rumination is one type of repetitive negative thought that has been implicated in the development and maintenance of psychopathology (Watkins & Roberts, 2020) and greater stress responses (Busch et al., 2017). The purpose of the present study was to conduct a scoping review of existing research examining the relationship between rumination and inflammation. This review summarizes evidence from 13 studies representing 14 samples and 1,102 unique participants. We included 8 biomarkers measured in plasma, serum and saliva. Study designs were cross-sectional, longitudinal, and experimental.

4.1 Summary of evidence

The included studies varied in the domains of study design, measure of rumination, sample characteristics, markers of inflammation, and collection of biological samples. Some of the strongest evidence comes from longitudinal studies. Notably, significant findings were most consistent for IL-6 in the longitudinal designs (Mitchell & Christian, 2019; Moriarity et al., 2018; Moriarity, Ng, Titone, et al., 2020). Moreover, these studies only found effects when looking at interactions with other psychosocial constructs, such that IL-6 was associated with rumination at high levels of SES (Mitchell & Christian, 2019), high anxiety (Moriarity et al., 2018) and high BAS (Moriarity, Ng, Titone, et al., 2020). This may suggest that rumination amplifies vulnerability. Notably, these were some of the only models that included covariates (i.e., cross-sectional correlations did not), and it may be that factors influencing inflammation were confounds. Another significant correlation was reported between IL-4 and rumination, measured as perseverative thought, in a single study (Mitchell & Christian, 2019), which may suggest bidirectional relationships.

The next strongest evidence comes from studies that have experimental designs or manipulations. Another pattern was that significant findings were most consistently found among studies that manipulated rumination or used acute stressors (Szabo et al., 2019; Woody et al., 2016; Zoccola et al., 2014). Rumination has been linked to activation of the HPA axis (Shull et al., 2016; Zoccola & Dickerson, 2012). In turn, hyperactivity of this system and glucocorticoid resistance can contribute to activation of pro-inflammatory markers and acute phase proteins (Raison & Miller, 2003). These results fit with the meta-analysis on physiological correlates of perseverative cognition, that did not include inflammation, which observed larger effect sizes for studies using experimental rather than correlational designs (Ottaviani et al., 2016).

There is some initial evidence that findings may vary by biomarker examined. IL-6 may be sensitive to stress and stress-reactive rumination (Moriarity, Ng, Curley, et al., 2020; Newton et al., 2017). At the same time, there was some evidence that reflection, a neutral type of repetitive thought, could be protective for IL-6 (Woody et al., 2016). Further, there was a trend for IL-1β measured in saliva to be increased following remembering personally relevant information (Futterman Collier et al., 2016; Newton et al., 2017). In contrast, results from cross-sectional studies were less consistent, with strongest support for IL-6 and CRP with significant results from two studies each.

A small literature with heterogeneity in terms of design and types of markers used limits generalization that can be made. The extant literature is limited by non-representativeness of

the samples for the general population. Most included participants were young and healthy, with only one sample (Silveira et al., 2020) being from clinical settings or recruited to meet criteria for a physical or mental health disorder and four other studies from three samples including some participants with mental health disorders or vulnerability to develop them (Knight et al., 2021; Moriarity et al., 2018; Moriarity, Ng, Curley, et al., 2020; Moriarity, Ng, Titone, et al., 2020). In addition to limiting generalizability to clinical samples, it is noteworthy because many analytes have low circulating levels in healthy adults. In terms of age, some evidence has suggested associations with rumination and both immune markers and healthcare utilization are observed in an elderly sample, but not a young adult sample (Thomsen et al., 2004). This may indicate that age is an important consideration in associations between rumination and health. In addition, none of these samples were primarily male. Some evidence suggests that men may be more sensitive to state rumination in the context of HPA axis activation (Zoccola et al., 2010) and male/female differences in both levels of inflammation and responses to acute stress responses have been noted in previous studies (Steptoe et al., 2002; Szabo et al., 2016; Yang & Kozloski, 2011), including one reviewed here (Knight et al., 2021), suggesting this may be an important area of future inquiry. Further, many of the included studies included relatively small samples, which would mean that they were likely only powered to detect medium to large effects. Most of the effect sizes observed here were small in magnitude, so this may contribute to the lack of significant findings.

