# THE RELATIONSHIP BETWEEN EMOTION REGULATION STRATEGY USE AND CARDIOVASCULAR DISEASE RISK AMONG MOTHERS OF CHILDREN DIAGNOSED WITH CANCER: THE ROLE OF DISTRESS AND INFLAMMATION LEVELS

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Mothers of children diagnosed with cancer are faced with numerous, prolonged stressors that can negatively impact their psychosocial functioning and thus their health. Consequently, identifying potential risk or health protective factors may be especially important for this population. In this regard, a growing number of studies suggest that individual differences in the use of emotion regulation strategies, such as expressive suppression and cognitive reappraisal, may modulate the negative emotional consequences of chronic/prolonged stressors. Though limited and cross-sectional in nature, studies have also started examining associations between emotion regulation strategies of suppression and reappraisal with inflammation—an important biomarker implicated in numerous immune-mediated illnesses, including cardiovascular disease. The main objective of the present study is to extend extant findings to a prospective examination of whether the use of emotion suppression and cognitive reappraisal influence symptoms of distress and inflammation among mothers of children recently diagnosed with cancer (N=120). In the present study, inflammation was indexed by circulating and stimulated levels of IL-6. Mothers were followed from approximately one month of their child's diagnosis (T1) to twelve months post-diagnosis. Results showed a decrease in level of distress and an increase in

circulating and stimulated measures of inflammation across the follow-up period. Higher self-reported use of reappraisal related to lower levels of distress at T1; however, it did not significantly predict rate of change in distress over time. Similarly, higher self-reported use of suppression related to higher levels of distress at T1, but it did not predict rate of change in distress level across the follow-up period. In regard to inflammation, reappraisal did not relate to initial levels or change in circulating or stimulated levels of IL-6. While we also did not observe a significant association between suppression and initial circulating or stimulated IL-6, suppression did predict significantly slower increases in stimulated IL-6 levels. A similar tendency was observed on analysis of circulating IL-6. Implications of these findings and future directions are discussed.

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# 1.0 INTRODUCTION

Mothers of children diagnosed with cancer are confronted with an intense and prolonged stressful life experience that is marked by not only a threat to their child's life but also significant disruption in their life due to numerous additional demands (e.g., taking their child to frequent hospital and clinic visits) and often to marital and financial strain (Long & Marsland, 2011). A review by Vrijmoet-Wiersma and colleagues (2008) examining the psychological and emotional adjustment of this population has shown that during the period immediately following their child's diagnosis, most mothers report a range of negative emotions including feelings of depression, anxiety, anger and guilt. While these symptoms gradually alleviate, for a subset of mothers these symptoms persist, which may be detrimental to both physical and mental health (Vrijmoet-Wiersma et al., 2008). While these intense feelings gradually decrease for most, a subset of mothers show persistent emotional distress, which may be detrimental to both physical and mental health (Vrijmoet-Wiersma et al., 2008). Consequently, recent attention has focused on risk and protective factors that can identify vulnerable individuals and be targeted through early intervention. In this regard, individual differences in strategies used to regulate emotions contribute to emotional adjustment and thus health outcomes among this population. Most existing studies examining associations of emotion regulation strategy use with distress and health factors are cross-sectional and examine undergraduate or non-stressed populations. Despite theoretical hypotheses that these strategies modify emotional experiences, to date, no longitudinal studies have examined the association of dispositional differences in use of emotion regulation strategies with distress among a population confronting an extremely stressful life event. For this reason, the present study examines prospective associations of the emotion

regulation strategies of reappraisal and suppression with distress and inflammation, a marker of physical health risk, among mothers of children newly diagnosed with cancer.

## 1.1 NEGATIVE HEALTH CONSEQUENCES OF PROLONGED NEGATIVE EMOTIONS

There is evidence that prolonged negative emotional states such as depression, anxiety, and anger that often accompany chronic stressors predict negative health outcomes, in particular the onset and progression of immune-mediated diseases including cardiovascular disease (CVD) (e.g., Everson-Rose & Lewis, 2005; Kiecolt-Glaser et al., 2002; Kubzansky & Kawachi, 2000; Joynt, Whellan, & O'Connor, 2003; Suls & Bunde, 2005). Pathways linking negative emotions to poor health outcomes remain unclear and are likely complex. However, growing evidence suggests that behavioral and physiological mechanisms play a role.

Behaviorally, emotionally demanding experiences are often accompanied by lifestyle changes such as increased substance abuse, decreased levels of physical activity, dietary changes, and sleep disruptions that may contribute to increased health risk in the face of chronic stress (Kiecolt-Glaser et al., 2002; Cohen, Janicki-Deverts, & Miller, 2007). Physiologically, negative emotional states are associated with central nervous system changes that result in the activation of peripheral physiological pathways. More specifically, limbic brain regions (e.g., amygdala or the anterior cingulate) that are activated in response to negative emotion eliciting situations have direct neural projections to brain stem areas, such as the nucleus tractus solitaries (NTS), or other limbic areas, such as the hypothalamus, that modulate peripheral physiological activity. In this regard, two interconnected central-to-peripheral pathways have been identified that play a role in the physiological consequences of stressful experiences: the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis.

### 1.1.1 The ANS

The ANS is divided into two subsystems: the sympathetic system (SNS) and the parasympathetic nervous system (PsNS). Activation of the SNS is associated with arousal and promotes a "flight or fight" response, preparing the body for activity by mobilizing energy and inhibiting digestion. Conversely, the PsNS is referred to as the "rest-and-digest" system that generally acts to preserve energy. These two branches of the ANS can act independently, reciprocally, or non-reciprocally (e.g., in a coactivating or coinhibiting manner; Berntson, Cacioppo, & Quigley, 1991, 1993) in regulating body systems and the allocation of metabolic resources to meet environmental demands. There is evidence, using pharmacological blockades and noninvasive indices of autonomic control, that negative emotional states, such as those evoked during acute psychosocial challenges (e.g., evaluative speech or mental arithmetic tasks) are characterized by a predominantly reciprocal alterations in activation of the two branches of the ANS, with increases in SNS and decreases in PsNS output resulting in peripheral changes (e.g., Berntson et al., 1994; Berntson, Cacioppo, & Fieldstone, 1996). There is also evidence that chronic negative emotional experiences, such as depression and various anxiety disorders, are characterized by similar alterations in activation of the two branches of the ANS, with increases in SNS and decreases in PsNS activity (Carney, Freedland, & Veith, 2005; Friedman, 2007; Rottenberg, 2007). This pattern of autonomic activation (i.e., greater SNS activity and/or lower PsNS activity), often referred to as autonomic dysregulation or dysfunction, has been shown to associate with increased risk for hypertension and CVD (e.g., Erdogan et al., 2011).

### 1.1.2 The HPA axis

The HPA axis can be characterized as an integrated system that begins with the release of corticotropic-releasing hormone from the paraventricular nucleus of the hypothalamus,

stimulating the release of adrenocorticotropic hormone from the anterior pituitary gland, which in turn results in the synthesis and release of glucocorticoid from the adrenal gland. In humans, the predominant glucocorticoid is cortisol. Stressful experiences result in activation of the HPA axis and peripheral release of cortisol. Furthermore, certain pro-inflammatory cytokines, such as IL-6, also stimulate the production of corticotropic-releasing hormone. Cortisol influences several physiologic systems, including metabolic and immune systems, and has been implicated in CVD risk (Walker, 2007). Both the ANS and the HPA axis modulate peripheral levels of inflammation, an accepted marker of risk for incident chronic inflammatory diseases, such as CVD.

## 1.2 INFLAMMATION AS A PATHWAY LINKING PROLONGED NEGATIVE EMOTIONS TO INCREASED HEALTH RISK

It is well-established that stress relates to increased circulating and stimulated levels of inflammatory markers, which may contribute to increased physical health risk (Kiecolt-Glaser et al., 2002; Sergerstrom & Miller, 2004). The inflammatory process is often defined as a non-specific, first line of defense reaction that is initiated when immune cells such as monocytes (or macrophages) detect tissue damage or the presence of invading pathogens. Local and systemic inflammatory responses are promoted through the release of pro-inflammatory cytokines, such as interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α. These inflammatory responses also involve the synthesis and release of acute phase proteins, such as C-reactive protein (CRP) and fibrinogen, which in turn bind to damage tissues or pathogenic organisms further promoting pro-inflammatory signaling. While adaptive in the short-term, prolonged elevation of systemic inflammation is implicated in the pathogenesis and course of immune-mediated illnesses such as CVD (Kaptoge et al., 2010).

The narrowing and hardening of blood vessels that is the primary cause of CVD results from progressive accumulation of plaque in vessel walls, termed atherosclerosis. A chronic inflammatory process underlies the development and progression of atherosclerosis that begins with damage to the endothelial lining of vessels, resulting in the infiltration of immune cells, platelets, lipids, and smooth muscle cells within the intima, the innermost layer of the vessel wall. Over time, this process results in the accumulation of cells and waste within the intima and the progressive narrowing of the artery, ultimately resulting in clinical CVD (Libby, Ridker, & Maseri, 2002; Steptoe & Brydon, 2009).

The ANS and the HPA axis play a primary role in modulating the magnitude of peripheral inflammatory responses and thus provide potential peripheral pathways linking emotional experiences to risk for atherosclerosis. Activation of the SNS results in the peripheral release of catecholamines, such as epinephrine, from the adrenal medulla, which act on beta-adrenergic receptors on immune cells to stimulate the expression and release of pro-inflammatory mediators, leading to higher levels of these markers in circulation (Rohleder, 2014). Activation of the PsNS, on the other hand, triggers the release of acetylcholine via the vagus nerve, which binds to receptors on immune cells and down-regulates the inflammatory response (Tracey, 2002). Similarly, activation of the HPA axis and the release of cortisol inhibits the production of pro-inflammatory cytokines by activating glucocorticoid receptors and decreasing pro-inflammatory cytokine gene expression. It is widely suggested that prolonged negative emotional experiences associate with chronic activation of the HPA axis, resulting in a downregulation of the sensitivity of cells to the actions of cortisol, which in turn maintains increased inflammation that may contribute to CVD morbidity (Miller, Chen, & Zhou, 2007; Cohen et al., 2012).

In sum, negative emotional states, such as depression, that associate with increases in the ratio of SNS to PsNS activation or increased HPA activation may result in elevated or prolonged inflammatory responses that may contribute to the initiation and progression of the atherosclerotic process and thus CVD (Black & Garbutt, 2002; Dowlati et al., 2010; Miller & Blackwell, 2006; Rohleder, 2014). Therefore, effective regulation of negative emotional responses may play a role in CVD risk.

## 1.3 EMOTION REGULATION STRATEGY USE AS A MODERATOR OF EMOTIONAL AND PHYSICAL OUTCOMES

In the context of negative emotions, emotion regulation is broadly defined as the down-regulation of emotional responses in order to facilitate an adaptive response to a situation (Gross, 1998, 2013). Generally, emotion regulatory strategies that are employed to regulate or manage emotional responses vary as a function of type of situation. However, evidence suggests that individuals show characteristic differences in emotion regulation strategy use that are stable across situations (Gross, 1998). One of the most referenced theoretical models of emotion regulation is the *process model of emotion regulation* (Gross, 1998). The basic premise of this model is that emotion regulation strategies implemented early (referred to as antecedent-focused), or before experiencing the 'full' extent of the emotion, require less effort and are more likely to alter the course of the entire emotional response than strategies implemented in the later stages of an emotional experience (referred to as response-focused). Thus, compared to response-focused strategies, antecedent focused strategies may be more effective in downregulating negative emotions.

To date, most of the research conducted referencing the process model of emotion regulation focuses on two specific strategies: reappraisal and expressive suppression.

