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Couple-Based Stress Management Intervention and Chronic Fatigue Syndrome (CFS) Biopsychological Processes

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COUPLE-BASED STRESS MANAGEMENT INTERVENTION AND CHRONIC
FATIGUE SYNDROME (CFS) BIOPSYCHOLOGICAL PROCESSES

By

Sara F. Milrad

A DISSERTATION

Submitted to the Faculty
of the University of Miami
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COUPLE-BASED STRESS MANAGEMENT INTERVENTION AND CHRONIC
FATIGUE SYNDROME (CFS) BIOPSYCHOLOGICAL PROCESSES

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<u>Couple-Based Stress Management Intervention</u>   (May 2018)
<u>and Chronic Fatigue Syndrome (CFS)</u>
<u>Biopsychological Processes.</u>

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Chronic fatigue syndrome (CFS) is a debilitating illness that is characterized by heterogeneous, systemic symptoms that impact patients' and their caregiving partners' quality of life. Extant literature has found hypothalamic-pituitary-adrenal (HPA) axis and neuroimmune biomarkers associated with the disorder, but the impact of relationship satisfaction and patients' communication satisfaction about symptoms on these CFS-relevant biological markers and on CFS patients' CFS symptom severity has not been examined. Like others suffering from incapacitating chronic illnesses, CFS patients are often homebound, on disability, and/or face unemployment; however, people suffering from CFS report significantly less social support and more stigma from society, as compared to other patient populations coping with the challenges of chronic and acute illnesses. CFS patients, at times, also report a lack of understanding from their surrounding support network.

Because of the unique challenges associated with this commonly misunderstood illness with no definitively known cause or cure, interventions have been developed to synergistically ameliorate the mental and physical toll this disorder causes. Specifically,

cognitive behavioral stress management (CBSM) has been developed to concurrently improve coping skills, stress, mood, physical symptoms, HPA and neuroimmune functioning in many patient populations, including CFS patients. To address the needs of CFS patients, and other patient populations for whom in-person therapy appointments are not feasible, this intervention has been adapted to dissemination via telephone and videophone/tablet.

The present dissertation study involved an analysis of the effects of relationship satisfaction (Dyadic Adjustment Scale, DAS), depression (Center for Epidemiologic Studies-Depression, CES-D, and patient symptom disclosure satisfaction (PSDS) on fatigue severity (Fatigue Symptom Index, FSI), overall CFS symptom severity (CDC CFS Symptom Scale), salivary evening cortisol, and serum pro-inflammatory cytokines in 150 patients with CFS who were enrolled, with their caregiving partner, into a randomized controlled trial testing the efficacy of a 10-week remotely-delivered group CBSM program versus an attention-matched health promotion (HP) control program. Depression and PSDS were examined as indirect variables of the hypothesized effects of relationship satisfaction on baseline CFS-related variables (Aim 1) using structural equation modeling (SEM) in Mplus. For Aim 2, changes in depression and PSDS were also studied longitudinally as mediators of the effects of intervention assignment on CFS-related outcomes (5 Month Follow Up- T2). Specifically, the intervention effects on the 5-month change in the mediators (T2-T1) and on the T2 outcomes were examined using repeated measures analysis of covariance (ANCOVA) and path analysis using structural equation modeling (SEM). Parallel multiple mediation modeling was used to test the indirect effects of the two mediators simultaneously.

An examination of cross-sectional, direct and indirect effect analyses for Aim 1 showed that relationship satisfaction (DAS Total) did not have a significant direct effect on the outcomes of interest (CFS symptom severity, fatigue severity, evening cortisol, and IL-6, and TNF-α). While relationship satisfaction did not exert a significant direct effect on any of the outcomes at baseline, greater relationship satisfaction consistently predicted greater PSDS and less depression in all models. For baseline analyses of CFS symptoms, both depression and PSDS significantly related to greater fatigue severity (p's < 0.05), while only depression was associated with greater CFS symptom severity (p < 0.01). Analyses of baseline inflammatory markers revealed that greater PSDS significantly related to greater TNF-α, even when relationship satisfaction was included in the model (p=0.02). IL-6 or evening cortisol was not significantly related to depression or PSDS.

The second part of the dissertation (Aim 2) compared the effectiveness of the interventions CBSM vs HP on the outcomes of interest measured at the 5 month follow-up using repeated measures analysis of variance (RANOVA). To examine the mechanism of action of the interventions, SEM was used to estimate the direct effect of group assignment and indirect effects of change in PSDS and depression (T2-T1) on the 5-month outcomes. Relationship satisfaction was not included in the longitudinal models as a covariate or predictor because it did not relate to CFS-related outcomes variables at baseline in Aim 1. There were no time by treatment intervention effects on any of the outcomes (CFS symptom severity, fatigue severity, evening cortisol, and IL-6, and TNF-α), nor on depression or PSDS at 5-months. Depression severity scores decreased and PSDS scores increased over time in both treatment arms, as expected, though this effect was not significant. Though the participants were randomly assigned to each intervention, the HP

group started the trial with significantly more depressive symptoms, worse relationship quality, and more severe CFS and fatigue symptoms at baseline (all p's < 0.05), which may explain the lack of significant group effects.

Using SEM, a between-group analysis of intervention effects showed that group assignment had a direct effect on fatigue severity, such that those assigned to the HP group experienced greater fatigue severity at 5 months (T2) (p= 0.02). Indirect effect analysis showed that greater magnitude of change in depression severity scores (becoming more depressed between T1 and T2 in both treatment arms) experienced greater fatigue severity at 5M. When baseline fatigue severity was added as a covariate, the previously significant group effects were no longer significant (p= 0.65), but the effect of change in depression remained significant (p<0.01).

Like fatigue severity outcomes, the direct effects and parallel mediation modeling showed that group assignment had a direct effect on CFS symptom severity. Those assigned to the HP group experienced greater CFS symptom severity at 5 months (T2). Indirect effect analysis showed that greater magnitude of change in PSDS severity scores (becoming more satisfied with communication between T1 and T2 within both treatment arms) predicted decreased fatigue severity at 5M. Importantly, these effects became non-significant when baseline CFS symptom severity was added to the model as a covariate (both p's >0.05). Group assignment did not exert any effects on evening cortisol, IL-6, or TNF-α, nor were there any significant indirect effects on the biological outcomes by change in depression or PSDS. In conclusion, both sets of analyses (ANCOVA and SEM) showed no intervention effects on change in the hypothesized mediators and outcomes at 5 months.

There were several study limitations and strengths. Importantly, this study did not look at the final follow-up time point at 9-months post-baseline, where there may have been intervention effects. By chance, the participants randomly assigned to the attention-matched health-promotion control condition (HP) began the intervention with significantly worse depressive and CFS symptoms, and worse relationship quality. Additionally, the effects of the HP could have been too strong (therapeutically) as it was delivered on an individual dyad basis rather than a group format used for the CBSM dyads. This could account for the lack of significant differences in effectiveness between treatment arms. One strength of the study was that it provided evidence that depression and PSDS may contribute to better relationship satisfaction in couples dealing with CFS. Second there was evidence that depression may also contribute to less fatigue. Further research should consider intervention design modifications, and delve deeper into mechanisms of change, especially considering dyad-relevant variables (e.g., effects of relationship satisfaction, perceived valence of partner comments) and stress management processes (e.g. perceived skill in using CBSM techniques), that may inform interventions aimed at improving mental and physical well-being of CFS patients and their caregiving partners, among other patient populations coping with chronic illnesses.

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CHAPTER 1: INTRODUCTION

Overview

Chronic fatigue syndrome (CFS), which overlaps with a condition referred to as myalgic encephalomyelitis (ME), is a hypothesized neuroimmune illness with debilitating, heterogeneous symptoms that negatively impact daily functioning and quality of life, and which is overrepresented among women (G. Broderick et al., 2012; Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue, Board on the Health of Select, & Institute of, 2015; Fischer et al., 2014; Fletcher, Zeng, Barnes, Levis, & Klimas, 2009; Smylie et al., 2013). Due to this overlap, I will refer to this condition as CFS/ME. Commonly experienced symptoms of CFS/ME include severe fatigue, post-exertional malaise, sore throat, headache, memory and concentration difficulty, dizziness, sensory abnormalities, and significant sleep-related issues (Carruthers et al., 2011; Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue et al., 2015; Fukuda et al., 1994; Milrad, Hall, Jutagir, Lattie, Ironson, et al., 2017).

Not only does this chronic illness negatively affect the patient's quality of life, but CFS/ME may also drastically change the patient's role in spousal and/or family and friend-related relationships, in larger social circles, within the workplace and within society at large, as many people with CFS/ME are unable to work at their premorbid level, if at all (Dimmock, Mirin, & Jason, 2016). A report issued by the National Academy of Medicine (NAM) reported that CFS/ME affects approximately 836,000 to 2.5 million Americans (Bested & Marshall, 2015; Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue et al., 2015; Dimmock et al., 2016). The economic consequences of this illness are staggering; the high rate of disability among people

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suffering from CFS/ME accounts for 18-24 billion dollars per year of lost productivity and medical costs in the United States (Bested & Marshall, 2015; Dimmock et al., 2016). It is estimated that 30% of people with CFS/ME and 51% of people suffering from CFS/ME and comorbid fibromyalgia are unemployed in the United States (Bombardier & Buchwald, 1996). The symptoms of the illness render patients more functionally impaired than those who suffer from other chronic illnesses such as congestive heart failure, multiple sclerosis, depression, and end-stage renal disease (Dimmock et al., 2016).

There remains no cure for the CFS/ME—only management through the treatment of its many symptoms (Adler, 2004). The disease is also unpredictable on many levels; most causes of the illness are still unknown, and the disease can remit or worsen at any time for no apparent reason (Adler, 2004). Like other inflammatory disorders (i.e. multiple sclerosis), the onset of the disease is typically precipitated by many factors, typically an environmental, physiological, and/or psychological stressor, and there also might be pre-disposing genetic factors as well (Adler, 2004).

CFS/ME may add stress and adversity to the patients' intimate relationships, especially in the context of partner caregiving burden due to disability and unemployment, which may precipitate or increase patients' depressive symptoms (Verspaandonk, Coenders, Bleijenberg, Lobbestael, & Knoop, 2015). Relationship compatibility and how couples cope with the illness may contribute to depression and illness burden (Blazquez, Guillamo, Alegre, Ruiz, & Javierre, 2012). Relationship compatibility has been conceptualized as "dyadic consensus" and reflects the degree to which the couples agree on lifestyle matters, such as religion, finances, and proper behavior (Spanier, 1976). The patient's satisfaction related to the efforts of the couple (often in a patient-caregiver

arrangement) to cope with an illness in response to the needs of the patient has not been formally conceptualized. For the purposes of the proposed research, will be called "patient symptom disclosure satisfaction."

One major focus of the proposed project will be to examine if dyadic consensus, measured with the Dyadic Adjustment Scale (DAS) (Spanier, 1976) and/or the couple-based coping strategies related to communicating support needs, measured with the Patient Symptom Disclosure Satisfaction (PSDS) scale (Porter, Keefe, Wellington, & de Williams, 2008) are associated with depressive symptoms and the experience of CFS/ME symptoms. Though the research regarding couples' satisfaction, depression and CFS/ME symptoms is relatively scarce, the evidence generally mirrors that of other relevant work in chronic illnesses, in that marital discord, and negative or solicitous (e.g. critical or patronizing comments and behavior) communication (by the partner) is detrimental to the CFS/ME patient's physical and mental well-being (Band, Wearden, & Barrowclough, 2015).