While the purpose of scoping reviews is to summarize the extant literature without critical appraisal of the quality of evidence (Peters et al., 2015), attention to these factors as additional research is generated will help with identifying patterns/themes in findings (Tricco et al., 2018). As such, the present study did not include a formal quality assessment with scores, particularly as there is no gold-standard design for the research questions posed here. However, we opted to provide an overview of several domains relevant for quality of studies examining rumination and inflammation, such as assay precision, validation of measures used, and handling non detectable inflammation samples, as well as factors associated with study quality more broadly, such as missing data, clear inclusion and exclusion, and confounding control.

4.2 Implications and Future Directions

The varying methodologies and findings limit the ability to make conclusions but offer directions for future research. Future research with consideration to the facets of design, measurement and analysis may be useful (Kline, 2009). Design refers to structural elements of a study, including the sample studied, the conditions or manipulations as well as the assignment to conditions, the data collected and the time schedule for measurement. In terms of design, experimental or longitudinal designs will provide more causal evidence than cross-sectional designs. Notably, some studies created an experimental condition to induce rumination. This offers internal validity, meaning the extent to which a causal association can be assumed. Another design that might inform causal relationships over time would use ecological momentary assessment or daily diary studies. Daily experience of emotion has been associated with inflammation (Sin et al., 2015) and daily diary studies are one design proposed to help clarify mechanistic relationships between inflammation

and depression (Mac Giollabhui et al., 2020), which is one well-known consequence of rumination. Another important element of design includes recruitment of participants. As highlighted above, few studies included participants with clinical diagnoses and many of the samples included adolescent or undergraduate student samples. Considering that rumination is a transdiagnostic factor for mood and anxiety disorders, and such disorders have been associated with negative health outcomes and systemic inflammation, researchers should consider examining associations between rumination and inflammation in a clinical sample. Overall, limiting the use of cross-sectional studies and increasing consideration of covariates and clinical samples are important next steps in this important line of inquiry.

Analysis refers to how data collected in the study is utilized to draw conclusions. Three considerations in the area involve defining the outcome of interest, handling non-detectable samples and controlling for potential confounds. Numerous factors influence inflammation, and peripheral levels of inflammatory markers can vary widely, even among healthy individuals (O'Connor et al., 2009). Health status, oral health, BMI, and age, may be important for studies of inflammation (see O'Connor et al., 2009 and Szabo & Slavish, 2021 for consideration of important confounds in health research using inflammation). Particularly for longitudinal or experimental studies, it may be important for researchers to consider controlling for baseline levels of inflammatory markers in order to better examine how rumination specifically impacts inflammation. Some studies included here used post-stress scores, controlling for baseline (Moriarity, Ng, Curley, et al., 2020; Szabo et al., 2019); notably both of these studies found significant effects. Controlling for baseline will allow researchers to detect residual changes in inflammation that may have been influenced by rumination but may be masked when looking at change scores alone. However, future research is needed to determine which has most predictive validity. Another important issue is how researchers handle non-detectable samples of analytes, which is a common problem in inflammation research. As described elsewhere (Riis et al., 2020; Szabo & Slavish, 2021), one approach is to impute a small or large value for each of these non-detectable (low end) or out of range (high end) in order to retain participants in analyses. This increases power and can increase the range of the outcome. In summary, one significant issue in inflammation research is the way in which non-detectable samples are handled and what is controlled-for in experimental research. Outcomes using change scores also may not be ideal for inflammation work due to large variability in biologically plausible values between participants and other methodology described above may be more useful.

One critical focus for future research is the measurement of constructs of interest. The extant literature reviewed here included several measures of ruminative thinking. Some measures of rumination are used to determine the likelihood or frequency an individual engages in rumination (trait rumination), while others assess active rumination, retrospective rumination, and intrusive rumination (state rumination). Assessing trait rumination alone does not allow researchers to determine whether an individual actively engaged in rumination during an experimental or cross-sectional study session in a way that measures of state rumination can. However, trait measures have been reliably linked to negative outcomes. Historical definitions of rumination conceptualize it as focused attention on mental representations of negative events, feelings, and thoughts (Rippere, 1977). In the 1990s, Dr. Nolen-Hoeksema's work focused on depressive rumination as a mechanism