'Reappraisal' is an antecedent-focused strategy that involves evaluating emotional stimuli from a more objective perspective by altering one's thoughts and focus. For example, individuals who tend to engage in reappraisal typically endorse statements such as "when I'm faced with a stressful situation, I make myself think about it in a way that helps me stay calm" (from the Emotion Regulation Questionnaire, ERQ, Gross & John, 2003). On the other hand, 'suppression', which is categorized as a response-focused strategy, involves actively inhibiting the external expression of emotions as a way of downregulating internally experienced affect. Here, individuals who engage in suppression tend to agree with statements such as "when I am feeling negative emotions, I make sure not to express them" (ERQ, Gross & John, 2003).

Consistent with theory, available evidence suggests that emotion suppression is less effective than reappraisal in downregulating a broad range of acutely experienced negative affect, as measured by self-report measures (see review by Webb, Miles, & Sheeran, 2012; Ehring et al., 2010). More specifically, the existing evidence highlights the relative ineffectiveness of emotion suppression and the possibility of long-term psychological consequences of its frequent use. For example, a growing literature suggests frequent use of emotion suppression relates to various psychological disorders including depression, anxiety, and eating and substance-related disorders, while the use of reappraisal may be protective against these disorders (see review by Aldao, Nolen-Hoeksema, & Schweizer, 2010). Therefore, habitual use of emotion suppression may have long-term negative emotional consequences. Conversely, using reappraisal as an emotion regulation strategy may be health protective (John & Gross, 2004).

However, to date, most of the studies that have examined the association between emotion regulation strategy and negative emotional states have been either cross-sectional or

primarily based on undergraduate student samples. Past studies have also focused on examining the association between emotion regulation strategy and negative emotions during acute stressors (e.g., laboratory stressors). As previously noted, the findings of these studies suggest that engaging in reappraisal may be more effective than suppression in downregulating negative affective responses (see review by Webb, Miles, & Sheeran, 2012). However, little is known about whether individual differences in emotion regulation strategy use relate prospectively to emotional adjustment among community populations experiencing chronic stress. As a result, the first aim of the current study is to examine prospectively how the use of emotion suppression and reappraisal relate to symptoms of distress among mothers of children diagnosed with cancer. It is hypothesized that greater use of reappraisal will relate to lower distress at time of diagnosis and a faster decline in distress across twelve months post-diagnosis. Conversely, greater use of suppression will relate to higher distress at the time of diagnosis and a slower decrease in distress across the twelve months follow-up period.

By moderating negative emotional responses to life's challenges, it is possible that individual differences in emotion regulation strategy use may also contribute to emotion-related physical health risk. In this regard, recent evidence relates emotion suppression to several behavioral factors implicated in disease risk. For example, Appleton, Loucks, Buka, and Kubzanky (2014) found that in a large representative sample of middle-aged adults the use of suppression was associated with higher rates of smoking, alcohol consumption, and higher body mass index (BMI), compared to the use of reappraisal. Furthermore, in the same study, Appleton and colleagues showed that emotion suppression was associated with a 10% increase in CVD risk in ten years, whereas individuals who endorsed using reappraisal more frequently showed a 5.9% decrease in risk. In this study, CVD risk was defined using an algorithm that integrated

age, total cholesterol, HDL cholesterol, systolic blood pressure, medication use, smoking, and Type II diabetes.

Studies have also examined associations between emotion regulation strategies and activation of specific brain regions. These studies show that use of reappraisal is associated with decreased activation of limbic areas (e.g., Drabant et al., 2009; Giuliani, Drabant, & Gross, 2011) and increased activation of areas of the prefrontal and temporal cortex that modulate limbic activation (Buhle et al., 2014). Conversely, available studies show that use of suppression is associated with increased activation in limbic areas such as the amygdala and insular regions (e.g., Goldin et al., 2008). As noted previously, these limbic areas have direct projections to other brain areas that modulate the actions of the HPA axis and ANS system. Taken together, these findings, along with findings showing that reappraisal may be generally more effective in the reduction of self-reported negative affect compared to suppression (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Webb, Miles, & Sheeran, 2012), suggest that individuals who endorse frequent use of emotion suppression may display patterns of autonomic output that have peripheral consequences for the development of CVD. In this regard, the majority of available studies find that, compared to reappraisal or control conditions, the use of emotion suppression is related to increased SNS activity (e.g., Demaree, Schmeichel, et al., 2006; Egloff et al., 2006; Gross & Levenson, 1993, 1997; Kunzmann, Kupperbusch, & Levenson, 2005; Roberts, Levenson, & Gross, 2008; Robinson & Demaree, 2007). These studies used skin conductance level, finger temperature, and pre-ejection period as noninvasive peripheral markers of SNS activity. Though limited in number, studies have also examined the association of suppression and reappraisal with a common peripheral marker of PsNS activity—heart-rate variability. Here, findings are not as consistent, with some studies showing emotion regulation strategies such as reappraisal

associate with higher PsNS activity, when compared to emotion suppression (e.g., Denson, Grisham, & Moulds, 2011), while other studies finding that both suppression or reappraisal associate with higher PsNS activity, compared to control conditions (e.g., Butler, Wilhelm, & Gross, 2006).

To date, only one study, Lam, Dickerson, Zoccola, and Zaldivar (2009) has examined the association between emotion regulation strategies of reappraisal and suppression with cortisol levels. They found that university students who endorsed more frequent use of emotion suppression showed greater cortisol reactivity to a social-evaluative task, compared to individuals who scored low on emotion suppression measures. Interestingly, in this study, they also found that individuals who were high on reappraisal showed an exaggerated cortisol response to the task. In sum, the few studies examining associations of cortisol levels and PsNS activity with emotion regulation strategies are inconsistent, making it difficult to draw conclusions. However, there is sufficient evidence that individuals who frequently employ emotional suppression show heightened SNS activation relative to those using reappraisal, which may be reflected in changes in the periphery, including increased systemic inflammation.

So far, only two studies have investigated the association between the emotion regulation strategies of reappraisal and suppression and markers of inflammation. In two separate cross-sectional studies, Appleton et al. (2013, 2014) found that individuals who endorse using emotion suppression as a primary emotion regulation strategy showed elevated CRP, when compared to individuals who endorse using reappraisal. Therefore, as an extension of this cross-sectional association, a second aim of the proposed study is to examine whether emotion regulation strategies of suppression and reappraisal relate to systemic inflammation measured prospectively across twelve months among mothers of children recently diagnosed with cancer. It is

hypothesized that greater use of reappraisal will relate to lower levels of systemic inflammation, as indexed by IL-6 levels, at time of diagnosis and a faster decline in inflammation across the twelve months follow-up period. Conversely, it is expected that greater use of suppression will relate to higher levels of inflammation at time of diagnosis and slower decline in inflammation across the twelve months post-diagnosis timeframe.

## 1.4 EXPLORATORY AIMS

As noted previously, a growing literature shows emotion regulation strategy use influences self-reported negative affect, which in turn has been shown to relate to inflammation levels. These associations raise the possibility that self-reported distress may be a mediator in the link between emotion regulation strategy use and systemic inflammation. As such, an exploratory aim of the proposed study is to investigate whether, at time of diagnosis, self-reported distress levels mediate the hypothesized association between emotion regulation strategy use and inflammation. This exploratory aim depends on whether we can confirm previous findings in the current study and show that a) suppression and reappraisal are related to T1 or change in distress levels, and b) distress levels are related to inflammation.

In addition to examining the main effects of reappraisal and suppression, the possibility that reappraisal and suppression are not independent predictors but interact in predicting distress and inflammation levels at time of diagnosis will also be explored. Of note, the reason for limiting interaction analyses to time of diagnosis and not exploring the possibility that reappraisal and suppression may interact to predict change in distress or inflammation is that the study is not adequately powered to explore 3-way interaction (i.e., suppression x reappraisal x time).

# 2.0 METHOD

## 2.1 PARTICIPANTS

The sample is a representative group of mothers of children under the age of 17 who were newly diagnosed with cancer. Participants (N=120) were recruited from the Division of Hematology and Oncology, Children's Hospital of Pittsburgh (CHP) as part of a randomized controlled study designed to examine the efficacy of a supportive stress management intervention. Approval was obtained from the hematology-oncology treatment team at CHP and the IRB institutional review at the University of Pittsburgh. Because of vast differences in course and length of treatment, mothers of children with central nervous system cancer or early stage lymphoma were excluded. Mothers of children with less than 4 months of life expectancy, as determined by primary oncologist, or those with a pervasive developmental disorder were also excluded. Inclusion criteria included: (1) 18 years of age or above; (2) being the legal guardian of a child who was newly diagnosed with cancer; (3) English fluency; (4) no reported clinical history of psychotic or bipolar illness, neurological disorder (stroke, transient ischemic attacks, Parkinson's disease, multiple sclerosis) or chronic disease known to influence immune function, including cardiovascular disease, cancer [within the past 2 years], or autoimmune disease; (5) not taking medications that might alter responses to questionnaires or indices of immune function (including major sedatives or glucocorticoid, anti-inflammatory, anti-retroviral, or immunosuppressant medication (6) not pregnant; and (7) not working nightshift. The last criterion was included because it is documented that nightshift work influences biological processes.

## 2.2 PROCEDURE

With the approval of the hematology-oncology treatment team, potentially eligible mothers were approached around 2 weeks after their child's diagnosis by a research team member to explain the study. Mothers who consented to participate were asked to complete paper-and-pencil questionnaires at three time points. The initial goal was to obtain data from mothers within 2 weeks, 3 months and 6 months from their child's diagnosis. However, actual data collection often deviated from this timeline. Average number of days from diagnosis that elapsed for the first, second and third data collection time points were 35.53 (SD =24.70), 204.40 (SD =58.23), and 382.21 (SD = 65.94). Therefore, data was collected, on average, at approximately 1 month (T1), 6 months (T2) and 12 months (T3) from the child's diagnosis. On each occasion, a study staff member met with the mothers in the Pediatric Clinical and Translational Research Center (PCTRC) at CHP and gave them individual questionnaire packets. Participants were asked to return all questionnaires within 3 weeks either by mail or in person during their next appointment in the PCTRC. If questionnaires were not returned within the designated period, participants were contacted. During all 3 visits to the PCTRC, mothers were also seen by a registered nurse who drew a blood sample (30 ml). At the time of the blood draw mothers reported a) no signs of infection or other acute inflammatory condition, and b) not having taken antibiotics for the prior 2 weeks or over-the-counter anti-inflammatory medications in the past 12 hours. If participants reported/showed symptoms of an infection or other acute inflammatory condition, had taken antibiotics in the past 2 weeks, or had taken over-the-counter anti-inflammatory medications in the past 12 hours, the appointment was rescheduled. All 3 assessments were scheduled at the same time of day to control for diurnal variations in systemic markers of inflammation. Participants were financially compensated $25 dollars for completing each assessment and a total of $75 for completing all three assessments.

## 2.3 MEASUREMENTS OF COVARIATES

### 2.3.1 Health history and demographic information

Mothers completed questionnaires assessing demographic (e.g., age, race, smoking status, body mass index, etc.) and personal history of psychiatric and medical illness.

### 2.3.2 Group status

Following the baseline period, mothers were randomly assigned to a usual care, control group or an intervention group. The usual care group received regular support care that is provided at the CHP for families of children diagnosed with cancer, which included access to clinical social workers. The intervention group received 6 sessions of psychoeducational and practical intervention in stress management over the course of 3 months. It is expected that over the course of the study these two groups will show differences in variables of interest, including distress, and inflammation levels.