Given that depressive symptoms and CFS symptoms have both been associated with alterations in neuroimmune processes it is reasonable to consider that neuroimmune processes may serve as an intermediary in the association between depressive and CFS/ME symptoms. Neuroimmune processes such as dysregulated hypothalamic pituitary adrenal (HPA) axis functioning and increased circulating pro-inflammatory cytokine levels, previously shown to occur under conditions of chronic stress and depression (Cohen et al., 2012), have also been shown in CFS/ME (Aggarwal et al., 2014; G. Broderick et al., 2012; Craddock et al., 2014; Demitrack et al., 1991; Fletcher et al., 2009; Light, White, Tadler, Iacob, & Light, 2012; MacHale et al., 1998; Nater et al., 2008; Rajeevan et al., 2007; Smylie et al., 2013; P. Strickland, Morriss, Wearden, & Deakin, 1998; Van Den Eede,

Moorkens, Van Houdenhove, Cosyns, & Claes, 2007; Vangeel et al., 2015). The mechanisms underlying the role of these neuroimmune processes in CFS/ME symptomology though still unknown (Fischer et al., 2014), may involve altered stress responding (D. L. Hall et al., 2014; Lattie et al., 2012) that can be understood in a psychoneuroendocrinological allostatic load framework (Arroll, 2013; Milrad, Hall, Jutagir, Lattie, Czaja, et al., 2017). Specific to the proposed study, it is hypothesized that increasing levels of depression may exacerbate altered HPA axis functioning and inflammatory signaling, which in turn contribute to a worsening of CFS/ME symptoms. Taken together, I hypothesize that greater depressive symptoms in CFS/ME patients, by way of poorer relationship compatibility and poorer dyadic coping and communication about CFS symptoms, may relate to greater CFS/ME symptoms via neuroimmunologic processes.

Review of Relevant Research

Couples Coping with CFS/ME

Illnesses of any nature do not affect the patient in a vacuum, but instead typically also affect the patient's spouse, family, friends, and colleagues, and influence the interpersonal dynamics within those relationships (Blazquez & Alegre, 2013; Dewa & Lin, 2000; Fehmidah Munir, Jones, Leka, & Griffiths, 2005; F. Munir, Leka, & Griffiths, 2005; Fehmidah Munir et al., 2007; Rees, O'Boyle, & MacDonagh, 2001; Sales, 2003). The debilitating symptoms caused by CFS/ME pose no exception to that experience (Blazquez & Alegre, 2013; Moss & Dyck, 1999; Sperry, 2012). Not only can the symptoms of illnesses impact relationship satisfaction and functioning, but negative relationship factors can affect symptom severity and/or duration of illness (Stroud, Turner, Jensen, & Cardenas,

2006), which can be manifested on a biochemical level (Slatcher, Selcuk, & Ong, 2015). Conversely, social support, among other positive relationship-related factors, provided by romantic partners, friends, and family-members can significantly enhance coping and treatment of chronic illnesses, including CFS/ME (Blazquez & Alegre, 2013).

Marriage and equivalent relationships are known to exert lasting effects on each individual's health and well-being. In general, being in a marital-like relationship is associated with better health outcomes (Reid, Ski, & Thompson, 2013; Robles, Slatcher, Trombello, & McGinn, 2014; Slatcher et al., 2015), including decreased mortality risk and increased positive health behavior change (Arden-Close & McGrath, 2017; Rogers, 1995); however, relationship quality or satisfaction are not usually measured in these large-scale epidemiological studies (Lewis et al., 2006). When relationship quality is taken into account, higher marital quality is associated with more ideal health outcomes, and consequently, not all marital-like relationships are beneficial for health (Lewis et al., 2006). These results can also differ by gender such that marital quality was especially predictive of decreased mortality in female heart failure patients, as compared to males, even when controlling for disease severity (Coyne et al., 2001; Lewis et al., 2006). Therefore, a closer look at the interpersonal dynamics behind relationships that are advantageous or deleterious to health is warranted, especially in the context of chronic illness.

Dyadic satisfaction and couple-based coping skills/support can affect psychological and physical well-being in healthy and chronically ill individuals, by way of affecting communication dynamics, and health behavior change (Robles et al., 2014; Stroud et al., 2006). For patients suffering from chronic pain and spinal cord injury, patients' reported partners' negative responses to pain were positively associated with pain intensity,

depressive symptom severity, and interference scores (Stroud et al., 2006). However, in the same study, social support satisfaction was inversely associated with depression symptom severity (Stroud et al., 2006). In a study of healthy couples undergoing an experimentally-induced stress task, receiving more positive dyadic coping and support from their partner resulted in faster recovery from the stress test (Meuwly et al., 2012), as did feeling more securely attached (Powers, Pietromonaco, Gunlicks, & Sayer, 2006). In the context of suffering from a chronic illness such as inflammatory arthritis, greater marital satisfaction was associated with less disease severity and inflammation (Çelİk & Pasİnlİoğlu, 2013). In osteoarthritis patients, higher levels of self-efficacy for pain communication were associated with lower levels of pain, physical and psychological disability, and pain catastrophizing (Porter et al., 2008). Within a sample of subjects with chronic low back pain, depression and partners' negative responses were found to mediate the relationship between relationship dissatisfaction and pain (Waxman, Tripp, & Flamenbaum, 2008).

CFS/ME is a debilitating illness that typically decreases a patient's quality of life, and puts added stress on a couple's relationship, and negatively affects the patient and partner, especially when the partner must assume caregiver and breadwinner roles (Blazquez & Alegre, 2013; Harris et al., 2016; Verspaandonk et al., 2015). Additionally, the experience of CFS and fibromyalgia can negatively affect sexual satisfaction and functioning among women, which can also strain a relationship (Blazquez, Ruiz, Aliste, García-Quintana, & Alegre, 2015; Blazquez et al., 2008).

However, some couple's relationships may actually benefit and strengthen as a result of coping with CFS/ME (Lingard & Court, 2014). One semi-qualitative pilot study shows anecdotal evidence of this. Partners reported greater appreciation for their

significant other, increased spirituality (within Christianity), greater couple resilience, and increased fondness and admiration for one another compared to life before caring for a CFS partner (Lingard & Court, 2014). Additionally, the couples expressed that coping with CFS/ME had helped them reappraise their relationship, and couples frequently discovered new strengths in their relationship, enhanced proactivity in addressing CFS/ME related concerns, self-improvement, improved relationships with other people, and greater capacity for sensitivity to the emotions of himself or herself, and his or her partner (Lingard & Court, 2014). However, it is important to keep in mind that these experiences may not generalize to most patients with CFS/ME and their partners. The sample was admittedly small, comprised of a majority of men who were diagnosed with CFS/ME, and excluded severe CFS/ME cases (Lingard & Court, 2014).

Dyadic satisfaction and communication-related variables can also affect treatment efficacy in CFS/ME. In a trial of CFS patients completing a Cognitive Behavioral Therapy (CBT) intervention, the degree of patients' relationship dissatisfaction was associated with less clinically significant improvements in fatigue after the intervention. Partners' solicitous responses to patient's symptoms also negatively affected the size of the improvements over time (Verspaandonk et al., 2015). Additionally, in another trial of CFS patients, frequency of negative social interactions (which was shown to predict fatigue severity) improved in CFS patients enrolled in CBT, versus those enrolled in guided support groups or the natural course condition (Prins et al., 2004).

These findings highlight the importance of interpersonal factors, especially relationship satisfaction and couple-based coping skills in managing a life with CFS/ME, and how these measures can affect CBT treatment potency.

Relationship and Communication Satisfaction During Illness

There are myriad relationship-related factors that can account for the impact of chronic illnesses on relationships (Robles et al., 2014). The experience of chronic illness can alter the interpersonal dynamics that were unique to that couple before the onset of the illness (Robles et al., 2014). One such mechanism of this effect involves non-verbal and verbally-explicit communication-related factors, specifically involving patient symptom disclosure (Stephens, Martire, Cremeans-Smith, Druley, & Wojno, 2006).

Both verbal and non-verbal expressions of pain and distress serve the purpose of eliciting sympathy and support from caregivers (Stephens et al., 2006). Some research on this topic comes from the study of chronic pain and osteoarthritis (OA). OA is comparable to the experience of CFS/ME because of the similarly experienced disabling pain and fatigue, which typically also impacts his or her caregiving partner. Additionally, pain and fatigue are considered "invisible" symptoms that are made known to others solely by the patient exhibiting verbal or non-verbal symptom-related communication and behavior.

In a study of women diagnosed with OA and their caregiving husbands, the relationship between husbands' life satisfaction with their wives' pain was moderated by the outward display of pain behavior from their wives over the course of 6 months, such that high pain behavior strengthened the association; this was not true of pain disclosure, but pain disclosure also negatively impacted the husbands' well-being (Stephens et al.,

2006). Not only were the wives' verbal pain expressions positively associated with depressive symptoms, the expressions might have detracted from spousal support, since greater pain was associated with lower levels of emotional support at high (but not low) levels of pain disclosure (Stephens et al., 2006). Additionally, the severity of the wives' pain and the frequency of expressing pain non-verbally was positively associated with how judgmental and critical husbands were of their wives' pain expressions (Stephens et al., 2006). Using hierarchical linear modeling of dyads coping with knee OA, daily empathic responsiveness by the partner explained the variance in linear change in patients' physical functioning across an 18-month follow-up period, even when controlling for patients' average levels of pain expression, spouses' average empathic responses across the diary period, age, years since OA diagnosis, and initial marital satisfaction (Wilson, Martire, & Sliwinski, 2017). Patients in dyads that showed stronger daily associations between patient pain expression and partner empathic responses demonstrated increased linear improvements in physical functioning (Wilson et al., 2017).

Patients' and partners' self-efficacy for pain communication also plays a role in the experience of coping with OA. A preliminary study of 38 patients with OA and their partners showed that higher levels of self-efficacy for pain communication were positively associated with lower levels of pain, physical and psychological disability, and pain catastrophizing (Porter et al., 2008). In contrast, higher levels of holding back pain communication were correlated with increased levels of psychological disability and pain catastrophizing (Porter et al., 2008). Therefore, the assuredness and perception of being able to communicate meaningfully with a partner about his or her symptoms is a significant

factor that affects mental and physical well-being of the patient suffering from OA. Symptom/pain communication self-efficacy has not yet been examined in the context of CFS/ME, until this present study.

These complex communication-related factors are not only relevant to each individual within the dyad, and to the quality of the relationship as a whole, but are also relevant to the experience and treatment of the illness or pain itself either directly, or indirectly by way of impacting the quantity and quality of social support received from the partner, for the patient's benefit. Additionally, caregiving partners may ignore or verbally punish their significant others, or may demonstrate solicitous actions (i.e. by taking over the patient's tasks), thereby negatively impacting the patient's mental and physical well-being (Martire, Schulz, Keefe, Rudy, & Starz, 2008). Solicitous responses can exert varying effects on patient's pain and activity levels, especially dependent on the dyad's relationship satisfaction (Flor, Kerns, & Turk, 1987; Schmaling, Smith, & Buchwald, 2000). In chronic pain patients, more solicitous responses were correlated with patients' higher pain intensity and lower activity levels (Flor et al., 1987; Schmaling et al., 2000). The patient's appraisal of their partner's responses is especially salient to pain intensity and consequent behavior, as the spouse's appraisals of the patient's pain did not predict pain intensity and behavior (Flor et al., 1987; Kerns et al., 1992). The authors posited that patients' perceived pain intensity did not elicit more solicitous behaviors from the partners, but instead, patients' pain intensity and pain-related behaviors were contingent on their partners' responses (Flor et al., 1987; Kerns et al., 1992). This underscores the importance of examining the patient's perception of their partner's responses in research on chronic illnesses.