for gender differences in depression, which may be used by women who traditionally are societally disempowered, have reduced agency and a more external locus of control to problem solve compared to men (e.g., Nolen-Hoeksema et al., 1999). Without resolution to these problems, vulnerability to depression is maximized (Nolen-Hoeksema & Jackson, 2001). More recent research has built on this work (i.e., the Response Styles Theory) by showing that two factors that are unconfounded by depression – brooding and pondering – may have unique predictive validity for psychosocial constructs (Treynor et al., 2003). Additionally, studies measured subtypes of trait rumination, such as stress-reactive rumination, brooding and reflection. More recent research has further elucidated the most maladaptive parts of rumination by focusing more specifically on the timing or nature of rumination. This research has suggested repetitive or anticipatory rumination is more closely related to depression and PTSD compared to problem-focused thoughts or counter-factual thinking (Roley et al., 2015). Indeed, most measures of rumination include subscales that measure repetitive rumination or brooding, compared to reflection. Future research would benefit from comparing different measures of rumination in their associations with inflammation within the same study. Better understanding of the construct of interest including convergence on rumination construct(s) that account for the most variance in inflammation work is an important goal for future research.

The study of rumination and inflammation would be aided by more objective measures of rumination. Rumination has been associated with “cold” cognition and executive functioning in some prior studies such as perseverative errors on a novel problem-solving test in those selected for a ruminative thinking style (Davis & Nolen-Hoeksema, 2000) and decreased inhibition on the Stroop task in dysphoric adults induced to ruminate (Philippot & Brutoux, 2008). More often studies use “hot” cognitive tasks with valanced-stimuli that are associated with rumination. Of the studies reviewed here, only Newton et al., 2017 used a performance-based “hot” cognitive task to measure rumination, and no association was found with either rumination or inflammation in this healthy sample. This ignore/forget task, adapted from Joormann and colleagues uses negatively-valenced words and was originally associated with depression (Joormann et al., 2010). Other versions of this task, which also use negative priming, have been associated with both depressive symptoms and rumination over time (Zetsche & Joormann, 2011). Another affective task-switching paradigm assesses the ability to attend to and disengage from emotional aspects of a visual stimulus. One study using this task found that better flexibility, or reduced switch costs when switching away from the negative to the neutral aspects of a visual stimulus, was associated with reappraisal, or ability to re-think negative information to be more neutral or positive (Malooly et al., 2013) and inflexibility on the task predicted rumination (Genet et al., 2013). On a similar task, rumination also fully mediated the association between negative switch costs and depressive symptoms after one year (Demeyer et al., 2012). It may be true that biased affective flexibility contributes to depression by increasing rumination given that shifting away from negative elements of stimuli may lead to longer times periods to process negative information, thus increasing rumination (e.g., Joormann & D’Avanzato, 2010; Koster et al., 2011; Wen & Yoon, 2019). Further research on “hot” cognitive tasks that tap shared neural correlates of rumination and inflammation, including their construct validity and associations with each rumination and inflammation, may be important and warrant future

study. Providing more objective measures including cognitive tasks that are predictive of rumination can be helpful future intervention targets and useful for measurement of treatment outcome.

Underscoring the utility of better understanding the links between rumination and inflammation, augmenting neural networks via interventions such as neurostimulation may also impact on inflammation as a potential mechanism of action for improved psychiatric symptoms. As an example, transcranial magnetic stimulation (TMS) is a form of neural stimulation that involves sending low dose magnetic pulses to a region of interest in order to stimulate synaptic firing to treat depression. While the mechanisms are not fully understood, one theory that has received support in the literature is that repetitive TMS (rTMS) to neural network nodes, including the DLPFC, impacts on network connectivity (Fox et al., 2012; Lantrip et al., 2017; To et al., 2018) and may result in improved affective symptoms via benefits to emotion regulation (Baeken et al., 2010; Lantrip et al., 2019). It may be that using rTMS focused on the DLPFC results in improvement in depression symptoms due to multiple factors including improved DMN/CCN connectivity, emotion regulation, and possibly inflammatory response given the link between network connectivity and IL-6 (Marsland et al., 2017). Limited resarch in this area using animal models suggests that the effect of rTMS on depression is via effects on neuroinflammation (Tian et al., 2020). Further studies testing the potential link between network connectivity, emotion regulation/ rumination and inflammation and impact by TMS are needed.