### 2.3.3 Treatment intensity

It is most likely that the child's prognosis or the intensity of the treatment s/he receives will influence the distress levels of mothers. As a result, based on the child's medical/treatment record, the treating oncologist provided a treatment intensity rating for each child of participating mothers. More specifically, information regarding type of cancer, stage or risk level, whether or not current cancer is a relapse, and type of treatment modality (e.g., surgery, chemo, radiation, etc.) were used to provide an overall rating of treatment intensity from 1 *(least intensive treatment)* to 4 *(most intensive treatment).*

### 2.3.4 Social Economic Status (SES)

Social economic status was evaluated based on education level (4-level category: high school diploma or lower, some college, bachelor's, or graduate degree). SES is an important

covariate to assess because of strong evidence of its link with psychological and physical health. For example, individuals from lower SES have been shown to experience more depression, anxiety, and anger (Gallo & Matthews, 2003; Lorant et al., 2003). They also report more negative social experiences and relationships (e.g., Gallo, Smith, & Cox, 2006). Similarly, several studies have linked low SES to elevated levels of inflammation (e.g., Friedman & Herd, 2010; Nazmi & Victora, 2007). Furthermore, more recently, studies have shown that SES may also relate to emotion regulation strategy use. For example, higher reappraisal scores have been shown to be related to higher educational attainment, while suppression scores were related to lower educational attainment and lower childhood SES (e.g., Appleton et al., 2014).

## 2.4 MEASUREMENTS OF STUDY VARIABLES

### 2.4.1 Emotion Regulation

The extent to which mothers endorse using reappraisal or suppression emotion regulation strategies was evaluated using the Emotion Regulation Questionnaire (ERQ; Gross & John, 2003). The ERQ is a 10-item self-report questionnaire that consists of two scales corresponding to the typical use of two different emotion regulation strategies: cognitive reappraisal (6 items; e.g., "when I want to feel less negative emotions, I change the way I'm thinking about the situation") and expressive suppression (4 items; e.g., "I keep my emotions to myself"). Each item on the questionnaire is rated on a Likert scale from 1 (*strongly disagree*) to 7 (*strongly agree*). The ERQ has demonstrated good internal consistency (Cronbach alpha of .79 for reappraisal and .73 for suppression) and a 3-month test-retest reliability of .69 (Gross & John, 2003). ERQ continued to show adequate internal consistency within this sample. Cronbach alpha values across the three time points ranged from .76 to .85 for reappraisal and .72 to .79 for suppression.

### 2.4.2 Measures of psychological outcome

Three different questionnaires were used to capture symptoms of depression, anxiety, and perceived general distress experienced by mothers during the course of the study.

#### 2.4.2.1 Depression

Mothers self-report of depressive symptoms were assessed using the 21-item Beck Depression Inventory (BDI; Beck et al., 1961). This scale is widely used to assess symptoms of depression. This scale has also been shown to be reliable with internal consistency coefficient alpha of .81 and test-retest correlations ranging from .6 to .9 in nonpsychiatric populations. Concurrent validity has also been demonstrated, with BDI correlating with clinical ratings (correlation of .60) and other measures of depressive symptoms (e.g., Hamilton Psychiatric Rating Scale for Depression; correlation of .74) (Beck, Steer, & Garbin, 1988).

#### 2.4.2.2 Anxiety

The State-Trait Anxiety Inventory (STAI; Spielberger, 1983) is one of the most frequently used measures of anxiety. It assesses as separate scales dimensions of "state" and "trait" anxiety. Each scale consists of 20 statements that require individuals to rate how they feel on a 4-point scale (e.g., calm, upset, etc.). The state measure asked people to describe how they feel *at a particular moment in time*. The trait scale measures a general propensity to experience symptoms of anxiety and asks how people *generally* feel. Internal consistencies coefficients ranged from .83 to .92 for the state scale and from .86 to .92 for the trait scale. Test-retest reliabilities for the trait scale have shown to be high, ranging from .73 to .86 (Spielberger, 1983).

#### 2.4.2.3 Perceived Stress

Levels of perceived stress among mothers was assessed using the 10-item Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983). This scale assesses the degree to

which a person appraises current stressors exceed his or her ability to cope. More specifically, respondents are asked how often in the last month they experience specific feelings, such as "feeling confident about your ability to handle personal problems," and "difficulties piling up so high that you could not overcome them." This measure has shown strong psychometric properties with coefficient alpha reliability ranging from .84 to .86.

### 2.4.3 Measures of physiological outcomes

Inflammation is the result of a complex and interactive network of systems. Most human studies are limited to quantitative and functional assessments of immune/inflammation parameters in peripheral circulation. Quantitative assessment strategies often include measuring absolute numbers or relative percentages of specific immune cells and/or their biochemical mediators (e.g., cytokines). Functional assessment strategies typically measure susceptibility to inflammation, by examining *in vitro* production of inflammatory mediators by immune cells stimulated with endotoxin. In the present study, to assess inflammation, the pro-inflammatory cytokine IL-6 was selected. As mentioned previously, IL-6 is a widely used marker of inflammation that stimulates the production of CRP, an acute phase protein released from the liver that serves as a marker of systemic inflammation and has been reliably associated with CVD risk (Libby & Ridker, 1999; Libby, Ridker, & Maseri, 2002).

#### 2.4.3.1 Circulating levels of inflammation

Circulating levels of pro-inflammatory cytokines, such as IL-6, provide a relatively stable, quantitative measure of systemic levels of inflammation at the time of the blood draw. Of the different inflammatory cytokines, IL-6 has a longer half-life and is more reliably detectable using high-sensitive assay kits even among asymptomatic individuals. In the proposed study, plasma concentrations of IL-6 were analyzed from frozen plasma samples processed in batches in the

Behavioral Immunology Laboratory at the University of Pittsburgh (Dr. Marsland, Director). Final IL-6 levels were quantified using a high sensitivity enzyme-linked immunosorbent assay (ELISA) kit run according to manufacturer's directions. All samples were run in duplicate. Values were accepted if average coefficients of variation (CV) between duplicates were < 20%. Average CV for circulating IL-6 were 7.14%, 7.59%, and 7.71% for T1, T2, and T3, respectively.

#### 2.4.3.2 Stimulated levels of inflammation

In addition to circulating levels of IL-6, the proposed study examined stimulated levels. As mentioned, stimulated levels of pro-inflammatory cytokines reflect the functional capacity of white blood cells to mount an inflammatory response following endotoxin stimulation (i.e., provide a measure of immune competence). This method is believed to capture immune responses that are localized *in vitro* and may not be necessarily reflected in systemic levels. Individuals vary in the magnitude of this measure of inflammatory potential, and it is suggested that individuals who mount 'exaggerated' responses may be at increased risk for inflammatory conditions and other illnesses. In the proposed study, IL-6 production was determined by stimulating whole blood with lipopolysaccharide (LPS) at a final concentration of 2.5 μg/ml. The samples were incubated at 37 degree Celsius with 5% Carbon Dioxide for 24 hours. Following incubation, harvested supernatants were frozen at -80 degree Celsius and analyzed in batches. Stimulated levels of IL-6 were determined using the same procedure as circulating levels. Average CV for stimulated IL-6 were 5.21%, 6.04%, and 6.56% for T1, T2, and T3, respectively.

## 2.5 DATA ANALYSES

Statistical analyses were performed using SPSS software package for Windows (SPSS Inc., Chicago, IL).

### 2.5.1 Preliminary analyses

Basic growth curve analyses were conducted to determine if there were significant differences in individual trajectory of emotion regulation strategy use across the three time points. More specifically, the statistical significance of the random effect of time in predicting reappraisal and suppression use was tested. A second set of basic growth curve analyses were conducted to test whether participants in the control or intervention group (i.e., group status) showed significant differences in reappraisal and suppression use across time. Here, emotion regulation strategy use of reappraisal and suppression were set as outcome variables and group status as a fixed predictor. If a significant estimate for group status in predicting emotion regulation strategy was observed or if there were significant differences in emotion regulation strategy use across time, then level of reappraisal and suppression was determined using scores from the initial point of assessment (i.e., T1). If there were no significant differences, individual use of reappraisal and suppression was determined by averaging scores for the first two time points to compensate for missing ERQ data at T1.

Bivariate correlations showed a high correlation among measures of distress at each of the three time points. For instance, at T1, symptoms of depression correlated with both state and trait anxiety levels and perceived stress with Pearson r values ranging from .75-.80. As a result, a combined measure of distress was calculated by aggregating scores from the three separate measures: symptoms of depression (BDI; Beck et al., 1961) and anxiety (STAI; Spielberger, 1983), and overall perceived stress (PSS; Cohen, Kamarck, & Mermelstein, 1983). Scores were

combined by calculating an overall mean and standard deviation across the three time points for each measure. This mean and standard deviation was then used to obtain a standardized score for each individual on each measure at each time point. Subsequently, standardized scores were averaged across the different measures of distress to obtain an averaged "distress" score for each individual at each time point.

Of note, actual data collection timeline varied widely among participants. As a consequence, instead of a structured "time" variable (i.e., 0, 1, 2), to capture individual time point variations, analyses were conducted using an unstructured "time" variable that reflected the actual time from diagnosis in months.

### 2.5.2 Hypotheses testing

#### 2.5.2.1 Hypothesis 1

Multi-level linear growth curve analyses were used to test the first hypothesis. More specifically, to determine whether emotion regulation strategy influenced levels of distress at T1 and over time, the significance of the fixed effects for the variables of reappraisal, suppression, and the cross-level time x emotion regulation strategy interaction terms on distress were evaluated. In these models, the fixed effects for the main covariates of the study including age, race, treatment intensity, group status, and SES (education) were included. Given that this study was a part of an intervention study, there is a possibility that there may be a group x time effect on outcome variables, including distress. As a result, in all models, the time x group interaction variable was included as a covariate.

#### 2.5.2.2 Hypothesis 2

To test the second hypothesis (i.e., levels of reappraisal and suppression use predicting change in IL-6 levels over time), similar analyses as hypothesis 1 were conducted, with IL-6 as

the outcome variable and the addition of BMI as a covariate. Here, we first checked to see if there were significant within-person differences in BMI across the three time points. To do this, we conducted another basic growth curve analysis and checked the significance of time on BMI. If BMI did not significantly change over time, we planned to control for BMI by including it in our model as a fixed effect. If there were, however, significant within-person changes across time then we planned to include the time x BMI interaction in the model.

**2.5.2.3 Exploratory hypotheses**

If we observed support for the first two hypotheses, we planned an exploratory examination of whether any associations between emotion regulation strategy and changes in inflammation over time were related to distress. Here, we planned to conduct mediational analyses using averaged slope estimate for change in distress as a mediating variable. We planned to obtain the distress and inflammation slope estimates by saving predicted estimates of basic growth curve analyses as separate variables (i.e., after examining the effect of time on distress and inflammation, controlling for covariates). Following the creation of these slope estimates as separate variables, we proposed using the PROCESS macro for SPSS (Hayes, 2013) to test the significance of the mediation. Of note, if we found that reappraisal and suppression were related to initial distress and inflammation, but not significantly related to change in distress and inflammation across the follow-up period, we planned in examining the significance of initial distress level as a mediator in the association between initial emotion regulation strategy use and inflammation.

In order to test our second exploratory aim (i.e., use of reappraisal and suppression may interact in the prediction of initial distress and inflammation), an interaction term was created after centering (using Z-scores) and multiplying scores of the reappraisal and suppression

variables. Subsequently, multiple regression analyses were conducted including this “reappraisal x suppression” interaction term (along with the main effect of reappraisal and suppression) as a predictor.

## 3.0 RESULTS

Participant characteristics are presented in Table 1 for the 120 participants.