In a follow-up study of chronic pain patients and their partners, solicitous and distracting responses predicted the greater frequency of distorted ambulation, expressions of pain (facial/audible), and help-seeking (Kerns et al., 1992). Within a sample of chronic pain patients, the mood and responses of the partner to the patient related to worse mood and sleep quality in older adults with chronic pain, such that daily solicitous responses intensified the negative effects of low positive mood on both sleep indicators, which can in turn affect patients' pain and daily functioning (Song, Graham-Engeland, Mogle, & Martire, 2015). While depression and marital dissatisfaction is common among dyads coping with chronic pain, and the relationship between them is robust, neither predict pain intensity; instead, only the relationship between spousal support and depression was significant (Kerns & Turk, 1984). In other work, pain-contingent partner responses predicted pain intensity, while global marital satisfaction did not, even though marital satisfaction predicted depressive symptom severity (Flor et al., 1987). Therefore, the perceived valence of partners' responses to symptoms such as pain, and the frequency of partners' solicitous behaviors can have broad, far-reaching effects on the patients' mood, symptoms, and behavior.

Patient-Caregiver Communication and CFS/ME

There is a relative paucity of patient-caregiver communication-related research in the context of CFS/ME, but a recent review of 14 articles details the associations between the responses of the significant other and CFS symptom outcomes (Band et al., 2015). CFS is a stigmatizing illness which is commonly misunderstood by both medical professionals and society in general (Looper & Kirmayer, 2004); expectantly, people suffering from CFS tend to feel distressed when their partners do not understand their symptoms or validate the

pain and distress caused by their CFS symptoms (Band et al., 2015; Dickson, Knussen, & Flowers, 2007). Furthermore, in one longitudinal study, negative interactions and perceived lack of social support at baseline predicted higher fatigue severity at 8 months (Prins et al., 2004). In this study, CFS and chronically fatigued (but not CFS diagnosed) patients received less social support and more negative interactions than breast cancer survivors and healthy controls (Prins et al., 2004). In sum, people with CFS are affected not only by their symptoms, but by their own emotional and behavioral response to their symptoms, and also by the responses of their partner and others in their social circle (Band et al., 2015; Dempster et al., 2011).

As alluded to previously, relationship satisfaction and the responses of the partner to patient symptoms can (in part) affect the patient's experience of CFS symptoms and its treatment (Romano, Jensen, Schmaling, Hops, & Buchwald, 2009; Schmaling, Fales, & McPherson, 2017; Schmaling et al., 2000; Verspaandonk et al., 2015). Patients and their partners may jointly cope with the illness or instead might experience incongruency about the interpretation of symptoms and their consequent management, which may affect the perceived and/or actual support given by partners and by a larger support network (Band et al., 2015; Brooks, King, & Wearden, 2014; Dickson et al., 2007).

Similar to the research exploring partners' responses to pain communication, solicitous partner responses were associated with increased fatigue severity and bodily pain in CFS/ME (Schmaling et al., 2000). Interestingly, distracting and punishing partner responses were not significantly associated with fatigue, pain, disability, or physical functioning (Schmaling et al., 2000). Relationship satisfaction, as measured by one item from the Dyadic Adjustment Scale (asking how happy he or she was with their relationship

on a 7-point scale), was also considered in these analyses (Schmaling et al., 2000). Similarly to what was found within pain subjects, relationship satisfaction played a moderating role in the relationship between partners' solicitous responses and fatigue-related disability, and fatigue severity in the context of CFS/ME (Schmaling et al., 2000). Here, the association between fatigue-related disability and solicitous responses under high relationship satisfaction conditions was significantly greater than under low relationship satisfaction and different than zero (Schmaling et al., 2000). When examining fatigue severity and solicitous responses, at three levels of relationship satisfaction (low, average, high), the solicitous response x fatigue association was significantly increased with each increasing level of relationship satisfaction (Schmaling et al., 2000).

In a hierarchical modeling analysis of dyads coping with CFS/ME and/or FM, or idiopathic chronic fatigue (ICF), more solicitous partner responses covaried with more tender points; also, more negative partner responses covaried with more bodily pain, more CFS symptom severity, worse physical functioning, and worse mental health over time (Schmaling et al., 2017). Interestingly, more distracting partner responses covaried with better mental health functioning over the same time period of 18 months (Schmaling et al., 2017). Importantly, the sample used participants who did not meet full criteria for CFS (ICF), and both CFS and FM are hypothesized to have distinct symptoms, yet heterogeneous patient populations; therefore, this data may not be fully generalizable to a "pure" CFS/ME sample, or possibly only to certain subtypes of CFS/ME.

While these analyses were preliminary, the results provide support that solicitous partner responses may act as a perpetuating factor in CFS/ME, as was suggested for pain behavior and partner solicitous responses (Schmaling et al., 2000).

Importantly, there is only a modest association between partners' actual, observed solicitous behavior and that which is perceived by the patient (Schmaling et al., 2000). Therefore, for that reason, among others, the proposed study will solely focus on patients' perception of the partners' responses.

Relationship and Communication Satisfaction and Depression

Discord among partners may affect mental health as well as physical health. Marital dissatisfaction and perceived inadequate support is associated with increased levels of depression in healthy and chronically ill individuals (Daneker, Kimmel, Ranich, & Peterson, 2001; Lal & Bartle-Haring, 2011; Uebelacker, Courtnage, & Whisman, 2003). The Marital Discord Model of Depression supports that marital discord is an antecedent in the development of a depressive episode, especially in those who are chronically dysphoric, and this effect generalizes across different sample factors including ethnicity (Beach & O'Leary, 1993; Beach, Sandeen, & O'Leary, 1990; Hollist, Miller, Falceto, & Fernandes, 2007). The effect is bi-directional, as baseline depressive symptoms can predict marital discord at follow-up (Whisman & Uebelacker, 2009).

Again, there is a relative scarcity of couple-related research in the context of CFS/ME; though, the existing research follows what would be expected—marital discord, and/or unhelpful communication styles are associated with worse mental and physical well-being, including increased depression (S. S. Goodwin, 1997; Sheila S Goodwin, 2000; Romano et al., 2009). Additionally, women suffering from CFS reported more symptoms when they reported conflicts with their partners and relationship discord (Sheila S Goodwin, 2000). In women with "chronic fatigue and immune dysfunction syndrome" (CFIDS), a condition synonymous with CFS/ME, marital adjustment scores and husbands'

self-empathy scores were associated with less symptom severity, while the wives' conflict scores were associated with greater symptom severity (S. S. Goodwin, 1997). While statistically controlling for demographic and marriage-related variables in the model, husbands' and wives' perceived marital support accounted for the most variance in CFIDS symptoms (S. S. Goodwin, 1997). Some work has implicated neuroimmune processes as one mechanism explaining the association between psychological factors and CFS/ME symptoms.

Hypothalamic Pituitary Adrenal (HPA) Axis Functioning, Inflammation, and Depression

HPA axis functioning has been shown to be dysregulated in individuals suffering from depression (Hsiao et al., 2010) as well as in patients with CFS/ME (Nater et al., 2008). Patients with CFS/ME have shown higher salivary evening cortisol profiles, as compared to chronically fatigued (not meeting criteria for CFS/ME) persons and healthy controls (Nater et al., 2008). Depression is commonly co-morbid in CFS/ME (Janssens, Zijlema, Joustra, & Rosmalen, 2015), therefore, depression may be associated with greater evening cortisol in CFS/ME patients.

Recent research has implicated the role of pro-inflammatory cytokines in the experience of depressive symptomatology and CFS symptoms (R. Dantzer, 2009; Robert Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Liu, Ho, & Mak, 2012; Milrad, Hall, Jutagir, Lattie, Czaja, et al., 2017; Raedler, 2011; Raison & Miller, 2011). Pro-inflammatory cytokines such as Interleukin (IL)-1β, IL-6, and Tumor Necrosis Factor (TNF)-α can precipitate and exacerbate "sickness behavior" processes that resemble the somatic experience of depression (Robert Dantzer et al., 2008; Himmerich et al., 2008; Kelley et al., 2003). Since cytokines can cross the blood-brain barrier, they affect the brain

and its related regulatory processes, in addition to acting systemically on the body (Robert Dantzer et al., 2008). Sickness behavior includes fever, changes in sleep architecture, HPA activation, reduction of food intake, and behavioral inactivation/ withdrawal (R. Dantzer, 2009). These symptoms are similar to what is experienced during CFS/ME and depression (Fukuda et al., 1994; Radloff, 1977; Wagner et al., 2005).

The relationship between inflammation, depression, and HPA functioning has been shown both "bench-side" and clinically. Experimentally-induced secretion of pro-inflammatory cytokines by lipopolysaccharide (LPS) causes symptoms of sickness behavior and depression in animals and humans (R. Dantzer, 2009). When pro-inflammatory cytokine therapy (Capuron, Ravaud, Miller, & Dantzer, 2004) is administered to patients (e.g. to treat cancer), which induces IL-6 and TNF-α production, depressive symptoms may be increased (Prather, Rabinovitz, Pollock, & Lotrich, 2009; Raison & Miller, 2011). There is substantial evidence that depressed individuals show increased inflammation, especially increased pro-inflammatory TNF-α (Dannehl et al., 2014; Himmerich et al., 2008) and IL-6 (Alesci et al., 2005) among other pro-inflammatory cytokines. Furthermore, levels of these cytokines decrease in response to pharmacological agents like anti-depressants (Liu et al., 2012; Raedler, 2011); however, this is not consistently shown, especially when methodological differences exist between studies (Marques-Deak et al., 2007). In sum, there is growing evidence that depression, HPA axis dysregulation and inflammation are associated, though the direction and the temporality of these associations is yet to be firmly determined.

Evening Cortisol, Negative Health Outcomes, and Inflammation

Evening cortisol levels are often used to characterize HPA axis dysregulation given that di-urnal cortisol levels should achieve their nadir in the evening and nighttime hours (Hsiao et al., 2010; Jarcho, Slavich, Tylova-Stein, Wolkowitz, & Burke, 2013). Previous research has shown that evening cortisol was related to greater pro-inflammatory cytokine levels that peak during the night (i.e. IL-6) (Logan & Sarkar, 2012; Nakamura et al., 2010; Vgontzas et al., 2002), and greater depressive symptoms (Goodyer et al., 1996; Van den Bergh & Van Calster, 2009). CFS/ME patients have shown increased salivary evening cortisol levels vs controls (Nater et al., 2008). Cross-sectional analysis of CFS/ME patients in our lab show that greater depressive symptoms are related to greater evening salivary cortisol (β=0.215, p<0.01) and greater pro-inflammatory IL-2, IL-6, and TNF-α levels (composite β=0.185, p<0.05), when controlling for covariates age, gender, and education (Milrad, Hall, Jutagir, Lattie, Czaja, et al., 2017). Thus elevated evening cortisol levels may play a key role in relations among depression, inflammation and CFS/ME symptoms in our biopsychosocial model. To the extent that some of these biopsychosocial factors may be modifiable, it is reasonable to review studies of psychosocial interventions in CFS/ME.