In order to fully inform health-oriented models, understanding factors that predict levels of rumination are of interest. Silveira and colleagues (2020) used machine learning to differentiate individuals with high versus low levels of rumination. The best fitting model included SES, illness severity, worry, anxiety and depressive symptoms, and current panic disorder among a sample of adults with one or more psychiatric disorders. Other identified correlates of rumination include such as childhood trauma (Conway et al., 2004; Szabo et al., 2020), as well as perfectionism (Randles et al., 2010) and poor sleep (Borders et al., 2015). Further, physical activity, a health behavior, has been associated with better cardiovascular recovery and less rumination in an acute stress study (Puterman et al., 2011). As these can each have implications for health and well-being, further study on these correlates and direction of some associations is warranted.

Much of existing theory posits a directional relationship whereby rumination impacts inflammation, particularly in the context of stress. However, it is also plausible that inflammation causes or promotes rumination, perhaps by acting on shared mechanisms. For example, experimental induction of inflammation using a low dose endotoxin was associated with brain activity in of the ventral striatum, associated with reward, which in turn was related to depression symptoms (Eisenberger et al., 2010) as well as amygdala activity while viewing socially threatening images (Inagaki et al., 2012). Further, changes in the ventral striatum pre to post mindfulness intervention correlated with IL-6 and CRP (Dutcher et al., 2021). Together these show that inflammation can act on neural correlates, particularly in regions associated with rumination. Additional research is needed to clarify the direction, or possibly bidirectionality, of associations between rumination and inflammation.

The present review focused on rumination, which has been described as one type of perseverative thinking. Rumination is distinguished from other forms of perseverative thought, such as worry, by repetitive focus on past events and its potential to prolong the experience of negative emotions such as anger or depressed mood (Peled & Moretti, 2010). Though it is a transdiagnostic factor identified in several psychological disorders, associations between rumination and depression onset, maintenance, and treatment resistance have been well established (Jones et al., 2008; Kertz et al., 2015; Schmaling et al., 2002). Conversely, worry is characterized by repetitive fearful thoughts about events that have not yet happen and may not occur, and is strongly associated with anxiety (Clancy et al., 2016). A large body of evidence suggests a bidirectional association exists between depression and inflammation (Beurel et al., 2020), while less is known about inflammation and anxiety (Costello et al., 2019). However, the relationship between inflammation and perseverative thinking more broadly warrants consideration. For example, the article included by Mitchell & Christian, 2019 included a measure of more broad perseverative thinking. This article found links with this measure and SES in inflammation. A broader measure of repetitive thought, construct derived of rumination, worry, reflection, brooding and pondering was associated with IL-6 post-vaccine (Segerstrom et al., 2008), suggesting perseverative thought may be a unique vulnerability for health. Thus, the unique contributions of different types of perseverative thought and their predictive validity for inflammation should be clarified in future research.

5. Conclusions

The present scoping review offers an up to date synthesis of the emerging research focused on rumination and inflammation. The most consistent findings were observed in studies that used an experimental task, manipulated rumination or tested the moderating effect of rumination on inflammation. There was little support for an association between rumination and inflammation in cross-sectional analyses. The relationship between inflammation and rumination may be contingent on both how rumination is conceptualized and measured, as well as the measure of inflammation (i.e., at rest or in response to stress). Our findings suggest a paucity of research in clinical samples. As future research unfolds, we offer guidance for research questions and methodological considerations. As more studies are assessed, more specific questions can be formulated and valuably addressed by a systematic review and meta-analysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Included studies in the review