### 3.1 PRELIMINARY FINDINGS

Circulating and stimulated levels of IL-6 were log transformed to better approximate a normal distribution. All other data were normally distributed. Preliminary correlational analyses showed age, SES, and treatment intensity were significantly related to several outcome variables (see Table 2), confirming the need to treat them as covariates in all multivariate analyses. For example, results showed increasing age tended to relate to endorsing reappraisal tendencies ($r = .18$, $p = .06$), experiencing less distress around the time of the child's diagnosis ($r = -.17$, $p = .07$), and displaying lower levels of circulating IL-6 at T1 ($r = -.18$, $p = .07$) and at T3 ($r = -.27$, $p = .02$). Consistent with previous findings, we also observed that higher education attainment/SES related positively to the use of reappraisal ($r = .23$, $p = .01$) and negatively to the use of suppression ($r = -.25$, $p < .01$) at T1. SES was also associated with lower distress levels at T2 and T3 ($r = -.21$, $p = .04$; $r = -.18$, $p = .10$, respectively) and lower T1 levels of circulating ($r = -.22$, $p = .02$) and stimulated IL-6 ($r = -.25$, $p = .01$). Surprisingly, we found that higher child treatment intensity related to lower circulating levels of IL-6 at all three time points (T1: $r = -.17$, $p = .07$; T2: $r = -.33$, $p < .01$; T3: $r = -.28$, $p < .01$). BMI was included as a fixed effect covariate for all analyses involving IL-6 data because it tended to relate positively to circulating IL-6 at all three time points (T1: $r = .16$, $p = .10$; T2: $r = .18$, $p = .10$; T3: $r = .27$, $p = .01$) and to stimulated levels at T3 ($r = .24$, $p = .04$). Because basic growth analysis showed that BMI did not significantly change over time ($\beta_{10} = .031$, SE = .960, $p = .131$), we did not control for a cross-level time x BMI interaction during hypotheses testing. Smoking status was not related to any of the outcome variables and thus was not included as a control variable in any analysis (see Table 2).

Basic growth curve analyses confirmed the time x emotion regulation strategy effect was not significant (Reappraisal: $\beta_{10}$ = .052, SE= .075, p = .490; Suppression: $\beta_{10}$= -.063, SE=.054, p =.250), suggesting that the use of reappraisal or suppression did not change over time. There was also no *significant* difference in reappraisal and suppression use across time between the intervention and control group (Reappraisal: $\beta_{10}$ = .285, SE =.960, p =.767; Suppression: $\beta_{10}$= -.147, SE = .844, p =.083). Therefore, average ERQ scores across the first two time points were used in the primary analyses. As expected, initial reappraisal and suppression use were not significantly correlated with each other (r = -.072, p = .457), highlighting that the two variables are largely independent. Therefore, we were also able to explore whether reappraisal and suppression interact in the prediction of distress and inflammation (second exploratory aim).

## 3.2 TESTS OF PRIMARY HYPOTHESES

### 3.2.1 Emotion regulation strategy and distress

There was a significant decrease in distress across the three time points with a mean rate of decline per month being $\beta_{10}$= -.044 (SE = .007, p <.01; Figure 1). We hypothesized that emotion regulation strategy use would relate to the initial levels of distress as well as rate of change in distress level. More specifically, we expected reappraisal to relate to lower initial distress and a faster decrease in distress over time. In contrast, we expected suppression to relate to higher initial distress and a slower decrease in distress over time. Findings partially supported our hypothesis. While reappraisal related to lower level of distress at time of diagnosis ($\beta_{01}$= -.254, SE = .087, p = .004), it did not relate significantly to rate of change in distress ($\beta_{11}$=.002, SE=.007, p = .792). Similarly, we found that initial suppression related to higher level of distress at time of diagnosis ($\beta_{01}$= .354, SE = .086, p < .01), but it did not predict rate of change in distress level ($\beta_{11}$= -.003, SE=.007, p = .628; see Table 4).

### 3.2.2 Emotion regulation strategy and inflammation

Both circulating and stimulated IL-6 levels significantly increased over time, at a rate of $\beta_{10}$= .039 (SE = .006, p <.01; Figure 2) and $\beta_{10}$= .035 (SE =.006, p <.01; Figure 3) per month, respectively. We hypothesized that reappraisal would relate to lower initial inflammation and a faster decline in inflammation levels across the twelve months, while suppression would relate to higher initial inflammation and a slower decline in inflammation across the follow-up period. In general, findings did not support our hypothesis (see Table 5 and 6). Reappraisal did not relate to initial circulating or stimulated levels of IL-6 (Circulating IL-6: $\beta_{01}$= .063, SE =.087, p =.468; Stimulated IL-6: $\beta_{01}$=.028, SE =.089, p =.749). Reappraisal also did not significantly relate to rate of change in circulating or stimulated IL-6 levels over time (Circulating IL-6: $\beta_{11}$= -.002, SE =.006, p =.700; Stimulated IL-6: $\beta_{11}$= -.004, SE =.005, p =.414). We also did not observe a significant association between suppression and initial circulating or stimulated IL-6 (Circulating IL-6: $\beta_{01}$= .028, SE =.089, p =.749; Stimulated IL-6: $\beta_{01}$=.002, SE =.069, p =.978). However, suppression did significantly predict rate of change in stimulated IL-6 levels ($\beta_{11}$ = -.016, SE=.006, p =.012). As illustrated in Figure 4, contrary to expectations, higher suppression scores related to slower increases in levels of IL-6. A similar but weaker pattern of association was observed with rate of change in circulating IL-6 levels ($\beta_{11}$ = -.011, SE=.007, p =.118).

### 3.2.3 Exploratory aims

One of the exploratory aims of the current study was to examine the possibility that self-reported distress mediates the hypothesized relationship between emotion regulation strategy use and change in inflammation. As previously indicated, while we did find suppression significantly predicted rate of change in stimulated IL-6 levels, results did not show that reappraisal or suppression significantly related to rate of change in distress levels. While current accepted

guidelines for conducting mediational analyses no longer require a significant association between the predictor (emotional regulation strategy) and outcome variable (inflammation), significant associations between the predictor and mediator (distress) *and* between mediator and outcome variables are still considered by most an essential precondition for mediational analysis (Hayes, 2013, p.88-89). For this reason, we were unable to conduct mediational analyses using slope estimates for change in distress as the mediating variable. Consequently, we proceeded to examine cross-sectional associations among emotion regulation strategy use, inflammation and distress only at T1. For this purpose, we conducted multiple regression analyses. Controlling for covariates, initial reappraisal was negatively related to distress ($\beta = -.233$, $p = .015$), while suppression was positively related with distress ($\beta = .335$, $p = .001$). Neither reappraisal nor suppression were significantly related to circulating or stimulated IL-6 at T1 (see Table 7). Furthermore, distress levels at time of diagnosis were not significantly associated with circulating ($\beta = .048$, $p = .492$) or stimulated IL-6 levels ($\beta = .021$, $p = .836$). For this reason, we were also unable to conduct mediational analyses using distress at T1 as a mediator of the association between emotion regulation strategy use and inflammation at T1.

Our second exploratory aim was to investigate the possibility that reappraisal and suppression interact to predict outcome variables. Here, we did not find significant associations between interaction terms and measures of distress or inflammation at T1 (see Table 7).

## 4.0 DISCUSSION

Consistent with Vrijmoet-Wiersma et al. (2008)'s review, the present study observed mothers of children diagnosed with cancer report high levels of negative emotions, such as symptoms of depression and anxiety, around the time of their child's diagnosis. For example, in the current study, average BDI score at T1 was 18.42 (SD = 11.69), which is classified as within the mildly depressed range (see Beck, Steer, & Carbin, 1988). By the end of the study (approximately 12 months post-diagnosis), on average, mothers showed a significant decrease in depressive symptoms and other negative affect (as measured by our combined distress measure). However, mean levels remained elevated when compared with normative levels. Average BDI at T3 was 13.63 (SD = 12.14) which falls just above the normative cutoff for possible clinical depression, which is 13 (see Beck, Steer, & Carbin, 1988). There was also considerable inter-individual variability in trajectories of distress. One important goal of this study was to examine the possibility that individual differences in use of emotion regulation strategies would influence emotional reactions among mothers of children newly diagnosed with cancer contributing to variability in levels of distress over time. Theory (i.e., Gross's *process model of emotion regulation*) and a number of studies highlight the emotional benefit of using reappraisal strategies when compared to suppression strategies. For example, individuals who employ reappraisal strategies show a less negative emotional response during acutely stressful situations than those who report using suppression strategies (see review by Webb, Miles, & Sheeran, 2012). Furthermore, growing evidence associates use of reappraisal strategies with better mental health (see review by Aldao, Nolen-Hoeksema, & Schweizer, 2010). Based on this, we anticipated that mothers who reported using reappraisal to manage emotions related to having a child diagnosed would show lower levels of distress at T1 and faster declines in distress across

time. Conversely, we expected that mothers who used suppression would show higher initial levels of distress and a slower rate of decline across the twelve months follow-up. Cross-sectional associations were consistent with our hypotheses, with reappraisal predicting lower distress levels around the time of diagnosis while suppression related to higher reports of distress. However, longitudinal analyses showed no associations of reappraisal or suppression with rate of change in distress. It is unclear why reappraisal and suppression related robustly to T1 distress levels but not to rate of change in distress over time. It is impossible to determine the direction of effects in cross-sectional associations, raising the possibility that distress at T1 influences the nature of the emotion regulation strategy that was used. More specifically, it is possible that at the peak of emotional intensity (i.e., T1), individuals that are highly distressed may tend to engage in suppression while those that are less distressed may be more likely to engage in reappraisal, contributing to a significant association between emotion regulation use and distress. However, as individuals adjust to the stressor and distress decreases, as it does in this study, intensity of distress may be less relevant to emotion regulation strategy use, minimizing the strength of association between emotion regulation strategy use and distress levels over time. In support of this possibility, studies have shown that individuals tend to engage in reappraisal regulatory strategy when confronted with a low-emotional intensity stressor compared to a high-emotional intensity situation. In the latter, the preference tended to be for individuals to engage in disengagement, distraction or other avoidant strategies (e.g., Sheppes, Scheibe, Suri, & Gross, 2011).

Another possible explanation for not finding an association of emotion regulation strategy and change in distress over time may relate to type and chronicity of the stressor. Drawing parallels from the coping literature, coping strategies are often categorized as problem-

focused strategies (e.g., problem-solving, engaging in reappraisal, etc.) or emotion-focused strategies (e.g., emotion avoidance, engaging in distraction, etc.). A number of studies suggest that the controllability of a stressor may determine the relative usefulness or adaptiveness of using problem-solving versus emotion-focused strategies. For example, Park, Armeli, and Tennen (2004) asked undergraduates to fill daily self-report measures of coping strategies, mood and controllability of a stressor for one month. They found that the use of problem-focused coping strategies was related to more positive mood when stressors were deemed controllable by participants. However, this association was not present when stressors were classified as uncontrollable. In the present study, participants are mothers who are exposed to a unique prolonged stressor most likely making the association between use of emotion regulation strategies and emotional adjustment even more complex. For instance, around the time of diagnosis, mothers are confronted with a need to juggle several tasks and responsibilities with time and financial constraints, which most likely challenges their problem-solving abilities and their ability to express their needs, emotional or otherwise, to others. At this time, mothers who endorse high suppression use may be at a disadvantage. However, as time passes and mothers adjust to new routines and schedules, suppression use may be less relevant. In support of this possibility, in exploratory analyses, we found that mothers who endorsed higher suppression use also reported receiving lower social support at T1 ($\beta = -.39$, SE =.08, $p < .01$), as measured by the Interpersonal Support Evaluation List (ISEL; Cohen et al., 1985)—a questionnaire that assesses both perceived emotional and tangible support received from others. However, suppression did not predict change in social support. On the other hand, reappraisal was not related to social support at T1 but tended to relate to greater increases over time in self-reported social support ($\beta = .01$, SE =.005, $p = .08$). Since we did not find that suppression and reappraisal were correlated

to each other, it is entirely possible that there are individual differences in frequent usage of one strategy over another, with some individuals being low or high in one strategy or on both strategies—potentially influencing different patterns of change in distress levels over time. Unfortunately, the present study was not adequately powered to explore how reappraisal and suppression interact to predict rate of change in distress. Furthermore, while reappraisal and suppression did not interact significantly to predict T1 distress, the effect size obtained ($\beta$ = -.147, p =.110) suggests the possibility that significance may be achieved in a larger sample.