Psychological Interventions for Patients with Chronic Illnesses and their Partners

While most of the intervention research in CFS/ME has used cognitive behavior therapy (CBT) techniques focused on reducing stress or changing the patient's interpretation of the source of CFS/ME symptoms, it is reasonable to examine interventions that include patients and partners together. Given the partner's important role in the patient's experience and treatment of a chronic illness, and considering the mental and physical well-being of the caregiving partner, some psychological interventions have been

developed to include both the patient and partner dyad when tailoring interventions for couples coping with chronic illness and/or mental health problems (Baucom, Shoham, Mueser, Daiuto, & Stickle, 1998; Berry, Davies, & Dempster, 2017; Schulz et al., 2009). As these interventions are designed to specifically target relationship-related issues and since relationship satisfaction can have major effects on mental and physical well-being, dyadic interventions can be more effective than those designed solely for the patients' benefit (Berry et al., 2017; Martire, Schulz, Helgeson, Small, & Saghafi, 2010; Schulz et al., 2009).

To assess the benefit of patient-caregiver interventions, caregivers of patients suffering from spinal cord injuries were randomized to either a dual-target intervention that was designed to address both caregiver and patient risk factors, a caregiver-only intervention that only targeted the caregiver's risk factors, and an information-only control group (Schulz et al., 2009). Caregivers of patients with a spinal chord injury who were randomized to the dual-target condition had improved quality of life at 12 months, as compared to the control condition, and had improvements in depression, caregiver burden, and health symptoms as compared to the caregiver-only condition (Schulz et al., 2009). When analyses were carried out using the dyad as a unit, dyads randomized to the dual-target condition had fewer health symptoms at 12 months, when compared to the control and caregiver-only intervention, and were also less depressed than those who were randomized to the caregiver-only condition (Schulz et al., 2009). Of note, this study enrolled patient-caregiver dyads that included spouses, relatives, partners, or a friend who was also suffering from a spinal cord injury (Schulz et al., 2009); therefore, this study is not directly comparable to couple-oriented interventions designed solely for the patient and

romantic partner. Indeed, interventions that target caregivers can differ in effectiveness depending on the type of relationship between caregiver and patient (i.e. spouse vs. daughter), at least in the context of caregivers of patients suffering from Alzheimer's disease (Belle et al., 2006; Eisdorfer et al., 2003).

A meta-analysis of couple-oriented interventions for a variety of chronic illnesses suggested that dyadic interventions had positive effects on patients' depressive symptoms, marital functioning, and pain-related outcomes, and they were more efficacious than usual care or psychosocial interventions delivered to the patient only (Martire et al., 2010). An important contribution of the proposed study was testing whether an established stress management intervention approach (described below), which was adapted to a patient-partner group-based format, was efficacious on a psychological, biological, and symptom level in patients with CFS.

Cognitive Behavioral Stress Management (CBSM) Intervention

Cognitive behavioral stress management (CBSM) is a biopsychosocial-minded, evidence-based intervention developed by Drs. Michael Antoni, Neil Schneiderman, and Gail Ironson and has consistently shown to be beneficial on both psychological and biobehavioral processes for many patient populations, including men and women who are seropositive for HIV, breast cancer patients, prostate cancer survivors, and CFS patients. Specifically, in women being treated for early-stage breast cancer, CBSM increased benefit finding, reduced serum cortisol levels, and improved lymphocyte functioning *(in vitro)* in one trial (Antoni et al., 2001; Cruess et al., 2000; McGregor et al., 2004). Breast cancer patients assigned to CBSM in a second trial showed decreased cancer-specific and general anxiety and social disruption; and increased psychological well-being, positive states of

mind, benefit finding, positive lifestyle change, positive affect, and confidence in being able to relax at will (Antoni et al., 2006; Phillips et al., 2008). The patients in the second trial who were enrolled in CBSM also showed biological changes including lower afternoon cortisol (Phillips et al., 2008), and greater Th1 cytokine response after adjuvant treatment (Antoni et al., 2009), and revealed decreased pro-inflammatory and pro-metastatic leukocyte gene expression as compared to a control group (Antoni et al., 2012). In a separate trial men who had completed treatment for prostate cancer who received CBSM showed increased benefit finding and quality of life (Molton et al., 2008; Penedo et al., 2004; Penedo et al., 2007; Traeger et al., 2013).

In HIV+ men, those assigned to a 10-week CBSM condition demonstrated lower self-reported depressive affect, anxiety, perceived stress, total mood disturbance, anger, and confusion, and also increased T-cytotoxic/suppressor (CD3+, CD8+) lymphocytes, decreased urinary cortisol and norepinephrine output and less DHEA-S decrements and less cortisol/DHEA-S ratio increments, as compared to men enrolled in a wait-list control group (Antoni, Cruess, Cruess, Lutgendorf, et al., 2000; Antoni, Cruess, Cruess, Kumar, et al., 2000; Cruess et al., 1999). Similar psychological results were found for HIV+ women with AIDS (Laperriere et al., 2005; Lechner et al., 2003) and HIV-infected women co-infected with Human Papilloma Virus (HPV) (Antoni et al., 2008, J. Psychosom Res; Lopez et al., 2014 J. Applied Biobehavioral Medicine).

CBSM Effects in CFS/ME

As CFS/ME is a hypothesized stress-exacerbated illness (Lutgendorf et al., 1995) which affects both mental and physical well-being, CBSM has been adapted for patients who are suffering from CFS (Lopez et al., 2011). In that pilot study, those who were

randomized to the CBSM group reported improvements in perceived stress (Cohen's D (d)=.41), total mood disturbance (d=.22), CDC symptom severity (d= -.20) and quality of life (d= .22) as compared to those who were randomized to the psychoeducation control group (Lopez et al., 2011). This intervention was then adapted for dissemination using telephones (conference calling) to help diminish uniquely CFS/ME-related barriers to treatment. Both the "live" (in-person) and telephone-delivered CBSM interventions were helpful in this patient population, as each were associated with decreased perceived stress post-intervention; however, in examining the CFS-symptom-related outcomes such as post-exertional malaise, chills, fever, and restful sleep, the live version was superior to the telephone version (Daniel L Hall et al., 2017).

Targeting stress management skills improvement by way of CBSM treatment appears to be advantageous for the CFS population and these skills may be related to neuroimmune processes noted previously. CFS patients who reported greater perceived stress management skills (PSMS) revealed less fatigue (p=0.019), emotional distress (p<0.001), greater diurnal (negative) cortisol slope (p=0.023), and lower IL-2 levels (p=0.043), and both PSMS and emotional distress's relationship to fatigue was strongest among patients in the top tertile of serum IL-6 (Lattie et al., 2012). In the same sample, greater stress management skills were related to less post-exertional malaise (PEM) and that was mediated by possessing a greater cortisol awakening response (CAR), although evening cortisol was not examined in that study (D. L. Hall et al., 2014). Therefore, decreasing depression by improving stress management skills via CBSM and measuring its impact on salivary cortisol and plasma inflammatory cytokines is a major focus of this research line.

Remotely-Delivered Psychological Interventions for Chronic Illnesses

Psychological interventions have evolved to accommodate the needs of elderly, disabled, chronically ill, or otherwise immobile or disenfranchised patients for whom live therapy sessions are not feasible or possible (Arnberg, Linton, Hultcrantz, Heintz, & Jonsson, 2014; Banbury, Nancarrow, Dart, Gray, & Parkinson, 2018; Cuijpers, Van Straten, & Andersson, 2008; Czaja, 2016; Czaja & Rubert, 2002; Eccleston et al., 2012; Inglis, Clark, McAlister, Stewart, & Cleland, 2011; Ljótsson et al., 2010; Palermo, Wilson, Peters, Lewandowski, & Somhegyi, 2009; Richardson, Christopher Frueh, Grubaugh, Egede, & Elhai, 2009; Schulz et al., 2009). As mentioned above, some interventions have been adapted to be disseminated by telephone (Czaja & Rubert, 2002; Daniel L Hall et al., 2017), or in the case of the proposed study, by videotelephone/tablet, so that treatment sessions can be attended in a location that is convenient for the patient (and his or her partner). Additionally, treatments have been modified to facilitate group sessions, to encourage the supportive impact of the sessions and to increase efficiency of dissemination and decrease overall cost (Richardson et al., 2009). A systematic review of tele-mental health (telephone and videoconferencing) in comparison to in-person psychotherapeutic treatments showed that patients are generally just as satisfied with tele-mental health treatment as compared to in-person treatment, and that therapeutic alliance is similar (Jenkins-Guarnieri, Pruitt, Luxton, & Johnson, 2015).

Specifically, a review of group videoconferencing used for chronic and mental illness intervention studies reported overall high patient satisfaction with the experience, high attendance (66-93.8%) and adherence (e.g. to homework assigned, 93%), and

significant changes seen in self-reported health-related quality of life HRQoL (p=0.04)(Banbury et al., 2018). Though there were trends evident in mental health and self-efficacy improvements, the pre-post treatment scores were not significant(Banbury et al., 2018). Similarly, there were no significant differences in emotional regulation, problem solving, and physical activity, among other related outcomes (Banbury et al., 2018). Bonding and cohesiveness were reported in all high-quality studies, especially among groups characterized by more stable memberships (Banbury et al., 2018).

As noted previously, our group has conducted RCTs of group-based CBSM for CFS patients delivered in different venues including live, telephone conferencing, and most recently, in a trial testing the efficacy of a novel group-based videophone/tablet format for patient/partner dyads. In the newly completed trial using the videophones/ tablets, within the CBSM treatment condition, up to five dyads were able to be seen at one time on the videophone/tablet screen during the session using the videoconferencing technology. They were also afforded the opportunity to listen to CBSM-based educational videos, expert videos and demonstration videos through the system during the 10-week intervention period. Those in the Health Promotion (HP) control condition also attended weekly dyadic sessions where they learned health-related information and also had the opportunity to listen to a video collection (but based on health-related content) during the 10-week intervention period (study conditions are described in detail in the Methods section).

Based on prior research, I hypothesized that the videophone/tablet-delivered CBSM (Remote-CBSM [R-CBSM]) intervention delivered to groups of patient/partner dyads would improve patient depression, CFS symptoms and neuroimmune processes because the intervention: (a) would hypothetically increase couple-based coping and

communication skills, (b) is delivered in a group-based format thereby hypothetically delivering more social support, and (c) makes use of new videophone/tablet technology which enables users to view the interventionist and other couples, thereby mimicking the original CBSM CFS/ME in-person trial, which was shown effective at improving CFS symptom severity and perceived stress (Lopez et al., 2011) and found to be superior to a telephone-delivered version that did not allow viewing of the interventionist or group members (Hall et al., 2017).

Summary: Synthesis of Literature

Relationship satisfaction and dyadic communications impact both mental and physical health in healthy and chronically ill individuals. In general, relationship satisfaction is associated with more favorable psychological and physical outcomes, also during treatment of and coping with chronic illness. Expectantly, relationship dissatisfaction is associated with and can precede depression and poorer health and treatment outcomes. Additionally, partners' responses to pain or fatigue symptoms and the patients' perceived communication self-efficacy can affect the patients' experience of living with the illness. These associations are expected to be evident in patients and partners coping with CFS/ME in the proposed study.

CFS patients report greater depressive symptoms than healthy controls. Depression is associated with poor health outcomes, including more severe and frequent CFS-related symptoms. Depressive symptoms are consistently linked with alterations in the hypothalamic pituitary adrenal (HPA) axis and increased inflammation, which are commonly measured by assessing abnormal salivary cortisol (e.g. increased evening cortisol levels) and increased circulating pro-inflammatory cytokines, respectively, and

which are already implicated in association with CFS symptoms. The proposed study is unique in examining the association of relationship satisfaction and patient symptom disclosure satisfaction (PSDS) with CFS patients' depressive and CFS-related symptoms, evening cortisol, and inflammatory cytokines in support of a biopsychosocial model of CFS.