Author & Country	Population	Design	Biomarker and Sample Type	Rumination measure	Results & Effect Sizes	Reported Funding source
Boren & Veksler, 2017; United States	College students, aged 18–23, 83% white, *n* = 63 for IL-6, *n* = 84 for CRP	cross-sectional	IL-6 (saliva); CRP (whole blood)	Co-rumination questionnaire	Bivariate correlations between co-rumination and each CRP (r = .06, p > .05) and IL-6 (r = −.22, p > .05) were not significant One-tailed partial correlations, controlling for anxiety, perceived stress and temperature, were significant for CRP: $t(48)$ = .42, p < .001 and IL-6: $t(48)$ = −.28, p = .024	Thomas Terry Research Grant & Faculty Student Research Assistant Program, Santa Clarita University
Futterman Collier et al., 2016; United States	46 women with moderate textile making experience (Mage = 53.5, *SD* = 14; range 18–77 years); 92% White.	experimental - women discussed an upsetting event for 8 minutes, then randomized to post task activity (textile art making, meditation, or expressive writing)	IL-1β saliva, measured after angry memory task and after 15 minute activity (25 minutes later)	Some participants were randomized to writing condition to maintain rumination.	Repeated measures ANOVAs for activity (between subjects) and time (post mood induction, post-activity; repeated measures) for IL-1β concentrations showed an overall effect for time, $F(1, 44) = 6.60$, p = .014. Follow up analyses suggest IL-1β increased significantly after the writing condition $t(11) = -2.37$, p = .039, d = −.715 [7]	N/A
Knight et al., 20201; United States	162 adults 25–65 (wave 2 n = 95, wave 3 n = 71) 64% African-American; 21% Hispanic 67% women, no history of inflammatory-related illness or psychiatric disorders beyond depression, and not taking potent immunosuppressive drugs	Cross-sectional and longitudinal observational study; LPS stimulated cytokine levels	CRP (plasma); basal and stimulated IL-1β, IL-6, IL-8, IL-10, TNF-α (plasma); 12 hour fasting blood samples taken at each time point	Reflection and Rumination subscales of the Rumination–Reflection Questionnaire	There was a significant baseline gender × rumination interaction correlating with stimulated cytokine composite (Men: b = 0.314 [0.052, 0.576], p =.020; Women: b = −0.186 [− 0.348, − 0.023], p = .026. Longitudinal multilevel coupling analyses across all waves showed significant gender × rumination interaction predicting stimulated cytokine composite (Men: 0.207 [− 0.023, 0.437]; Women 0.174 [− 0.325, −0.024], p not reported). Analyses controlled for age and BMI, robustness analyses examined depression symptoms and menopausal status. There were no significant associations between reflection and stimulated cytokines, basal cytokines, or CRP. There were no significant associations between rumination and basal cytokines or CRP.	National Institute of Health (NIH) grants R01 AG039409 (Sliwinski, PI), R01 AG042595 (Graham-Engeland and Engeland, mPIs), and T32 AG049676 (Knight, via Pennsylvania State University)
Mitchell & Christian, 2019; United States	66 pregnant women between 6–29 weeks gestation; 76.1% White; Mean age 29.8 (*SD* = 5.3), n = 66 for IL-4 and 60 for IL-6	longitudinal - two time points 30 days apart	IL-4 and IL-6 (serum); measured at time 1	Perseverative Thinking Questionnaire (PTQ); measured at time 2	Negative correlation between IL-4 and PTQ (r = −0.24, p = 0.05), but not IL-6 (r = 0.07, p = 0.62) Cumulative SES moderated association with PTQ and IL-6 ($F(8,50) = 3.08$, p < 0.01, R^2 = 0.33), such that PTQ was more strongly associated with IL-6 only for those with high SES (b = 0.01, $t(50)$ = 2.24, p = 0.03, 95% confidence interval [0.001, 0.012], ΔR^2 = .07, ΔF = 5.00); a relationship was not observed for IL-4. Analyses controlled for covariates of race, BMI, gestational age, medical conditions.	National Institute of Health (R01 NR01366, LMC) and National Center for Advancing Translational Science Grant Award Number UL1TR001070G