Given the strong literature linking negative emotional states such as anxiety and depression and inflammation levels (e.g., Kiecolt-Glaser et al., 2002; Sergestrom & Miller, 2004; Irwin & Miller, 2007), we expected that distress and inflammation would be related across time in the current study. In our preliminary analyses, we found that while distress levels decreased over time, inflammation, as measured by circulating and stimulated levels of IL-6, increased significantly over the course of the study. While unexpected, the finding that inflammation increased as more time elapsed from diagnosis is not unprecedented. While there is a consistent literature showing an association between acute/brief stressors and elevated inflammation, findings are less consistent and suggest a more complex association between type of chronic stressors and the immune system (Sergerstrom & Miller, 2004). Furthermore, there is an existing literature examining inflammation levels among caregivers of individuals with chronic illnesses—a similar stress paradigm to the present study. Here, studies have shown that caregivers tend to exhibit increasing levels of inflammation over time, including circulating IL-6, CRP and TNF-α (Kiecolt-Glaser et al., 2003; von Känel et al., 2012), which may place them at risk for future negative health outcomes, including CVD (Vitaliano et al, 2003; von Känel et al., 2012).

Furthermore, while in the present sample we found that mothers exhibited an *average* decrease in distress, as mentioned previously, studies of this population suggest that a subset of these mothers report persistently elevated or increasing levels of distress for a period of up to five years (Vrijmoet-Wiersma et al., 2008). It is possible that this subgroup with elevated distress contributes disproportionately to increases in inflammation over time. In support of this possibility, other works from our lab, using the same sample of mothers, have revealed that around 35% of mothers show an increase or fail to show a decrease in distress levels over time (*note*: distress in these studies was measured monthly using PSS only). In addition, this subgroup of mothers showed significant increases in circulating ($\beta_{10}$=.036, SE = .009, p <.001) and stimulated levels of IL-6 ($\beta_{10}$ =.033, SE= .014, p=.026) across the follow-up period, after controlling for relevant covariates. In contrast, mothers who showed a decrease in distress over time showed no significant change in circulating IL-6 ($\beta_{10}$ =.018, SE = .016, p=.296) and the increase in stimulated IL-6 was weaker ($\beta_{10}$ =.027, SE = .015, p =.072).

There may also be a methodological explanation for the lack of significant association between distress and inflammation over time. In the current study, distress was measured using questionnaires asking participants to recall experienced negative emotions. Inflammation, on the other hand, was assessed using an objective biological marker. It is possible that, as more time elapsed, mothers psychologically habituated to the increased demands of having a child diagnosed with cancer and may have appraised their situation as less stressful. However, these taxing demands continue to result in physiological consequences. Therefore, it is possible that inflammation levels may be capturing the accumulated effect of the chronic stressor, which self-reported, time-limited measures might not fully capture. This idea of chronic stress evoking potentially harmful changes in physiology due to repeated and/or prolonged stressors has

garnered increasing attention among health researchers within the context of the theory of *allostatic load* (McEwen & Stellar, 1993). It is suggested that prolonged activation of brain-to-peripheral stress systems (i.e., sympathetic-adrenal- medullary (SAM) axis and the HPA axis) leads to disruption of feedback regulating these systems, which results in dysregulation of peripheral physiology, including elevations in systemic inflammation that contribute to disease risk (Juster, McEwin, & Lupien, 2010). In other words, it is possible that self-reported, retrospective assessment of psychosocial stress may be imprecise and thus underestimate the relationship between distress and inflammation.

Another important goal of the present study was to extend the cross-sectional findings of Appleton and colleagues (2013, 2014) to a longitudinal examination of associations between emotional strategy use and inflammation. More specifically, amending our original hypothesis to incorporate the fact that inflammation increased over time in our sample, we expected that individuals who tend to engage in reappraisal would show lower initial levels and slower increases in both stimulated and circulating IL-6 over time compared to those who engage in suppression. Our findings did not support this relationship. We did not see a cross-sectional relationship between emotion regulation strategy use and IL-6 levels at time of diagnosis. Longitudinally, the only significant findings showed that individuals who endorsed greater initial use of suppression showed slower increases in inflammation levels (*note*: the finding with circulating IL-6 was a trend and not statistically significant), which is contrary to our predictions. One explanation for our largely null findings could be, as previously mentioned, the nature of the stressor. Indeed, given the enormity of the threat and the lack of ability to control the situation, it is possible that emotion suppression is adaptive in the early months following diagnosis.

We also saw that strength of association between suppression and slower increases in IL-6 was different between circulating and stimulating levels. Inconsistent findings between circulating and stimulated levels are not unusual in the literature. For example, in their metaanalytic review of acute laboratory stressors and changes in IL-6, Steptoe, Hamer, and Chida (2007), found a modest overall effect for circulating levels of IL-6 with significant increases in IL-6 following acute stressors but negligible/nonsignificant effects for stimulated IL-6. This inconsistency is primarily due to the fact that circulating and stimulated levels assess different aspects of immunity. As mentioned earlier, stimulated levels (i.e.., *in vitro* assays) provide information about the functional ability of specific immune cells. However, to maximize accuracy of quantification, these cells are removed from the host and, as such, do not reflect an accurate estimate of systemic levels of inflammation. Furthermore, stimulated methods assess cytokine production (in this case, IL-6) by white blood cells alone. On the other hand, circulating levels (i.e., *in vivo* assays) provide an integrated assessment of IL-6 released systemically from a wide range of sources that include smooth muscle cells and adipocytes as well as immune cells. While still debated, generally it is thought that increased production of pro-inflammatory mediators in response to acute stress is adaptive, preparing the body for defense against external or internal threats (Vedhara, Fox, and Wang, 1999). For instance, among mothers of children diagnosed with cancer becoming ill due to an infection would hinder their ability to take care of their child and the family as a whole. Therefore, in this regard, our finding that suppression related to slower increases in IL-6 among these mothers may be interpreted as a less adaptive immune response. In contrast to health-protective effects of increased inflammatory responses in the context of acute stress, it is proposed that chronic elevations of systemic inflammation no longer serve an adaptive function and may be detrimental to health. In other words, while

elevated levels of inflammation may be protective in the short-term (e.g., decreasing risk for infection, improving recovery from injury, etc.), in the long term, they may place individuals at risk for inflammation-mediated diseases, such as CVD. Following this viewpoint, suppression relating to slower increases in IL-6 indicates that it may be a protective factor.

## 4.1 LIMITATIONS

The proposed study has limitations that may provide several directions for future studies. One limitation of the study is both emotion regulation strategy use and distress were evaluated using self-reported/subjective measures. As a result, it is possible that some significant associations reflect common method biases and/or the contribution of other factors such as social desirability or dispositional negative affect that systematically impact how individuals respond (Brett et al., 1990; Crowne & Marlowe, 1960; Podsakoff, P., MacKenzie, Jeong-Yeong, & Podsakoff, 2003; Watson & Clark, 1984). Second, and a related point, the current study did not control for potential personality confounds. It has been suggested that certain personality traits may play a role in emotion regulation use and, as a result, in differences in physiological responses to a stressor; especially among samples that are stressed or samples that are asked to report on dispositional rather than situation-specific factors (Conner-smith & Flachsbart, 2007), which is the case in this study. In a meta-analytic review, Conner-Smith and Flachsbart (2007) concluded that extraversion and conscientiousness predicted engaging in problem-solving and cognitive reappraisal coping strategies. Neuroticism, on the other hand, associated with strategies such as wishful thinking, withdrawal, and emotion-focused strategies. It has also been proposed, but few studies have concretely shown, that physiological and/or health consequences of emotion regulation may be moderated by personality (Sergestrom, 2000).

One explanation provided for the links among personality, emotion regulation and physiology is that people who are high in certain traits, such as neuroticism, may expand more effort in regulating their emotions (Tobin et al., 2000), resulting in higher physiological arousal to stressors. Others suggest that the physiological consequences of a given emotion regulation strategy may depend on the extent of a mismatch between personality-driven emotion regulation strategy preference and actual behavior. In other words, it is possible that individuals with certain personality traits may find suppressing the expression of emotions more aversive and, depending on the stressor, may experience this mismatch leading to higher physiological reactivity or slower recovery from the stressor (Engebretson, Matthews, and Scheier, 1989; Gračanin, Kardum, and Hudek-Knežević, 2013). Thus, for the purposes of the present study, we cannot exclude the possibility that some of the associations may be explained by a third confounding personality factor.

In addition to the methodological shortcomings of the present study, there are important theoretical limitations of this area of study that may further explain some of our null and unexpected findings and provide additional avenues for future research. To date, the focus of studies has been on highlighting potential negative health consequences of emotion suppression or the benefits of using reappraisal strategies. However, more recently researchers have suggested that individual differences in flexibility in emotion regulation strategy may be more relevant to health than the use of a given strategy (Rozanski, Blumenthal, Davidson, Saab, & Kubzansky, 2005). Recent reviews (Aldoa, 2013; Bonanno & Burton, 2013), however, highlight a lack of consistency in conceptualizing and operationally defining "emotion regulation flexibility". Although this research is in its infancy, it is suggested that engaging in suppression may be adaptive in some situations. In support of this possibility, a growing number of studies

(e.g., Bonanno et al., 2004; Westphal, Seivert, & Bonanno, 2010) show that the ability to flexibly alternate facial expressions from suppressing to expressing emotions predicted better psychological outcomes. This finding is relevant for the interpretation of our results because items of the *expressive suppression* subscale of the ERQ that are used in the current study revolve around external expression of emotions. Furthermore, mothers of children diagnosed with cancer address a range of challenges across the first year following their child's diagnosis, including helping their child deal with chemotherapy and the ups-and-downs of potential remission or relapse. It is possible that while emotion regulation strategy use is conceptualized as a trait-like characteristic and we did not find a significant *average* change in emotion regulation strategy use over time, there may be a subset of mothers who show changes in reappraisal and/or suppression use to meet their environmental demands. To test this possibility, we visually examined change over time trajectories for reappraisal and suppression for each individual (illustrated in Figure 5). We observed that approximately 25% of participants reported increased reappraisal use over the three time points, while 18% showed decreased use. In regards to suppression, 23% endorsed increasing suppression tendencies while 32% showed decreasing levels. While beyond the scope of the present study, individual differences in patterns of emotion regulation use may relate to distress and inflammation levels in important ways that inform our understanding of how emotional regulation strategy use relates to health outcomes.

Unfortunately, studies that have examined the long-term physical health benefits of flexibility in emotion regulation are limited. However, it is plausible that individuals who endorse more rigid use of one strategy, regardless of that strategy, may experience long-term health consequences, including CVD. For instance, our findings show that suppression related to greater self-reported distress, but not inflammation, at T1. In contrast, suppression did not relate to change in distress

over time, but predicted slower increases in IL-6. These results underline the complexity of relationships between the use of suppression and health factors.

Another limitation of this literature is that studies exploring the physiological consequences of suppression or reappraisal do not differentiate positive and negative emotional expressiveness. The lack of investigation in this area raises a few questions. For example, do individuals who endorse frequent expressive suppression inhibit the display of negative and positive emotions equally? Are there differential physiological and long-term CVD consequences between suppressing negative and/or positive emotions? It has been argued that when experiencing negative affect, people do not typically show purely negative emotions, but rather they tend to display a blend of negative, neutral, and even positive expressions (Davidson et al., 1994). However, studies that have examined the positive health correlates of displaying or suppressing positive emotions are limited. One of the few studies in this area, Davidson, Mostofsky and Whang (2010) measured positivity displayed on the faces of almost 2000 participants during a structured interview. They found that individuals who displayed higher levels of positive affect were at 22% reduced risk of developing heart disease over a 10-year period, after controlling for both major coronary risk factors and measures of negative affect. While this study used observational measurement, future studies can build on this finding by evaluating the extent that individuals report differential positive and negative emotion suppressive behaviors and relate it to health outcomes.