Proposed Study

The proposed study utilized data from a randomized controlled trial (RCT) examining the biopsychosocial effects of a 10-week videophone/tablet-delivered couple-based CBSM group, tailored to improve stress in couples facing CFS-related challenges. The data of interest included baseline relationship satisfaction, depression, and PSDS as they relate to neuroimmune processes and CFS symptoms. The study also compared changes in patients' depression, PSDS, neuroimmune processes and CFS symptoms over time in those assigned to CBSM vs an attention-matched Health Promotion (HP) control condition.

This dissertation study tested the hypothesis that (1) CFS patients who report more compatible relationships will show less depression, greater symptom disclosure satisfaction (PSDS), less neuroimmune dysfunction (lower evening cortisol and circulating pro-inflammatory cytokines), and less severe and interfering CFS symptoms at baseline; and (2) the relationship between relationship satisfaction and these variables will be at least partially explained by PSDS and/or depression at baseline. This study also proposed to test the hypothesis that (3) CFS patients assigned to a patient-partner CBSM group intervention (vs attention-matched patient-partner control condition) will experience less depression, greater PSDS, less neuroimmune dysfunction, and less CFS symptomology

over time; and (4) CBSM effects on depression, neuroimmune dysfunction and symptoms will be mediated by increased PSDS and/or decreased depression.

Using baseline data, I first investigated the associations among patient reports of relationship satisfaction, couples' coping and communication about symptoms, depression, and CFS symptoms; and neuroimmune processes determined from saliva and blood samples. Second, I tested couples' coping and communication about symptoms and patients' depressive symptom severity as an intermediary between associations of poorer relationship satisfaction, neuroimmune processes and CFS symptoms. Third, I tested the effects of a remotely delivered group CBSM intervention for patient-partner dyads on patient reports of couples' coping and communication about symptoms and depression at 5 months, and related those changes to CFS symptoms, and neuroimmune processes measured at 5 months follow-up. Finally, I tested whether the effects of CBSM neuroimmune processes and CFS symptoms over a 5-month period are mediated by its effects on couples' coping and communication about symptoms and/or depression over the initial 5 months of the trial.

The specific aims of the proposed study were as follows.

Aims.

Aim 1. To investigate the association between trait-like relationship satisfaction (Dyadic Adjustment Scale [DAS] total score), and state-like couple's coping and communication quality (Patient Symptom Disclosure Satisfaction, PSDS), depressive symptoms (Center for Epidemiologic Survey for Depression [CES-D], neuroimmune processes (HPA axis dysregulation [evening salivary cortisol] and inflammatory cytokine levels [(tumor

necrosis factor-alpha [TNF- α], and interleukin-6 [IL-6]), and CFS symptomology (fatigue, CDC CFS symptom severity) in support of a biopsychosocial model in CFS patient-partner dyads at study entry.

Hypothesis 1: Greater relationship satisfaction (DAS Total Score) is associated with less CES-D depressive symptoms, greater PSDS, lower evening salivary cortisol, lower plasma pro-inflammatory cytokine levels (TNF- α and IL-6), and less CFS symptomatology in CFS patients.

Hypothesis 2: There is an indirect effect of PSDS and/or depression on associations between greater relationship satisfaction (DAS Total Score) and evening cortisol, pro-inflammatory cytokines, and CFS symptoms. Thus, greater PSDS and/or decreased depression serves as an intermediate variable in the associations between relationship satisfaction and depressive symptoms, neuroimmune processes and CFS symptoms.

Aim 2. To compare the effects of CBSM vs a Health Promotion control (HP) on change in PSDS and depression at 5-month follow-up, and test whether these changes relate to improved CFS symptoms and neuroimmune processes at 5-month follow-up.

Hypothesis 1: CBSM significantly improves PSDS and depression relative to the HP condition over a 5-month period.

Hypothesis 2: CBSM improves neuroimmune processes and CFS symptomology vs HP condition over a 5-month period.

Hypothesis 3: Improvements in PSDS and/or depression at 5 months mediate the effects of CBSM vs HP on reductions in neuroimmune processes, and CFS symptoms over time.

CHAPTER 2: METHODS

Participants and Procedures

Participants in this study were recruited for a trial of the biopsychosocial effects of a remotely-delivered stress management intervention (CBSM) for CFS patients and their partners. All participants received a physician-determined CFS diagnosis, as defined by the CDC criteria (Fukuda et al., 1994). Therefore, all references to study participants will be referred to as "CFS patients" for the remainder of the dissertation, though the new nomenclature and criteria (CFS/ME) is addressed and included throughout to reflect the current literature. Recruitment methods included physician referral, support groups, CFS conferences and advertisements in CFS-related websites. The CFS sample for the extant RCT was selected from the patient population of Dr. Klimas' Center for the Study of CFS Pathogenesis at the University of Miami Miller School of Medicine (UMMSOM), and her Chronic Fatigue Center for Research and Treatment for Neuroimmune Disorders at Nova Southeastern University; Dr. Ferrence's chronic pain, CFS, and fibromyalgia clinic within UMMSOM; community based physicians in Miami-Dade, Broward and Palm Beach Counties; and via community support groups, newspaper and web advertisements, and CFS related internet sites.

Inclusion of women and minorities. A total of 150 patient-partner dyads (N = 300) between the age of 21 and 75 were recruited for the RCT during the period July 2010 – September, 2016. The sample reflects the sociodemographic profile of CFS patients in Miami-Dade, Broward, and Palm Beach Counties.

Inclusion criteria: A documented diagnosis of CFS as designated by the Fukuda criteria (Fukuda et al., 1994). These included experiencing prolonged, persistent fatigue for at least 6 consecutive months that is not explained by another medical condition, in addition to at least four of the following concurrent symptoms: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, new headaches, unrefreshing sleep, and post-exertional malaise. All subjects were required to be fluent in English, partnered (living together or separately) and willing to be randomized and followed for nine months. All subjects were willing to cooperate with the objectives of the study and signed an informed consent stating this.

Exclusion criteria. Subjects were excluded for the following reasons: less than 21 years or more than 75 years of age; history of significant inability to keep scheduled clinic appointments in past; or positive serology for Lyme's disease. All patients were assessed for psychiatric diagnosis at the time of recruitment with a detailed screening questionnaire including selected SCID-IV modules. Based on this assessment, we excluded subjects with DSM-IV diagnoses for schizophrenia, bipolar disorder, or substance abuse or if they were actively suicidal, as assessed by a brief screening measure adapted from the Structured Clinical Interview for the DSM-IV (First, Gibbon, & Spitzer, 1997). Participants were also excluded if they showed markedly diminished cognitive capabilities, as evidenced by making four or more errors on the Short Portable Mental Status Questionnaire (Pfeiffer, 1975) or a score of less than 20 points on the Telephone Interview for Cognitive Status (TICS)(Brandt, Spencer, & Folstein, 1988).

Presence of another condition (e.g., AIDS, lupus, rheumatoid arthritis) that might influence biological processes associated with CFS symptomatology, or taking medications that

would modulate immune or neuroendocrine functioning excluded participants from the study. Potential participants were also excluded from the study if they reported untreated obstructive sleep apnea (OSA).

Procedures. Participants (and partners) were recruited in cohorts of up to 8 dyads. After signing informed consent, and completing all baseline assessments participants were randomly assigned to either the CBSM or a health promotion (HP) condition. Participants in the CBSM condition participated in 10 weekly 1-hour CBSM sessions at their homes delivered through videotelephones or tablets, and participants in the HP condition participated in a time-matched weekly videotelephone/tablet session targeting health-related knowledge and health behaviors. Upon completion of the 10 sessions, all participants completed an assessment battery, saliva collection, and blood draw at T2 (Week-20), the 5-month follow-up and T3 (Week 36), the 9-month follow-up, as shown in Figure 1.

To ease the burden of commuting to assessments, all participants were assessed wherever was most convenient for them; electronic surveys were emailed to them via a secure, online survey platform called SurveyMonkey (SurveyMonkey Inc., California, USA) and could be completed on their tablet or computer. Survey responses could be saved and returned to at a later time, if participants could not finish the assessment all in one sitting. Saliva collection supplies (for self-administration) and blood collection supplies (for use by a phlebotomist) were sent to participants with return shipping kits to send to the laboratory for analysis. Saliva kits consisted of a total of 9 salivettes (8 for each diurnal cortisol measurement, and 1 practice salivette), and ice pack, a cooler bag, a pre-set alarm

for the afternoon and evening measurements, and a pre-paid package containing a cooler box. Blood kits consisted of 3 blood tubes and a pre-paid bio-hazard shipping package. Procedures to ensure safety of our assessors (e.g. assessor accompanied by a staff member with cell phone) and to assure minimal intrusion into the participant's environment (e.g., flexibility in scheduling, option to conduct assessment at our facilities) were followed. Survey responses, saliva and blood sample collection were all completed within a 10-day window at each time point. After completing survey answers and providing blood samples, participants were compensated with $50.

Study Conditions

Participants were assigned at random (via a computer program) to one of two conditions: remotely-delivered CBSM (CBSM) or remotely delivered Health Promotion (HP). The content of R-CBSM comprised two broad domains: Cognitive, behavioral and interpersonal skills training and relaxation/imagery. **The Cognitive, Behavioral and Interpersonal skills** component presents information concerning stressors and stress responses from a biopsychosocial perspective. These weekly modules focus on: (a) the importance of appraisals in the stress response and in symptom occurrence; (b) understanding automatic thoughts and cognitive distortions; (c) identifying and monitoring automatic thoughts; (d) disputing and restructuring cognitive distortions into more rational thoughts, and (e) learning adaptive problem-focused and emotion-focused coping skills. **The Relaxation/Imagery component** includes targeting anxiety reduction through training in progressive muscle relaxation, deep breathing, guided imagery and meditation. The control condition (HP) was designed to provide equal amounts of attention and contact time focused on providing health behavior information (diet, patient-physician

communication, sleep hygiene) without any active treatment (CBSM) being given. HP is designed to control for common factors such as attention, supportiveness, empathy and enthusiasm.

Measures

Psychosocial Functioning. Participants (and partners) completed measures of stress, depression, relationship quality, coping, social disruption and social support using an online link to a questionnaire. For the present study, only patient data was used in analyses.

Dyadic Adjustment Scale (DAS). The 32-item DAS (Spanier, 1976) was used to assess 4 aspects of relationship functioning including dyadic satisfaction, dyadic consensus, dyadic cohesion, and affection expression, as well as a composite score of the 4 subscales, as a global measure of relationship satisfaction. Global scores range from 0-151; a higher score indicates higher relationship functioning. The DAS Total score is reliable at baseline, in our sample (α=0.924).

Patient Symptom Disclosure Satisfaction (PSDS) was measured by the Patient Pain Communication Self-Efficacy measure that was adapted to this patient population from other communication efficacy scales (Lorig, Chastain, Ung, Shoor, & Holman, 1989; Porter et al., 2008). Patients rate their ability to communicate their symptoms to their partner using a scale from 10 (very uncertain) to 100 (very certain). Patients are asked "1. How certain are you that you can let your partner know how much your ME/CFS symptoms are bothering you? 2. How certain are you that your partner understands how much your ME/CFS symptoms bother you? 3. How certain are you that your partner will respond to

your ME/CFS symptoms in a way that meets your needs?" In our sample, the subscale is reliable (α=0.875).