Author & Country	Population	Design	Biomarker and Sample Type	Rumination measure	Results & Effect Sizes	Reported Funding source
Moriarity et al., 2018; United States†	140 adolescents ages 16–17 (*n* in analyses ranged 86–140) who were part of a longitudinal study (ACE) on depression in adolescence.	longitudinal - provided blood on two separate visits (T1 and T2; mean = 13.5 months, *SD* = 5.9) and completed at least one additional follow-up session (T3)	IL-6, IL-10, IL-8, TNF-α, CRP (plasma); only present IL-6 and CRP (T1 and T2)	Children's Response Styles Questionnaire rumination subscale (measured at T1)	Correlations with rumination and each CRP @T1 (r = −.134, p > .05) & IL-6 @T1 (r = −.017, p > .05); CRP @T2 (r = −.053, p > .05), IL-6 @ T2 (r = .075, p > .05). Anxiety symptoms and rumination interacted to predict interleukin-6 @ T2 such that higher rumination was associated with higher IL-6 (b = .0004, *SE* = .0002, t = 2.0985, p = .0392). This interaction did not significantly predict CRP at T2 (p = .75).	National Institute of Mental Health Grant MH101168 awarded to Lauren B. Alloy
Moriarty et al., 2020a; United States	109 adolescents 14–19, screened for moderate to high reward sensitivity (32 had a history of bipolar spectrum disorder). 52% female, 57% White, 43% non-white, mean age at blood draw = 21.5, *SD* = 2.1. *n* = 103 for CRP analyses	longitudinal	CRP, IL-6, IL-8, IL-10, and TNF-α (plasma); CRP, IL-6, IL-8 and TNF-α analyzed as an inflammatory composite (ICS) at follow up	Rumination on Positive Affect (PA) Scale; Brooding subscale of the Ruminative Responses; administered at baseline,	Self-focused rumination and CRP (r = .103), IL-6 (r = .037), IL-8 (r = −.086) and TNF-α (r = −.059, all *ps* > .05). Brooding and CRP (r = .333, p < .01), IL-6 (r = .252, p < .01), IL-8 (r = .056, p > .05) and TNF-α (r = .143, p > .05). Reward responsiveness and self-focused rumination interaction was associated with ICS (b = .032, *SE* = .014, t = 2.312, p = .023), such that higher reward responsiveness and higher self-focused rumination on PA was associated with greater ICS (> 95th percentile of rumination; b = .134, *SE* = .067, t = 1.987, p = .050) and low reward responsiveness combined with low rumination on PA to predict greater ICS (<6th percentile of rumination; b = −.152, *SE* = .076, t = −1.987, p = .050). The interaction between reward responsiveness and brooding was not associated with the ICS. ICS findings were driven by significant associations with IL-8.	National Institute of Mental Health Grant MH077908 and MH102310 awarded to Lauren B. Alloy and MH100117 awarded to Robin Nusslock
Moriarty et al., 2020b; United States†	89 participants who were a subset of ACE and had completed a modified Trier Social Stress Task (mTSST) Mean age 18.3 years (*SD* = 1.4), 50.6% female, 37.1% Caucasian, and 62.9% African American.	longitudinal and experimental - participants completed mTSST (slightly modified adolescent version of the TSST developed by Hankin et al. (2010) to better suit adolescents.	IL-6, IL-8, IL-10, TNFα, and CRP; plasma), but only present IL-6 and IL-8. Blood was drawn before and 60-minutes after the mTSST.	Children's Response Styles Questionnaire - rumination subscale. Completed at visit closest to the date of the mTSST (*M* = 8.5 months prior, *SD* = 9.6 months).	Bivariate correlations: CRSQ and BL IL-6: (r =.09, p > .05); IL-8 (r =.02, p > .05) CRSQ and diff IL-6 (r =−.04, p > .05), (IL-8 r = −.03, p > .05) The interaction between behavioral approach system (BAS) drive and rumination predicted change in IL-6 (b = 0.003, *SE* = 0.001, t = 2.048, p = 0.044, 95% CI = 0.0001 − 0.0052), such that drive predicted greater increases in IL-6 as rumination increased.	NIMH MH79369 and MH101168 awarded to Lauren B. Alloy and MH118545 to Lauren M. Ellman. Daniel P. Moriartiy was supported by National Research Service Award F31MH122116. Erin Curley was supported by NSF Graduate Research Fellowship 1650457. Brae Anne McArthur was supported by a Banting Postdoctoral Fellowship from the Social Sciences and Humanities Research Council.
Newton et al 2017(Study	68 young adults 71% female, *M* = 20.53 (*SD* = 2.73), African American /	Laboratory - Visit 1: participants completed a	IL-1β, IL-6, and TNF-α (saliva), collected using	reaction time-based task that measures	There were no statistically significant associations between proinflammatory cytokines and rumination in rest or distraction condition (combined for	This research was supported by funding from the