Lastly, the current study and indeed the bulk of existing studies on expressive suppression (or reappraisal) have primarily focused on the regulation of negative affect experience. The few available studies that examined the association between the use of emotion suppression and positive emotions have shown that emotion suppression is related to decreases

in self-reported positive affect to positive and negative stimuli (e.g., Gross & Levenson, 1997). A growing literature highlights an association between positive affect and health outcomes, including CVD (e.g., Pressman & Cohen, 2005). Furthermore, it has been proposed that individuals who experience more positive emotions throughout a stressful process, regardless of the presence of negative emotions, may have different physiological health outcome trajectories (Pressman & Cohen, 2005). For instance, studies have shown that positive emotions facilitate cardiovascular recovery following a stressor due to decreases in SNS activity (e.g., Fredrickson & Levenson, 1998; Fredrickson et al., 2000). Others have suggested positive emotions may relate to increases in PsNS activity (e.g., McCraty et al., 1995). As noted earlier, the autonomic nervous system plays a central role in modulating the inflammatory process. SNS activity induced beta-adrenergic receptor stimulation of immune cells (macrophages) results in increased production and release of pro-inflammatory cytokines while increased PsNS activity and the release of acetylcholine binding to immune cells downregulates pro-inflammatory gene expression. Taken together, it is conceivable that individual differences in expressivity and experience of negative and positive emotions may have distinct neurobiological effects on inflammation that can in turn inform CVD risk, which the extant literature has yet to fully investigate.

## 4.2 CONCLUSIONS AND POTENTIAL IMPLICATIONS OF THE PRESENT STUDY

A childhood cancer diagnosis is highly distressing to parents and disruptive to the functioning of the entire family. This distressing event may be particularly impactful for mothers who, in addition to dealing with the potential loss of their child, often carry most of the day-to-day added burdens of caring for a chronically ill child (Long & Marsland, 2011). As a consequence, this group may be particularly at risk for impaired psychological and physical

health outcomes, which may in turn further negatively affect the child and the family as a whole (Cousino & Hazen, 2013; Barakat et al., 2007). It is understood that emotion regulation, including the ability to display appropriate affect, is an emblem of mental health, with several psychiatric disorders characterized by disruptions in these abilities. A review by Kennedy-Moore and Watson (2001) identified several clinical benefits of expressing negative emotions, including reducing the intensity of those emotions, improving likelihood of developing insight about one's ability, and facilitating social support; all three factors would lower distress and alleviate suffering. The present study shows that mothers who engage in reappraisal reported lower levels of distress around the time of their child's diagnosis. Conversely, those who engaged in suppression reported higher levels of distress. Therefore, it is possible that certain mothers may benefit from intervention focused on modifying emotion regulation abilities. In this regard, acceptance/mindfulness (e.g., Robins et al., 2012), expressive writing (e.g., Niles et al., 2014), and cognitive-behavioral skills training (e.g., Berking et al., 2008) have all been shown to be effective in modifying and improving emotion regulation abilities. Equally important, however, the findings from this study highlight the need for further prospective examinations of whether emotion regulation strategy use, as measured by the ERQ, influence emotional and physiological adaptation to chronic stress—an important step to back the claims of health protective or risk effects of individual differences in emotion regulation strategy use that is purported by the existing literature.

## APPENDIX

## TABLES AND FIGURES

Table 1. Participant characteristics

| Characteristic | Total Sample (n =120) |
|---|---|
| Age (mean in years) | 38.37 (SD =7.87) |
| Group status (control) | 61 (50.8%) |
| Race (white) | 102 (86%) |
| BMI (mean in $kg/m^2$) | 28.97 (SD =7.60) |
| Smoking status (smokers) | 48 (36.9%) |
| Relation to child | |
| Biological | 114 (95%) |
| Foster Parent | 3 (2.5 %) |
| Guardian Parent | 1 (~1%) |
| Other | 2 (~2%) |
| Marital Status | |
| Married | 71 (59.7%) |
| Never Married | 31 (26.1%) |
| Remarried | 7 (5.9%) |
| Widowed | 6 (5%) |
| Separated | 2 (1.7%) |
| Divorced | 2 (1.7%) |
| SES/Educational Attainment | |
| High school diploma or less | 30 (25.2%) |
| Some college | 59 (49.6%) |
| Bachelor's degree | 18 (15.1%) |
| Graduate degree | 12 (10.1%) |
| Treatment Intensity received by child* | |
| Least intensive | 0 (0%) |
| Moderately intensive | 34 (28.6%) |
| Very intensive | 67 (56.3%) |
| Most intensive | 18 (15.1%) |

*Note*. SES =socioeconomic status. BMI=Body Mass Index. Marital status and BMI that are reported were obtained at the initial assessment (T1). * = determined by treating oncologist.

Table 2. Summary of bivariate correlations between measured covariates (age, group status, BMI, race, SES, smoking status, marital status and treatment intensity) and variables of interest (T1 reappraisal, T1 suppression, distress, circulating and stimulated IL-6)

| Measure | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|
| 1. Age | _ | -.21* | .29* | .06 | .11 | .20* | .16^ |
| 2. Race | _ | _ | -.18* | -.07 | -.05 | -.06 | .12 |
| 3. SES | _ | _ | _ | .00 | -.12 | .04 | .02 |
| 4. Group | _ | _ | _ | _ | .08 | -.17^ | .02 |
| 5. Smoking status | _ | _ | _ | _ | _ | -.15 | .04 |
| 6. BMI | _ | _ | _ | _ | _ | _ | -.14 |
| 7. Treat_Int | _ | _ | _ | _ | _ | _ | _ |
| T1 reappraisal | .18^ | .01 | .23* | .01 | -.04 | .00 | .09 |
| T1 suppression | -.12 | -.02 | -.25* | -.17^ | .13 | -.02 | -.06 |
| Distress | | | | | | | |
| @T1 | -.17^ | .05 | -.07 | -.07 | -.08 | -.00 | -.00 |
| @T2 | -.16 | -.10 | -.21* | -.19^ | .11 | .03 | -.01 |
| @T3 | -.05 | -.08 | -.18^ | -.15 | .01 | .00 | -.08 |
| Ln_Circ_IL-6 | | | | | | | |
| @T1 | -.18^ | .02 | -.22* | -.11 | .08 | .16^ | -.17^ |
| @T2 | -.14 | -.01 | -.12 | -.03 | .00 | .18^ | -.33* |
| @T3 | -.27* | -.02 | -.18 | -.02 | .03 | .27* | -.28* |
| Ln_Stim_ IL-6 | | | | | | | |
| @T1 | -.19^ | .12 | -.25* | -.03 | -.04 | .07 | -.06 |
| @T2 | .01 | .03 | .01 | .01 | .11 | .11 | -.12 |
| @T3 | -.14 | .15 | -.09 | .03 | -.02 | .24* | .00 |

*Note*. Significance indicators: ^ = < .10, * = ≤ .05 Mother's relation to child was not examined as a covariate because of limited variability with 95% of mothers reporting child undergoing treatment is their biological child. Due to the large percentage (86%) of sample being white, race was recoded as 0 = white, 1 = non-white. SES = socioeconomic status. BMI = body mass index. Smoking status coding: 0 = non-smoker, 1 = smoker. T1 = initial assessment (~1 month of diagnosis). T2 = second assessment (~ 6 months post- diagnosis). T3 = third assessment (~ 12 months post-diagnosis). Treat_Int = treatment intensity. Group = Group status (1=control, 2=intervention). Circ_ = circulating. Stim_ =Stimulated. Ln= natural log transformed

Table 3**.** Summary of intercorrelations, means, and standard deviations for variables of interest (T1 reappraisal, T1 suppression, distress, circulating and stimulated IL-6)

| | T1 | | | | | T2 | | | T3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Measures | 1 | 2 | 3 | 4 | 5 | 3 | 4 | 5 | 3 | 4 | 5 | M (SD) |
| ***T1*** | | | | | | | | | | | | |
| 1. Reappraisal | -- | -.07 | -.25$^{*}$ | -.04 | -.04 | -.30$^{**}$ | .13 | -.07 | -.31$^{**}$ | .02 | -.08 | 28.23 (5.28) |
| 2. Suppression | -- | -- | .34$^{**}$ | .10 | .06 | .38$^{**}$ | .05 | -.12 | .37$^{**}$ | -.03 | -.17 | 12.74 (1.93) |
| 3. Distress | -- | -- | -- | .09 | .07 | .74$^{**}$ | .04 | .05 | .62$^{**}$ | .10 | .06 | .24 (1.02) |
| 4. Ln_Circ_IL-6 | -- | -- | -- | -- | .46$^{**}$ | .12 | .62$^{**}$ | .20$^{\wedge}$ | .15 | .68$^{**}$ | .28$^{*}$ | .06 (.91) |
| 5. Ln_Stim_IL-6 | -- | -- | -- | -- | -- | .14 | .26$^{*}$ | .64$^{**}$ | .27$^{*}$ | .21$^{\wedge}$ | .44$^{**}$ | 4.64 (.67) |
| ***T2*** | | | | | | | | | | | | |
| 3. Distress | -- | -- | -- | -- | -- | -- | .10 | .06 | .80$^{**}$ | .08 | .09 | -.13 (1.12) |
| 4. Ln_Circ_IL-6 | -- | -- | -- | -- | -- | -- | -- | .46$^{**}$ | -.00 | .85$^{**}$ | .48$^{**}$ | .24 (.78) |
| 5. Ln_Stim_IL-6 | -- | -- | -- | -- | -- | -- | -- | -- | .05 | .26$^{*}$ | .66$^{**}$ | 4.89 (.60) |
| ***T3*** | | | | | | | | | | | | |
| 3. Distress | --. | -- | -- | -- | -- | -- | -- | -- | -- | .00 | .01 | -.24 (.84) |
| 4. Ln_Circ_IL-6 | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | .44$^{**}$ | .59 (.78) |
| 5. Ln_Stim_IL-6 | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | 5.00 (.60) |

*Note.* Significance indicators: $^{\wedge}$ = < .10, $^{*}$ = ≤ .05, $^{**}$ = ≤ .01. T1 = initial assessment (~1 month of diagnosis). T2 = second assessment (~ 6 months post- diagnosis). T3 = third assessment (~ 12 months post-diagnosis). Circ_ = circulating. Stim_ =Stimulated. Ln= natural log transformed.

Table 4. Fixed effects estimates for models predicting Distress

| Parameter | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| Intercept | **.250**$^{**}$ (.094) | **.173**$^{*}$ (.086) | .264 (.550) |
| MonthsSinceDX | **-.044**$^{**}$ (.007) | **-.043**$^{**}$ (.007) | **-.048**$^{*}$ (.024) |
| Reappraisal | | **-.254**$^{**}$ (.087) | **-.247**$^{**}$ (.092) |
| Suppression | | **.354**$^{**}$ (.087) | **.347**$^{**}$ (.092) |
| MonthsSinceDX*Reappraisal | | .002 (.006) | . 001 (.007) |
| MonthsSinceDX*Suppression | | -.003 (.007) | -.003 (.007) |
| Age | | | -.001 (.011) |
| Race | | | -.140 (.249) |
| SES | | | -.001 (.095) |
| TreatIntensity | | | .047 (.125) |
| Group | | | -.091 (.181) |
| Group*MonthsSinceDX | | | .003 (.015) |

*Note*. Standard errors are in parentheses. Significance indicators: $^{\wedge}$ = < .10, $^{*}$ = ≤ .05, $^{**}$ = ≤ .01. Model 1: Basic growth curve; Model 2: Uncontrolled model; Model 3: Controlled model. MonthsSinceDX = continuous time variable measures the number of months that elapsed since diagnosis. TreatIntensity = treating oncologist's rating of child's treatment intensity.