Fatigue Symptom Inventory (FSI). The 14-item FSI assessed fatigue intensity using a 4-item subscale and fatigue interference using a 7-item subscale (Hann et al., 1998). Items from both subscales were scored on an 11-point scale. Here 0 indicated feeling "not at all fatigued" and 10 indicated feeling "as fatigued as I could be" for the 4 fatigue intensity items. For the 7 fatigue interference items, 0 indicated "no interference" and 10 indicated "extreme interference." The FSI is reliable in our sample (α=0.894 and 0.897 at baseline for fatigue intensity and interference, respectively).

Center for Disease Control and Prevention (CDC) CFS Symptom Inventory. The 21-item CDC CFS Symptom Inventory was used to assess the frequency and severity of CFS symptoms over the last 30 days (Wagner et al., 2005). Participants were asked yes or no questions about specific symptoms, and if the symptom was present, the symptom was rated based on how often it was present, with 1 indicating "a little of the time" and 5 indicating "all the time." Then, the participants rated the severity of the symptom on a 5-point scale, with 1 indicating "very mild" and 5 indicating "very severe." The frequency and intensity scores for all items were averaged to create an Average Symptom Frequency Score and an Average Symptom Intensity score. If a symptom (e.g., post-exertional malaise, PEM) was not endorsed, a PEM score was entered as 0 (α=0.835 at baseline).

Center for Epidemiologic Survey Depression Scale (CES-D). The CES-D (Radloff, 1977) is a 20 item measure that assesses depressive symptomatology over the past week. Participants were asked questions such as "I felt sad" and responded on a 4 point scale

ranging from "Rarely or none of the time (<1 day)" to "Most or All of the Time (5-7 days)."

A score of 16 or above indicates clinically significant depressive symptoms. The measure

is reliable ($\alpha = 0.698$, at baseline) and has been shown to be sensitive to change in prior

CBSM trials in medical populations (Antoni et al., 2001).

Biological (Neuroimmune) Measures

Circulating pro-inflammatory cytokines. Peripheral venous blood samples were obtained

from each patient into appropriate tubes within the same range of time (1pm – 4pm) each

visit at T1, T2, and T3. Plasma samples were used to assay for a set of pro-inflammatory

and anti-inflammatory cytokines using a Microarray system (Quansys Biosciences, Logan,

Utah), as described previously (G. Broderick et al., 2012; Fletcher et al., 2009). Cytokines

IL-6, and TNF-α were chosen as outcome measures for the proposed study due to their

involvement in depression, CFS symptoms and HPA axis functioning.

Blood was centrifuged and plasma stored at −80°C within 4 hours of collection until the

samples were assayed in batches and in duplicate. Circulating cytokines IL-1β, IL-2, IL-4,

IL-6, IL-10 and TNF-α were measured from blood plasma as previously described using

an ELISA-based test (Q-Plex™ Human Cytokine –Screen, Quansys Biosciences Logan,

Utah). Images were captured using Quansys Imager, driven by an 8.4 megapixel Canon

20D digital SLR camera, and analyzed using Quansys Software. In order to assure

compatibility with measurements of cytokines in previously published studies in the field

(Chiswick, Duffy, Japp, & Remick, 2012; Trune, Larrain, Hausman, Kempton, &

MacArthur, 2011; Wong et al., 2008), the antigen standard concentrations used by Quansys

(R&D) were referenced to "gold standard" for each cytokine represented on the multiplex

plate as previously described (Lattie et al., 2012). The average coefficients of inter and intra-assay variation are 0.20 and 0.09. respectively (Gordon Broderick et al., 2010).

Diurnal Cortisol Regulation. Salivary cortisol was measured 4 times per day on 2 consecutive days at T1, T2 and T3. Participants collected the first sample of the day upon waking, the second 30 min later, the third at 4 to 5 pm and the final sample at 9 to 10 pm. Specimen collection within 60 minutes after a major meal, and within 12 hours after consuming alcohol, was avoided. Cortisol values at each time point were averaged across the two days. These values and the calculated diurnal slope measure to determine variation in cortisol and its relation to clinical symptoms are not being used in the present analyses (in part because of the large variation in waking times), but might be investigated if necessary in the future. The derived measure of cortisol used for this study is the average evening cortisol concentration across the two collection days. Salivary cortisol was assayed using Salimetrics high sensitivity ELISA kit (State College, PA) with a manufacturer-reported sensitivity of <0.007 ug/dL (D. L. Hall et al., 2014; Lattie et al., 2012).

Descriptive and Control Measures. Demographic variables such as age, race, ethnicity, Hollingshead index for socioeconomic status (SES), education, employment status, current living situation, and relationship status were assessed at study entry. Age and body mass index (BMI) were used as theoretically-derived covariates in the final models, as they are shown to contribute to the variability in psychosocial, neuroendocrine and immunological measurements (O'Connor et al., 2009). Preliminary descriptive analysis of our baseline sample shows that most of the sample has completed some or all of college; therefore, I am not including "education" as a covariate in these analyses. Similarly, I did not use "gender" as a covariate, as the majority of the sample are women (Table 1).

Statistical Analyses

Descriptive statistics. Descriptives were computed for every variable to ensure that all values are within expected ranges and to identify and eliminate any data entry or collection errors that may have occurred. Some variables were not normally distributed (e.g. cortisol and cytokines), so I transformed these variables using log transformations (ln[x+1]) and used non-parametric statistics on non-transformed data. Estimates of internal consistency (Cronbach's α) for all scales used in this proposal (CES-D, FSI) were computed and met $\alpha \geq .70$ (Nunnally & Bernstein, 1978). Outlier scores or biomarker values were Winsorized as needed.

Missing Data. The data collected from the 150 subjects were used in an intent-to-treat analysis. Since the missing data within this sample was missing not at random (MNAR), the Full Information Maximum Likelihood (FIML) is employed by default within Mplus software version 8 (Muthen and Muthen, Los Angeles, CA) to generate maximum likelihood estimates of simultaneous equations for use in structural equation modeling (Markus, 2012; Wothke, 2000).

Estimates of Direct and Indirect Effects. For both cross-sectional (Aim 1), and longitudinal (Aim 2), direct and indirect effects will be estimated simultaneously using structural equation modeling (SEM) in Mplus (Markus, 2012), using age and BMI as covariates. Bootstrapping (10,000 iterations) was used to estimate the effects (Hayes, 2009, 2017). Model fit indices were compared against Root Mean Square Error of Approximation (RMSEA)≤ 0.06, Comparative Fit Index (CFI) ≥ 0.95, Standardized Root Mean Square Residual (SRMR) ≤ 0.08, and Chi-square tests at $\alpha= 0.05$ (Hu & Bentler, 1999).

Parallel Mediation Models. For Specific Aims 1 and 2, parallel mediation modeling (Hayes, 2017) was performed using hypothesized, concomitant mediators patient symptom disclosure satisfaction (PSDS) and depression. This design tests the hypothesis that one mediator does not cause changes in the other (as indicated in the serial mediator model), but that both change synergistically, which is expected for our intervention that targets both depression and couple-related communication factors about illness. Parallel mediator modeling increases the power available to detect indirect effects, and provides the ability to compare the sizes of the indirect effects (e.g. through PSDS and depression)(Hayes, 2017). The technique also affords the ability to compare the differential effects of the mediators (e.g. depression vs PSDS) on the outcome of interest (Hayes, 2017). Therefore, this method provides additional information about the mechanism/s implicated in the expected improvements being assessed as part of this study.

Each mediator will be tested separately while controlling for all other predictors and mediators in the model, and its effect is referred to the "specific indirect effect" (Hayes, 2017). In a model with k mediators, the total indirect effects of all mediators in the model of X on Y:

Total indirect effect of X on Y=

$$\sum_{i=1}^{k} a_i b_i$$

The mediators are represented by this formula:

$$M_i = i_{M_i} + a_i x + e_{M_i}$$

$$i = 1$$

The regression equation for a parallel multiple mediator model is such:

$$Y = i_Y + c'X + \sum_{i=1}^{k} b_i M_i + e_Y$$

In a parallel multiple mediator model with two mediators (M1 and M2), the total indirect

effect of X and Y is $a_1b_1 + a_2b_2$.

$$M_1 = i_{M_1} + a_1 x + e_{M_1}$$
$$M_2 = i_{M_2} + a_2 X + e_{M_2}$$
$$Y = i_Y + c'X + b_1 M_1 + b_2 M_2 + e_Y$$

The sum of the direct and indirect effects is the total effect of the predictor X:

$$c = c' + \sum_{i=1}^{k} a_i b_i$$

In summary, the parallel multiple mediator models we are using in this study follows that

the total effect: $c = c' + a_1b_1 + a_2b_2$, and the total indirect effect is equal to the difference

between the total and direct effects of X: $c - c' = a_1b_1 + a_2b_2$ (Hayes, 2017). A theoretical

model of parallel multiple mediation is shown in Figure 2 (Hayes, 2017).

Testing Specific Aim 1

Specific Aim 1 examined different facets of a biopsychosocial model that investigates the

effects of relationship satisfaction (Dyadic Adjustment Scale-DAS Total Score), patient

symptom disclosure satisfaction (PSDS), depressive symptoms, HPA functioning, pro-

inflammatory cytokines (TNF- α, IL-6) and CFS symptoms (Figure 5). Hypotheses (direct

and indirect effects) were assessed using structural equation modeling using Mplus version

8 (Baron & Kenny, 1986). Age and BMI were entered as covariates for all analyses since

they significantly predict variance associated with depression and markers of inflammation in both men and women (Kiecolt-Glaser, Derry, & Fagundes, 2015; O'Connor et al., 2009). Power analysis using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) showed that regression analysis using 150 subjects, with 1 predictor and 3 covariates afforded power of at least 0.92 to detect a small to medium effect size ($f^2 > 0.10$). To analyze indirect effects (Baron & Kenny, 1986; Hayes, 2017), 150 subjects was sufficient to detect a combined (a*b) small to medium effect of $f^2 > 0.05$ (power= 0.84, using 1 direct predictor, 2 indirect predictors, and 2 covariates). The alpha was set at $p < 0.05$ to avoid Type 1 error.

Testing Specific Aim 2

Specific Aim 2 compared the effects of CBSM vs. a Health Promotion control (HP) on changes in PSDS and depression at 5-month follow-up, and tested whether these changes are associated with improved CFS symptoms (fatigue, CDC Total Symptom Severity), inflammatory cytokines (IL-6 and TNF- α), and evening cortisol at 5-month follow-up (see Figure 6). Hypotheses were assessed using 2 (condition: CBSM, HP) x 2 (Time: baseline and 5 months) ANCOVA's for the PSDS and depression analyses using SPSS.

Structural equation modeling was used to estimate direct and indirect effects using Mplus (Baron & Kenny, 1986; Hayes, 2017; Markus, 2012). Age and BMI were entered as covariates for all analyses (O'Connor et al., 2009).

A 2 x 2 repeated measures ANCOVA was performed to test intervention effects on PSDS and depression at 5 months and then a 2 x 2 repeated measures ANCOVA was performed to test intervention effects on the outcomes of interest at 5 months. Sample size was sufficient to detect a medium effect size (f=0.25) using 150 subjects (Power=0.84,

using 2 groups, measuring 5 outcomes)(Faul et al., 2007). I expected a medium effect size based on a previous trial of CBSM effects on evening cortisol for women with non-metastatic breast cancer (Phillips et al., 2008) and small to medium effect sizes on psychological outcomes in the CFS pilot study of CBSM (Lopez et al., 2011).