Author & Country	Population	Design	Biomarker and Sample Type	Rumination measure	Results & Effect Sizes	Reported Funding source
1); United States	Black 16%; Asian American 7% European American /White 63%; Latino/Hispanic American 3% Multiethnic 6%; Other 4%	rumination task. Visit 2: self report measures, an angry memory retrieval task, and a randomly assigned rest or distraction post stressor condition	passive drool and adjusted for flow rate (pg/min). Samples were taken at baseline (10 min before TSST) and 50 min after stressor onset	interference control mechanisms (visit 1). Stress-reactive rumination Scale (visit 2)	analysis). For IL-6 reactivity, a positive zero-order correlation with stress-reactive rumination reached statistical significance, (r =.26, $p \leq .035$), but not for, ignoring (r = −.02, $p > .05$) or forgetting (r = −.06, $p > .05$). For change in IL-1β and rumination (r = .04, $p > .05$), ignoring (r =.12, $p > .05$) and forgetting (r = −.07, $p > .05$). For change in TNF-α and rumination the correlation (r = .12, $p > .05$), ignoring (r = −.06, $p > .05$), forgetting (r = −.15, $p > .05$).	American Psychological Foundation, and by a University of Louisville Intramural Research Incentive Grant.
Newton et al 2017(Study 2); United States	68 young adults, 71% female, *M age* = 20.53 (*SD* = 2.73), African American / Black 16%; Asian American 7%; European American / White 63%; Latino/Hispanic American 3% Multiethnic 6%; Other 4%. For IL-1β, n = 43 (rest condition only)	Laboratory - Visit 1: participants completed a rumination task. Visit 2: self-report measures, an angry memory retrieval task, and a randomly assigned rest or distraction post-stress condition	IL-1β, IL-6, and TNF-α (saliva), collected using passive drool and adjusted for flow rate (pg/min). Samples were taken at baseline (10 min before memory retrieval) and 50 min post stressor onset	reaction time-based task that measures interference control mechanisms (visit 1). Stress-reactive rumination Scale (visit 2) retrospective rumination: post event processing questionnaire	For change in IL-1β and stress-reactive rumination (r = .04, $p > .05$), ignoring (r =.003, $p > .05$) forgetting (r =−.04, $p > .05$). For change in IL-6 and stress-reactive rumination (r = −.02, $p > .05$), ignoring (r = −.09, $p > .05$), forgetting (r = −.08, $p > .05$). For change in TNF-α and stress-reactive rumination (r = −.03, $p > .05$) ignoring (r = −.02, $p > .05$) forgetting (r = .11, $p > .05$). Change in IL-1β and intrusive rumination, r =.01, p > .05. Difference between baseline IL-1β and postretrieval levels were significant for the rest condition $F(1,45) = 39.27$, $p < .0001$, $d = 0.92$), but not for the distraction condition ($F(1, 21) = 5.71$, $p = .026$, $d = 0.50$.	This research was supported by funding from the American Psychological Foundation, and by a University of Louisville Intramural Research Incentive Grant.
Silveira et al 2020; Brazil	200 adults, 37.5% male, age: 44.14 ± 12.8 .	cross-sectional	IL-6, IL-1β, IL-10, TNF-α and CCL11 (serum)	Ruminative Response Scale (RRS) 10-item revised	This study employed a machine learning approach to examine correlates of high brooding. The results did not find any significant association between inflammatory markers and higher brooding.	This work was supported by grants from the National Science and Technology Institute for Translational Medicine (INCT-TM), Coordenação de Aperfeiçoamento de Nível Superior (CAPES), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and Fundo de Incentivo à Pesquisa – Hospital de Clínicas de Porto Alegre (FIPE-HCPA).
Szabo et al., 2019; United States	71 women, screened to be physically and mentally healthy (including oral health).	experimental - modified TSST (no confederate) and rested for 35 minutes	IL-1β, IL-10, IL-1β/IL-10 (saliva), measured 10 min before acute stressor (baseline) and 35 minutes after the onset of a 10 minute stressor	Momentary rumination - participants indicated what they had been thinking about during post-stress or coded as 0 = did not think about stressor at all	After adjusting for baseline cytokine levels, rumination was associated with increased post-stress IL-1β (β = 0.16, p = .03; $F(2, 68) = 63.44$, p < .001) and increased IL-1β/IL-10 (β = 0.17, $p = .01$; $F(2, 68) = 92.16$, $p < .001$), but not with post-stress IL-10 (β = −0.05, $p = .62$). for models adjusting for BMI, age, and hormonal birth control use the pattern of findings was unchanged	Research was supported by grant funding from Psi Chi, Louisville College of Arts & Sciences, and the Graduate Student Council at the University of Louisville as well as a sponsorship from the University's Women's Center