Table 5. Fixed effects estimates for models predicting circulating IL-6

| Parameter | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| Intercept | .005 (.083) | -.006 (.086) | 1.099^ (.635) |
| MonthsSinceDX | **.039**** (.006) | **.041**** (.006) | .033 (.022) |
| Reappraisal | | -.007 (.090) | .063 (.087) |
| Suppression | | .108 (.089) | .028 (.089) |
| MonthsSinceDX*Reappraisal | | -.000 (.006) | -. 002 (.006) |
| MonthsSinceDX*Suppression | | -.010(.006) | -.011 (.007) |
| Age | | | -.018^ (.010) |
| Race | | | -.046 (.232) |
| SES | | | -.154^ (.092) |
| BMI | | | .019^ (.010) |
| TreatIntensity | | | -.210^ (.121) |
| Group | | | -.122 (.173) |
| Group*MonthsSinceDX | | | .004 (.013) |

*Note*. Standard errors are in parentheses. Significance indicators: ^ = < .10, * = ≤ .05, ** = ≤ .01. Model 1: Basic growth curve; Model 2: Uncontrolled model; Model 3: Controlled model. MonthsSinceDX = continuous time variable measures the number of months that elapsed since diagnosis. TreatIntensity = treating oncologist's rating of child's treatment intensity.

Table 6. Fixed effects estimates for models predicting stimulated IL-6

| Parameter | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| Intercept | **4.616**$^{**}$ (.061) | **.4.612**$^{**}$ (.065) | **4.938**$^{**}$ (.505) |
| MonthsSinceDX | .**035**$^{**}$ (.006) | **.034**$^{**}$ (.006) | **.044**$^{*}$ (.020) |
| Reappraisal | | -.018 (.067) | .025 (.069) |
| Suppression | | .045 (.066) | .002 (.064) |
| MonthsSinceDX*Reappraisal | | -.004 (.006) | -.004 (.005) |
| MonthsSinceDX*Suppression | | **-.014***(.006) | **-.016*** (.006) |
| Age | | | -.007 (.008) |
| Race | | | .086 (.186) |
| SES | | | -.107 (.073) |
| BMI | | | .007 (.007) |
| TreatIntensity | | | -.061 (.096) |
| Group | | | .005 (.137) |
| Group*MonthsSinceDX | | | -.007 (.013) |

*Note*. Standard errors are in parentheses. Significance indicators: $^{\wedge}$ = < .10, $^{*}$ = ≤ .05, $^{**}$ = ≤ .01. Model 1: Basic growth curve; Model 2: Uncontrolled model; Model 3: Controlled model. MonthsSinceDX = continuous time variable measures the number of months that elapsed since diagnosis. TreatIntensity = treating oncologist's rating of child's treatment intensity.

Table 7. Hierarchical Multiple Regression Analyses predicting distress and inflammation at time of diagnosis from emotion regulation strategy use

| | Distress | | Ln_Circ_IL-6 | | Ln_Stim_IL_6 | |
|---|---|---|---|---|---|---|
| Predictor | $\Delta R^2$ | β | $\Delta R^2$ | β | $\Delta R^2$ | β |
| Step 1 | .019 | | .138* | | .075 | |
| Covariates† | | | | | | |
| Step 2 | .161** | | .002 | | .002 | |
| Initial Reappraisal | | -.233* | | .042 | | .040 |
| Initial Suppression | | .335** | | .033 | | -.010 |
| Step 3 | .019 | | .009 | | .000 | |
| Initial Reappraisal x Initial Suppression | | -.147 | | .101 | | .006 |

*Note*. †Covariates included group status, race, education, treatment intensity and BMI. Significance indicators: ^ = < .10, * = ≤ .05, ** = ≤ .01. Circ_ = circulating. Stim_ =Stimulated. Ln= natural log transformed.

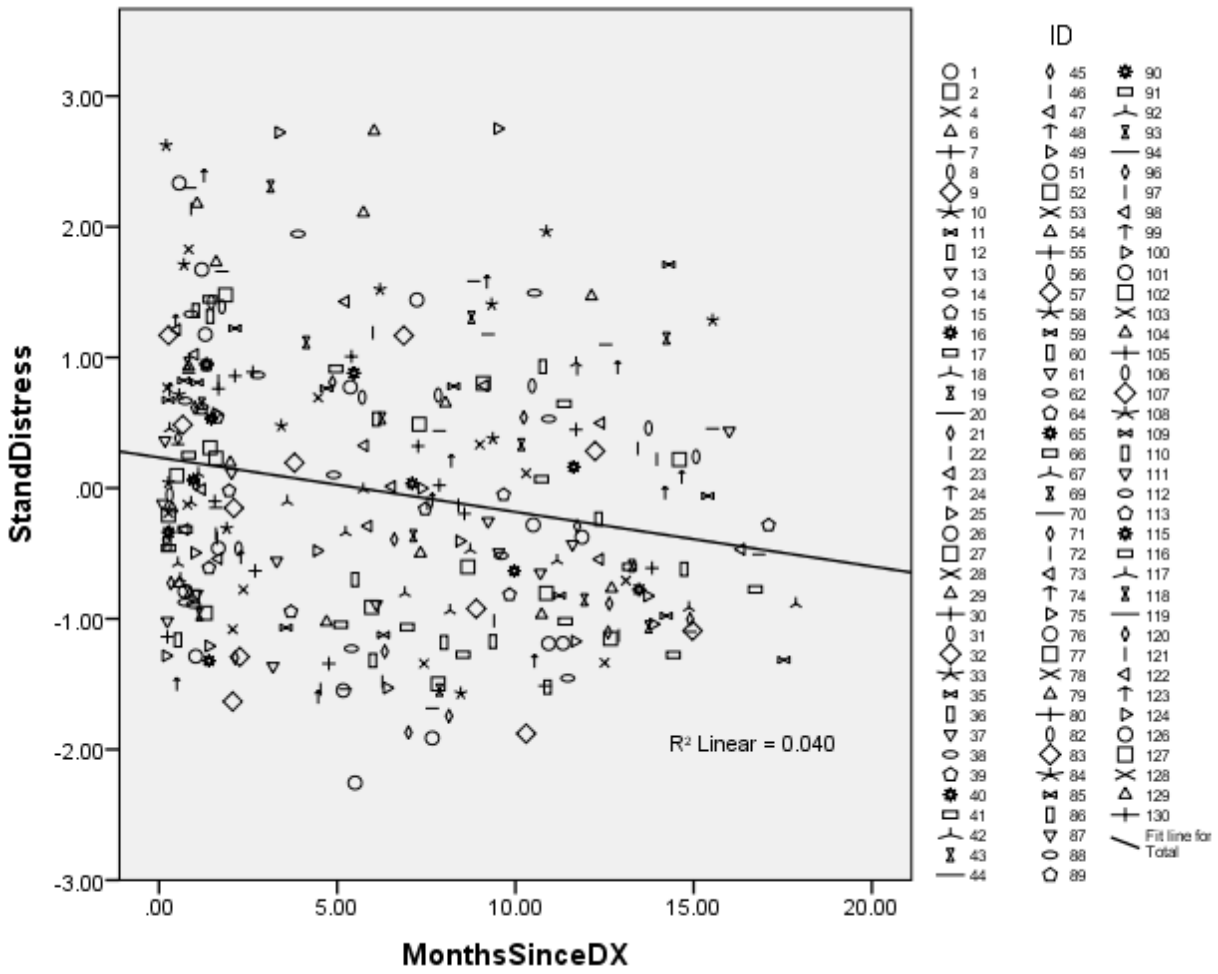


Figure 1. Distress levels as a function of time, as measured by months since diagnosis. On average, there was a decrease in distress over time

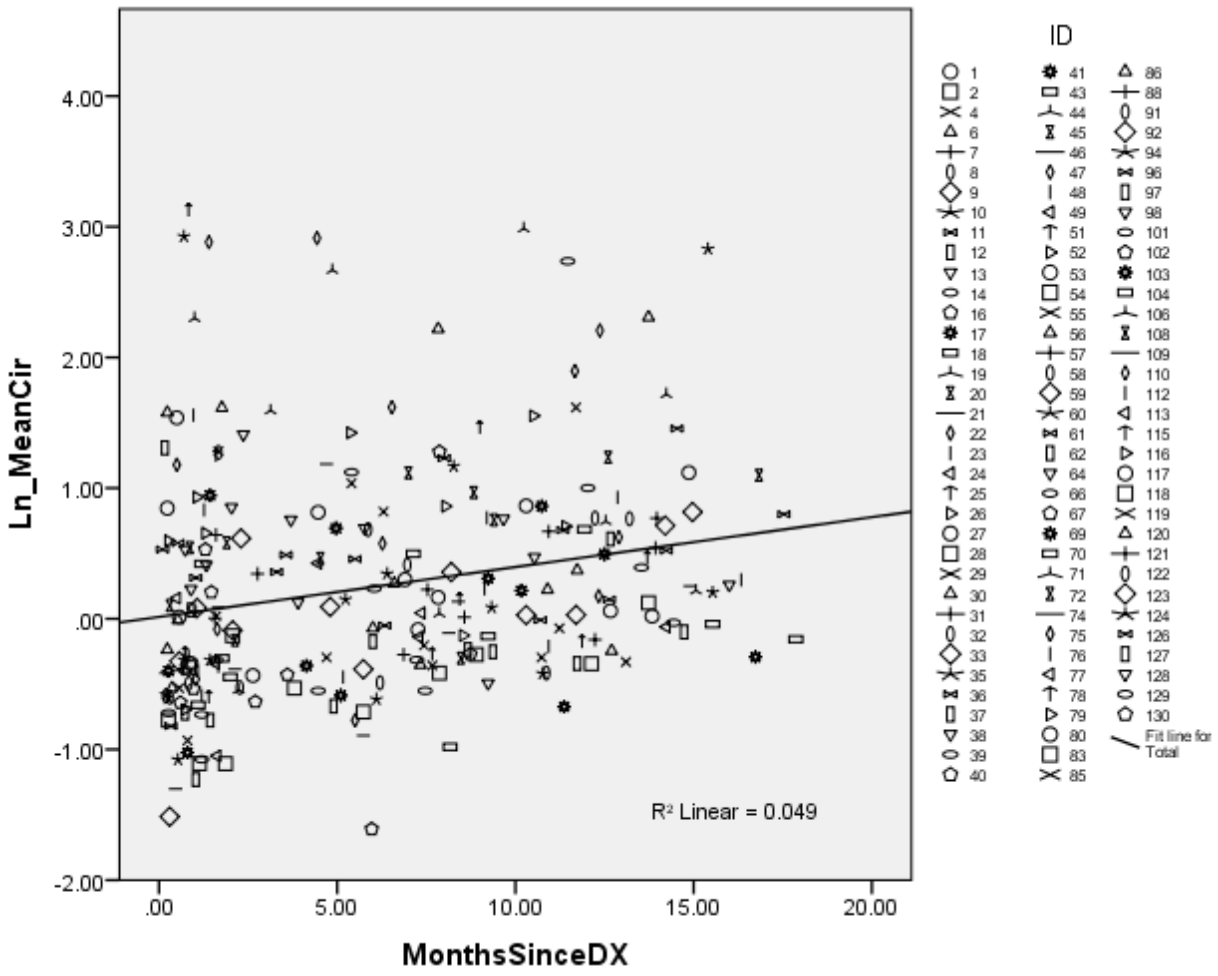


Figure 2. Circulating IL-6 levels as a function of time, as measured by months since diagnosis. On average, there was an increase in IL-6 over time