Change in PSDS and depression (at 5 months), conceptualized by a change score (T2-T1) (Llabre, Spitzer, Saab, Ironson, & Schneiderman, 1991) was tested as a mediator of 5 months outcomes (comparable to tests of indirect effects at baseline in Aim 1) using structural equation modeling in Mplus. Group (intervention assignment) was entered as the predictor, and age and BMI were entered as covariates in all analyses. Power analysis using G*Power (Faul et al., 2007) showed that a regression analysis using 150 subjects, with 1 predictor and 2 covariates afforded power of at least 0.93 to detect a small to medium effect size (f^2>0.10). To analyze indirect effects (Baron & Kenny, 1986; Hayes, 2012), 150 subjects was sufficient to detect a combined (a*b) small to medium effect of f^2>0.10 (power= 0.91, using 1 direct predictor, 2 indirect predictors, and 2 covariates). The alpha was set at p<0.05.

CHAPTER 3: RESULTS

Sample Description

As seen in Figure 2, 150 adults and their partners were randomized to receive videophone/tablet-delivered CBSM (CBSM, N = 75) or receive videophone/tablet-delivered health promotion intervention (HP, N = 75). The mean age of this sample was 48.0 years (SD= 11.3). The sample was predominately non-Hispanic White (65.3%), highly educated (62% were enrolled in college, received a college or graduate degree). There were slighty more married couples in the HP group (66 vs 62 in CBSM) but this was not significantly different between groups (p > 0.05). There were 8 and 11 men as CFS patients in CBSM and HP, respectively. No significant differences in age, gender, ethnicity, employment status, or education were seen between participants who were randomized to each treatment condition (Tables 1a and 1b, all *p*'s >0.05).

Importantly, participants who were randomly assigned to the HP group had more severe CFS symptoms (p=0.04), fatigue (p<0.01), and depressive symptoms (p=0.03), and less relationship satisfaction (p=0.03) at baseline than those who were assigned to the CBSM condition (Table 2). Additionally, those assigned to the CBSM condition attended significantly more sessions than those assigned to HP (9.31 vs 8.19 sessions on average, Table 2). Those assigned to the CBSM group had a total DAS score of 114.73, which was comparable to that found in Spanier's assessment of married couples (114.8), but different from divorced couples (70.7)(Spanier, 1976). The symptom disclosure measure (PSDS) ranges from a score of 30-300, with higher scores indicating greater satisfaction. Overall, patients in both treatment arms were satisfied with their partners' ability to listen to and

adequately respond to their communicating about their CFS symptoms. Patients randomized to the CBSM group had greater PSDS scores than those assigned to HP (208.78 vs 200.68), respectively, though this was not a significant difference ($p > 0.05$). Though they were significantly different at baseline, mean fatigue severity scores for both groups were indicative of clinically significant fatigue (scores $\geq$3)(Donovan, Jacobsen, Small, Munster, & Andrykowski), and the sum total fatigue severity score in our CFS sample (24.53) was comparable to that of another CFS sample (26.74)(Lattie et al., 2012). For reference, both study groups' mean scores were higher than that of breast cancer patients (3.4) and age and gender-matched healthy controls (2.8)(Hann et al., 1998). CDC CFS symptom inventory total score for both groups (average=39.27) was comparable to that reported in the measure's validation study of CFS patients (36.22)(Wagner et al., 2005). Both CBSM and HP groups in the present study had depressive symptom severity scores on the CES-D (22.13) above the clinical cut-off of 16(Radloff, 1977), and were comparable to another CFS patient population (25.37)(Lattie et al., 2012).

Evening cortisol levels (0.08-0.09 ug/dL) were within range of another CFS sample (M=0.14, SD=0.21, Range=0.0007-1.380 ug/dL) (Lattie et al., 2012) Another study found evening salivary cortisol levels of 1 nmol/L= 0.04 ug/dL for patients with CFS, and 1.5 nmol= 0.05 ug/dL for both otherwise healthy controls who are depressed and those who were not depressed(Paul Strickland, Morriss, Wearden, & Deakin). Serum pro-inflammatory cytokine values in the study sample for IL-6 (M=2.36, SD=3.31 pg/mL) and TNF-α (M=11.53, SD=14.55 pg/mL) were within range for expected values of IL-6 (M=11.9, SD=19.4, Range= 0.80-84.08 pg/mL) and TNF- α (M= 25.80, SD= 46.20, Range= 0.00-215.31 pg/mL) for CFS patients, and higher than what is expected for healthy

controls (IL-6: M=7.2, SD=12.3, Range=0.0-8.90 pg/mL; TNF- α: M=18.2, SD= 39.1, Range= 0.0-40.3 pg/mL) (Lattie et al., 2012).

Missing Data. Little's test for data that is Missing Not Completely at Random (MCAR) was significant ($p<0.01$), indicating that the data was not MCAR. A variable was created to represent the presence of missing data at 5 months, and was coded "0" for non-missing and "1" for missing data. There was no difference in missing data at 5 months between groups (Table 2); however, there was a significant difference in intervention attendance, such that participants in the active treatment arm (CBSM) attended more sessions than those randomized to the control treatment (HP). On average patients assigned to CBSM attended 9.31 sessions and those assigned to HP attended 8.19 sessions (χ^2= 28.00, p= 0.01).

Preliminary Analyses

No variables of interest were correlated with withdrawal at 5 M (all *p*'s > 0.05) (Table 3); however, group (treatment arm) was positively associated with baseline depression ($p < 0.05$), CFS symptom severity ($p < 0.05$), and fatigue severity ($p < 0.01$) and negatively associated with relationship satisfaction ($p < 0.05$) (Table 3). Group was coded "1" for CBSM and "2" for HP, therefore, it seems worse depression, CFS symptom and fatigue severity, and less DAS satisfaction was related to being assigned to the HP group even though there were no significant group differences seen in those variables at baseline (Table 2) (all p's > .05). As expected, greater attendance was related to less withdrawal at 5 months ($p < 0.01$) (Table 3). Attendance was positively related to PSDS ($p < 0.05$) and negatively related to CFS symptom severity at baseline ($p < 0.05$) indicating that patients with greater perceived partner support and those with greater symptom severity went on to have better attendance at intervention sessions. Interestingly, age was

positively related to greater PSDS (p < 0.05). BMI was positively related to depression, as expected (p < 0.01). PSDS was negatively related to depression (p < 0.01), and positively related to relationship satisfaction (p < 0.01), as expected, but unexpectedly, positively related to baseline TNF-α (p < 0.05). Depression was negatively correlated with relationship satisfaction (p < 0.01) and positively correlated with both CFS symptom and fatigue severity at baseline (both p's < 0.01). CFS symptom severity was positively correlated with fatigue severity (p < 0.01) and evening cortisol (p < 0.01). All baseline correlations for the entire sample are reported in Table 3.

When looking at both groups combined for 5 month correlations (Table 4), attendance was not related to any of the mediator or outcome variables at 5 months (p > 0.05); however, greater attendance was related to change in depression (p < 0.05), but only in the HP group (Table 5). A negative depression change score (T2-T1) indicates a desired improvement in depression symptoms; therefore, in the HP group, more attendance was related to greater declines in depression from baseline to 5 months. Overall, among both groups, greater reductions in depression (T2-T1) was related to greater increases in PSDS from baseline to 5 months (p < 0.05). Greater reductions in depression over this period were also related to greater fatigue and CFS symptom at 5 months (p < 0.01, p < 0.05, respectively) (Table 4). The correlation between change in depression and change in PSDS was only significant for the HP group (p < 0.05) (Table 5). Additionally, the positive correlation between change in depression and 5 month fatigue severity was significant only for the CBSM group (p < 0.01) (Table 5). Fatigue and CFS symptom severity (T2) remain highly correlated in both groups (both p's > 0.01) (Table 5). There were no other significant correlations between variables when analyzed separately within groups (Tables 4, 5).

Specific Aim 1

Baseline Fatigue Severity

Baseline models were tested using structural equation modeling to determine the total, direct and indirect effects. The total effect of relationship satisfaction on fatigue severity was not significant (b= -0.00, se= 0.00, p=0.91). Covariates age and BMI also did not significantly relate to fatigue severity at baseline (all p's>0.05). The model fit the data and was just identified (RMSEA= 0.00, CFI= 0.00, TLI=1.00, SRMR= 0.00, $\chi^2(0)$= 0.00, p < 0.01.

Next, the parallel multiple mediator model was examined. The model fit the data moderately well (RMSEA= 0.09, CFI= 0.99, SRMR= 0.02, $\chi^2(1)$=2.19, p = 0.14) and the direct effect of relationship satisfaction remained non-significant when the mediators were added to the model (b= -0.00, se=0.01, p=0.74). Relationship satisfaction and BMI related to (M_1) Depression, while only relationship satisfaction significantly related to (M_2) PSDS, indicating that greater relationship satisfaction was associated with less depression and greater PSDS at baseline. Greater BMI significantly related to greater depression, and had no significant effect on PSDS. Age was not significantly related to the mediators or outcomes. Both mediators significantly related to baseline fatigue severity, even with age and BMI included in the model. Results are summarized in Table 6, Figure 7.

There was an indirect effect of Depression on Fatigue Severity (a_1b_1= -0.01, SE=0.01, p=0.02). There was a marginally significant indirect effect of PSDS on Fatigue Severity (a_2b_2= 0.01, SE=0.01, p=0.06). The direct and total effect of relationship satisfaction did not significantly relate to fatigue severity; however, when the mediators were added to the model, relationship satisfaction was related to fatigue severity, by way

of depression mostly and PSDS secondarily. Relationship satisfaction was positively related to PSDS (b=.17, se= 0.03, p<0.01) and negatively related to depression (b= -0.20, se= 0.05, p<0.01), as expected theoretically. Interestingly, both mediators were positively related to fatigue severity, even with relationship satisfaction in the model, such that greater depression and greater PSDS was related to greater fatigue severity (Table 6, Figure 7).

Baseline CDC CFS Symptom Severity

A similar model was tested for the baseline CDC CFS Symptom Severity score. The total effect of relationship satisfaction on CFS symptom severity was not significant (b= -0.00, se=0.00, p=0.87).The model fit the data and was just identified (RMSEA= 0.00, CFI= 1.00, SRMR= 0.00, χ^2= 0.00, p > 0.01),.

The parallel mediator model fit the data (RMSEA= 0.09, CFI= 0.99, SRMR= 0.02, $\chi^2(1)$=2.22, p= 0.14). The direct effect of relationship satisfaction on CFS symptom severity was not significant (b=0.00, se=0.01, p=0.55) when the mediators were included in the model. Relationship satisfaction, and BMI related to (M_1) Depression, while relationship satisfaction, and age significantly related to (M_2) PSDS. Only depression was positively related to CFS Symptom severity, even with relationship satisfaction in the model, such that greater depression was related to greater CFS symptom severity (b=0.03, se= 0.01, p<0.01) (Table 7, Figure 8).

There was a significant indirect effect of Depression on CFS Symptom Severity (a_1b_1= -0.01, SE=0.00, p<0.01) but no significant indirect effect of PSDS on CFS Symptom Severity (a_2b_2= 0.00, SE=0.00, p=0.28). Relationship satisfaction was negatively related to (M1) Depression (b= -0.21, se= 0.05, p<0.01), and positively related to (M2) PSDS (b= 0.17, se= 0.03, p<0.01). Only depression was positively related to CFS symptom severity

(b= 0.03, se= 0.01, p<0.01), even with relationship and communication satisfaction in the model (Table 7, Figure 8).

Baseline Evening Cortisol

As seen in Table 8, none of the predictors tested significantly related to evening cortisol. Additionally, there were no direct or indirect effects of relationship satisfaction (by way of depression and/or PSDS) on evening cortisol at baseline.