Author & Country	Population	Design	Biomarker and Sample Type	Rumination measure	Results & Effect Sizes	Reported Funding source
				or 1 = thought about the stressor.		
Woody et al 2016; ; United States†	30 healthy female undergraduate students. After outlier exclusion, TNF-α n = 27, CRP n = 30, IL-6 n = 30.	Experimental - stressor was 5 min speech task followed by a 5 minute randomly assigned post-stressor condition of rumination or distraction	plasma IL-6, TNF-α, CRP	Reflection and Rumination subscales of the Rumination–Reflection Questionnaire; experimental manipulation	Bivariate correlations: Reflection and baseline IL-6: (r = .09, p > .05) baseline TNF-a: (r = .05, p > .05) baseline CRP (r = −.25; p > .05) Rumination and baseline IL-6: r =.19, TNF-α: (r = − .11, p > .05) CRP: (r = −.24, p > .05); Rumination and cytokine response: IL-6 (r = −.22, p > .05), TNF-α (r = .22, p > .05) and CRP (r = .19, p > .05). Trait reflection was a significant predictor of IL-6 response β = −.43, p = .019; $F(1,28)$ = 6.24, p = .019, R^2 = .18, f^2 = .22†. None of the covariates (including trait rumination) were significant predictors of IL-6 response (ps > .06). The interaction of experimental rumination condition and reflection did not predict IL-6 response (β = 1.32, p = .177). Trait reflection did not predict TNF-a response (β = .05, p = .869) or CRP response (β = .22, p = .407) in the presence of covariates.	This study was supported with funding from the Ohio University Research Committee
Ysseldyk et al., 2018; Canada	54 undergraduate women participated in the study; (age M = 19.52, SD = 2.20).	Cross-sectional	TNF-α, IL-10 (plasma)	The Ruminative Responses Scale - brooding, reflecting and depressive subscales	Bivariate correlations: TNF-a: Reflective: (r = .01, p >.05), depressive (r = .24, p < .10), brooding (r = .13, p >.05); IL-10: reflective: (r =.10, p >.05), depressive: (r = −.08, p >.05) brooding (r = −.07, p >.05). Rumination was not a mediator of association between ingroup ties, ingroup affect or identity centrality and inflammation.	This research was funded by the Canadian Institutes of Health Research grant #86477 awarded to K.M. and Natural Sciences and Engineering Council of Canada grant #10891 awarded to H. A.
Zoccola et al., 2014; United States†	34 healthy female undergraduate students (73.5% white; 20.7 ± 2.3 years old). After outlier exclusion sample sizes for analyses were 34 for IL-6, 30 for CRP, and 34 for TNF-α.	Experimental - participants gave a 5-min speech in front of two evaluators and video camera, followed by either a 5 minute rumination condition of rumination (RUM; n = 18) or distraction (DIST; n = 16) task, then both groups rested and completed questionnaires for 45 min	CRP, IL-6 and TNF-a (plasma); Blood samples were taken pre-stressor as well as 20-, 43-and 62-min post stressor onset	rumination condition	There was a linear increase in CRP concentrations over time, $F(1, 80)$ = 6.55, p < .01, f^2 = .08. but differed for the RUM and DIST groups, ($F(1, 78)$ = 6.46, p = .01, f^2 = .18. RUM group demonstrated linear increases in CRP, $t(79)$= 3.54, p = .001, f^2 = .22. Follow-up contrasts indicated that CRP values were greater in the RUM 62-min poststressor onset compared to DIST, $t(75)$ = 3.38, p = .001, but not at the other time points; there were no differences in circulating TNF-a or IL-6 levels between groups.	This study was supported with funding from the Ohio University Research Committee.

Note.

† = non independent sample

† Calculated using information available in the paper; mTSST = modified TSST