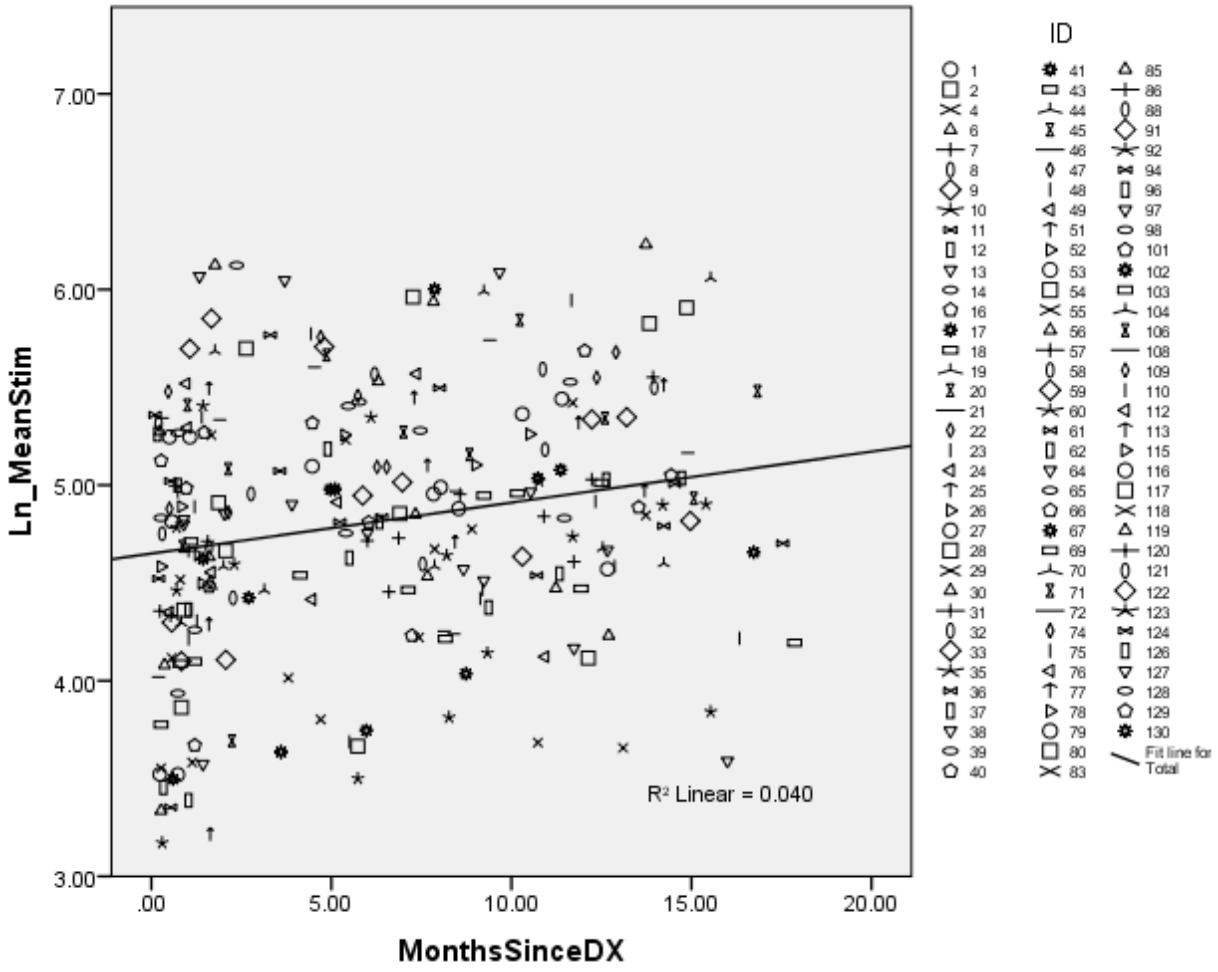


Figure 3**.** Stimulated IL-6 levels as a function of time, as measured by months since diagnosis. On average, stimulated production of IL-6 increased over time

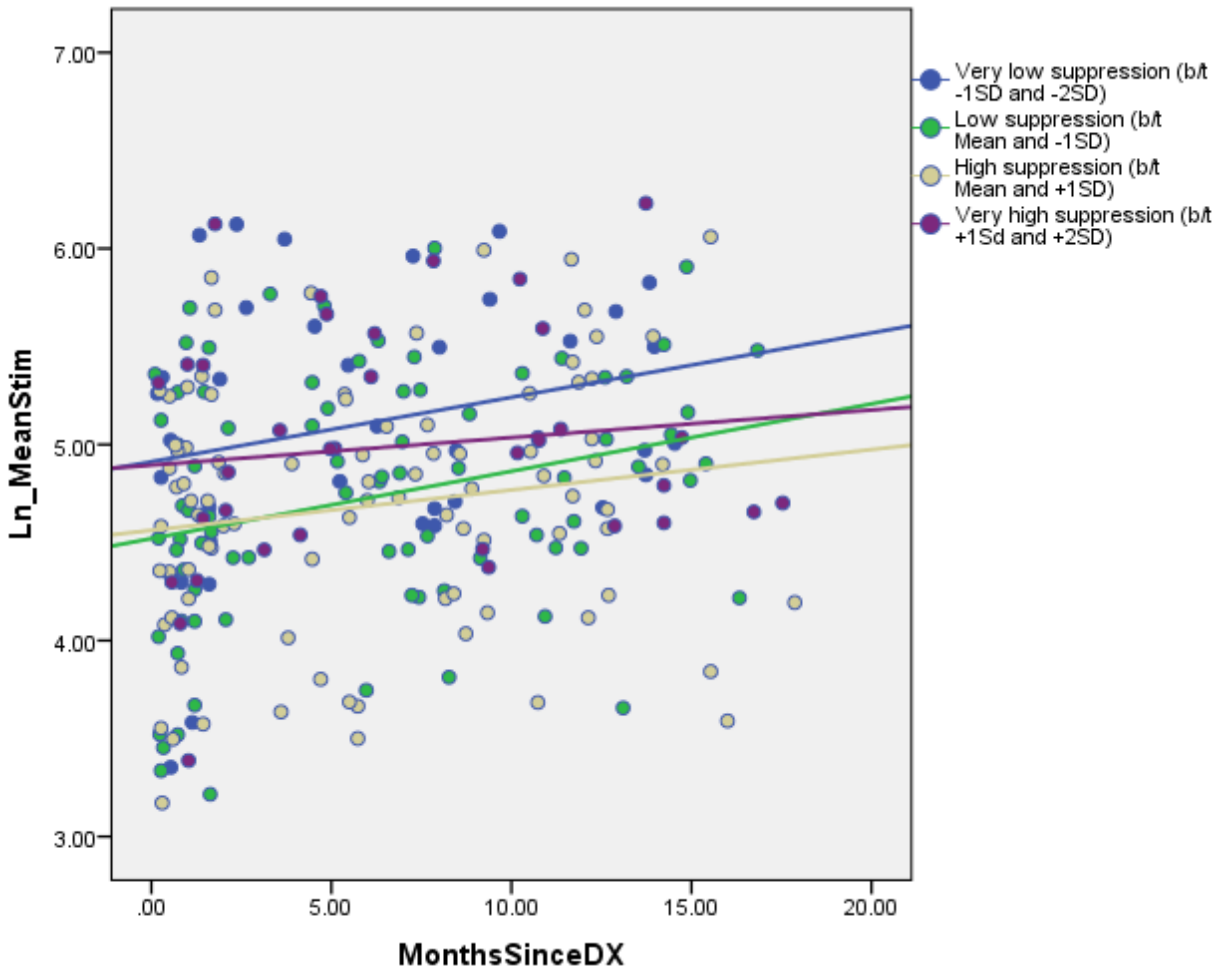


Figure 4. Stimulated IL-6 levels as a function of time x suppression. Generally, higher suppression scores related to slower increases (i.e., less steep slopes) in IL-6 levels

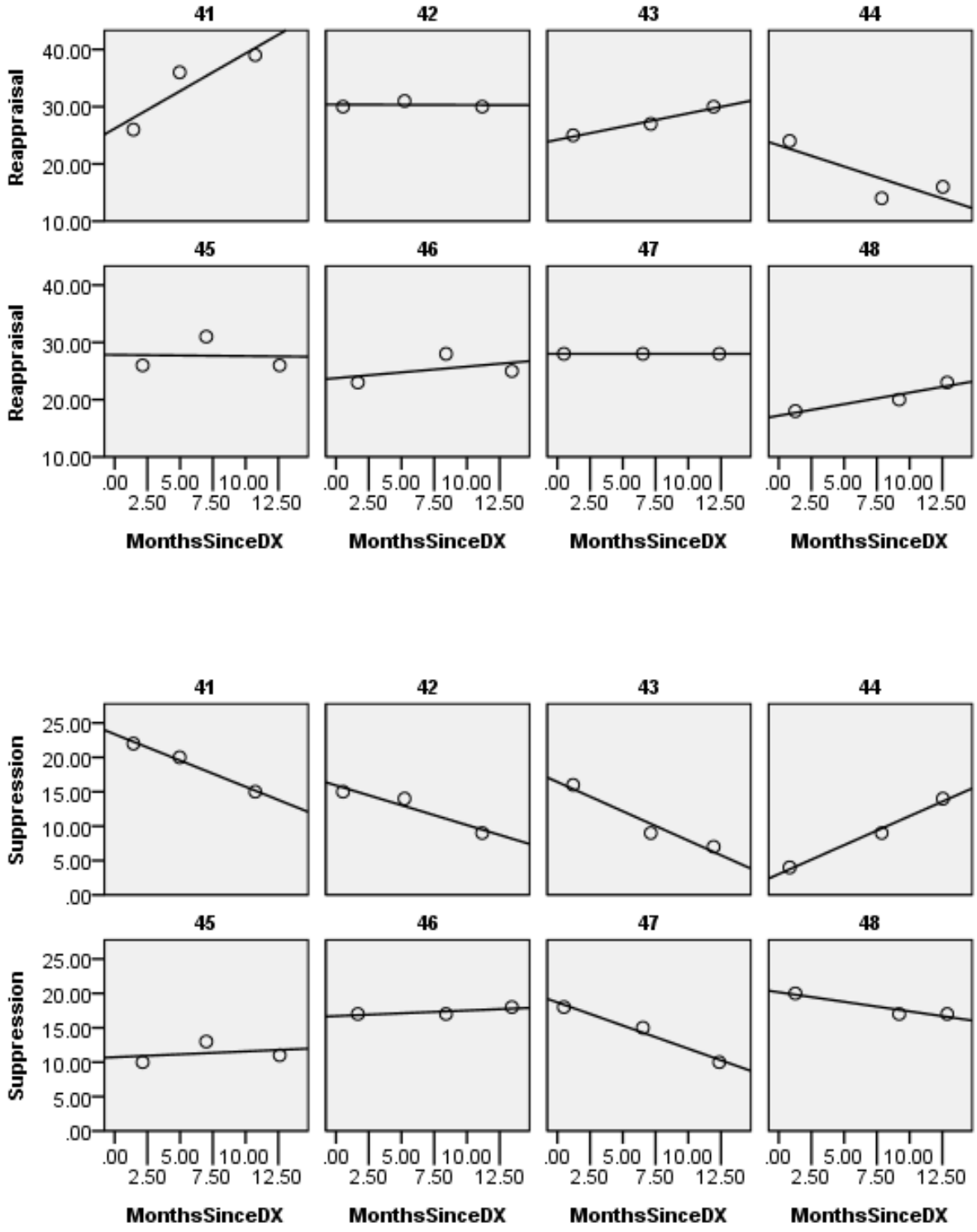


Figure 5. Individual trajectories for suppression and reappraisal for a subset of participants (participant #41 through participant #48)

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