Baseline Interleukin (IL)-6

Similarly, when IL-6 was tested as the dependent variable in the model, none of the predictors or hypothesized mediators had any direct or indirect effects (all p's>0.05), as shown in Table 9.

Baseline Tumor Necrosis Factor (TNF)- α

The total effect of relationship satisfaction on TNF-α was not significant (b= -0.00, se=0.00, p=0.70); The model fit the data and was just identified (RMSEA= 0.00, CFI= 0.00, TLI=1.00, SRMR= 0.00, $\chi^2(0)$= 0.00, p > 0.01).

In contrast to the non-significant effects shown when testing the other biological outcomes, when testing the direct and indirect effects on inflammatory TNF- α, baseline PSDS (b= 0.03, se= 0.01, p=0.02) and the indirect effect of relationship satisfaction by way of PSDS was significant (a_2b_2= 0.01, se=0.00, p=0.02) indicating that PSDS was positively associated with TNF-α, even when relationship satisfaction was included in the model. The direct (b_1) or indirect effect (a_1b_1) of depression was not significant; however, the sum of the indirect effects approached significance ($a_1b_1+a_2b_2$= 0.01, se=0.00, p=0.06). The summary of these effects are shown in Table 10, Figure 9. The model fit the data (RMSEA= 0.09, CFI= 0.98, SRMR= 0.02, $\chi^2(1)$=2.27, p= 0.14).

In all models studied, with and without the indirect variables depression and PSDS included, relationship satisfaction (DAS Total) did not have a significant effect on the outcomes of interest (CFS symptom severity, fatigue severity, evening cortisol, and IL-6, and TNF-α). Therefore, DAS Total was not included in subsequent models testing the longitudinal effects of the intervention.

Specific Aim 2

Repeated Measures Analysis of Covariance (ANCOVA) of Mediators and Outcomes

Repeated Measures Analysis of Covariance (ANCOVA) was conducted using SPSS, version 24, using age and BMI as covariates, in order to test intervention effects on the variables of interest.

Depression

There were no significant within-person ($F(2, 111) = .31$, p= 0.73, partial $\eta^2 = 0.01$) or between-subjects difference ($F(2,111) = 0.63$, p=.54, partial $\eta^2 = 0.01$) in depression symptom severity over time. The average CES-D score for T1 was 21.57 (SD= 10.65), while the average for T2 was 20.60 (SD= 11.11). Split by treatment arm, average depression severity scores were 19.17 (SD= 9.57) at T1 and 18.67 (SD= 11.16) in the CBSM group, and 24.02 (SD= 11.21) at T1 and 22.66 (SD= 10.77) at T2 for the HP group. There was no significant time by intervention effect on depression severity scores, with and without covariates age and BMI; however, pairwise contrasts showed significant overall differences between the intervention arms in depression scores (Mean difference= -4.27, SE= 1.70, $F(1,111)=6.28$, p= 0.01, partial $\eta^2 = 0.05$).

Depression severity scores decreased over time in both treatment arms; however, both groups' mean depression severity score remained over the clinical cut-off score for depression at each time point (≥ 16 on CES-D).

Patient Symptom Disclosure Satisfaction (PSDS)

There were no significant within-person ($F (1, 114)= 47.35$, $p=.36$, partial $\eta^2= 0.02$) or between-subjects differences ($F(2, 114)=1.00$, $p=.37$, partial $\eta^2= 0.01$) in PSDS over time (all p's >0.05). The average PSDS score for T1 was 20.70 (SD= 7.75), while the average for T2 was 21.67 (SD= 7.50). Split by treatment arm, average PSDS scores were 21.18 (SD= 7.84) at T1 and 22.34 (SD= 6.49) at T2 in the CBSM group, and 20.20 (SD= 7.70) at T1 and 20.98 (SD= 8.42) at T2 for the HP group. There was no significant time by intervention effect on PSDS scores, with and without covariates age and BMI; however, the trend showed that PSDS scores increased over time in both treatment arms (Figure 11). Pairwise contrasts showed no significant overall differences between the intervention arms in PSDS scores (Mean Difference= 1.18, $F(1, 114)=.88$, $p=0.35$, partial $\eta^2= 0.01$).

Fatigue Severity

There were no significant within-person ($F(2, 106)= .36$, $p=.70$, partial $\eta^2= 0.01$) or between-subjects difference ($F(1,106)= .26$, $p=.77$, partial $\eta^2= 0.01$) in fatigue severity over time. The average fatigue severity score for T1 was 6.02 (SD= 1.94), while the average for T2 was 5.86 (SD= 2.15). Split by treatment arm, average PSDS scores were 5.51 (SD= 2.06) at T1 and 5.51 (SD= 2.16) in the CBSM group, and 6.54 (SD= 1.68) at T1 and 6.20 (SD= 2.11) at T2 for the HP group. There was no significant time by intervention effect on fatigue severity scores, with and without covariates age and BMI. Fatigue severity scores

did not decrease in either treatment arm (Figure 12). Pairwise contrasts showed significant overall differences between the intervention arms in fatigue severity scores (Mean Difference= 0.902, $F(1, 106)=7.17$, p=0.01, partial $\eta^2= 0.06$).

CFS Symptom Severity

There were no significant within-person ($F(2, 116)= .90$, p=.41, partial $\eta^2= 0.02$) or between-subjects difference ($F(2,116)=1.23$, p=.30, partial $\eta^2= 0.02$) in CFS symptom severity over time. The average CFS symptom severity score for T1 was 2.55 (SD=0.88), while the average for T2 was 2.78 (SD= 0.68). Split by treatment arm, average CFS severity scores were 2.32 (SD= 0.92) at T1 and 2.65 (SD= 0.74) in the CBSM group, and 2.78 (SD= 0.77) at T1 and 2.92 (SD= 0.59) at T2 for the HP group. There was no significant time by intervention effect on CFS symptom severity scores, with and without covariates age and BMI; however, pairwise contrasts showed significant overall differences between the intervention arms in CFS symptom severity scores (Mean difference= -0.39, SE=0.124, $F(1,116)=6.28$, p<0.01, partial $\eta^2= 0.08$). Trends are shown in Figure 13.

Evening Cortisol

There were no significant within-person ($F(2, 99)=0.26$, p=.77, partial $\eta^2= 0.01$) or between-subjects difference ($F(2, 99)=0.26$, p=.77, partial $\eta^2= 0.01$) in evening cortisol over time. The average evening cortisol value for T1 was 0.08 (SD= 0.11), while the average for T2 was 0.08 (SD=0.10). Split by treatment arm, average evening cortisol values were 0.07 (SD= 0.12) at T1 and 0.09 (SD= 0.11) for T2 in the CBSM group, and 0.08 (SD= 0.10) at T1 and 0.08 (SD= 0.09) at T2 for the HP group. There was no significant time by intervention effect on evening cortisol, with and without covariates age and BMI. Pairwise contrasts showed no significant overall differences between the intervention arms in

salivary evening cortisol (Mean Difference= -.003, F(1, 99)=.04, p=0.83, partial η^2= 0.00).

Trends are shown in Figure 14.

Interleukin (IL)-6

There were no significant within-person (F(2, 102)= .03, p=.97, partial η^2= 0.00) or between-subjects difference (F(2, 102)=0.62, p=.54, partial η^2= 0.01) in serum interleukin (IL)-6 over time (all p's >0.05). The average IL-6 value for T1 was 1.00 (SD= 0.56), while the average for T2 was 0.95 (SD= 0.65). Split by treatment arm, average IL-6 values were 0.97 (SD= 0.50) at T1 and 1.00 (SD= 0.69) in the CBSM group, and 1.03 (SD= 0.62) at T1 and 0.91 (SD= 0.61) at T2 for the HP group. There was no significant time by intervention effect on IL-6, with and without covariates age and BMI. Pairwise contrasts showed no significant overall differences between the intervention arms in serum IL-6 (Mean Difference= Mean Difference= 0.00, F(1, 102)=0.00, p=1.00, partial η^2= 0.00). Trends are shown in Figure 15.

TNF-α

There were no significant within-person (F(2, 102)= .43, p=.65, partial η^2= 0.01) or between-subjects difference (F(2,111)=0.63, p=.54, partial η^2= 0.01) in serum Tumor Necrosis Factor (TNF)-α over time. The average TNF-α value for T1 was 2.09 (SD=0.78), while the average for T2 was 2.16 (SD=0.88). Split by treatment arm, average TNF-α values were 2.10 (SD= 0.85) at T1 and 2.17 (SD= 0.85) in the CBSM group, and 2.08 (SD= 0.71) at T1 and 2.15 (SD= 1.06) at T2 for the HP group. Pairwise contrasts showed no significant overall differences between the intervention arms in serum TNF-α (Mean Difference= 0.00, F(1, 102)=.001, p=0.97, partial η^2= 0.00). There was no significant time by intervention effect on TNF-α, with and without covariates age and BMI. Trends are

shown in Figure 16. A summary of the mean differences between groups are shown on Table 11.

Specific Aim 2.2 Estimates of Intervention-Specific Direct and Indirect Effects

As in Specific Aim 1, structural equation modeling (SEM) was used to achieve estimates of total, direct and indirect effects. Direct effects for Group (Intervention arm) were evaluated for the T2 (5 Month) outcome measures fatigue severity, CFS symptom severity, evening cortisol, IL-6, and TNF-α. The indirect effects of change in Depression and PSDS (both T2-T1) were evaluated as mediators for the hypothesized effect of treatment arm on the outcome measure. Relationship satisfaction (DAS Total) was not used as a predictor, given its lack of direct effects on the baseline levels of outcome variables, as shown in Specific Aim 1. Age and BMI were included as covariates in all analyses.

Fatigue Severity (5M)

The total effect of Group on fatigue severity was examined with only age and BMI as covariates (the parallel mediators not included). The model fit the data was just identified (RMSEA= 0.00, CFI= 1.00, SRMR= 0.00, χ^2 (0)=0.00, p <0.01). Group had an effect on fatigue severity (b=0.80, se= 0.38, p=0.04) such that those assigned to the HP group experienced greater fatigue severity at 5 months (T2). Age and BMI did not have a significant direct effect (all p's>0.05).

Next, the parallel mediator model was tested and the model partially fit the data (RMSEA= 0.16, CFI= 0.76, SRMR= 0.04, χ^2 (1)= 4.69, p= 0.03). The direct effect of Group on fatigue severity was significant (b= -0.84, se=0.36, p=0.02), such that participants assigned to the control condition (HP) experienced greater fatigue severity, even with age, BMI, and the mediators in the model. Additionally, the direct effect of

change in depression was highly significant (b= 0.07, se= 0.02, p<0.01), such that greater magnitude of change in depression severity scores (becoming more depressed between T1 and T2) predicted greater fatigue severity at 5M. Group assignment, age, and BMI did not significantly predict change in depression severity or PSDS from T1 (baseline) to T2 (5 months) (all *p*'s < 0.05).

The sum of the indirect effects were not significant (b = -0.04, se = 0.14, p = 0.78). The specific indirect effect of Group on fatigue severity by way of change in depression was not significant (a_1b_1= -0.05, SE=0.13, p=0.67), nor was the specific indirect effect of Group on fatigue severity by way of change in PSDS (a_2b_2= 0.01, SE=0.05, p=0.79). The lack of indirect effects of change in depression was due to the lack of a significant effect of group on change in depression (b= -0.83, se= 1.89, p= 0.66). Spontaneous change in depression (independent of group assignment) significantly predicted fatigue severity at 5M (b= 0.07, se= 0.02, p<0.01). These estimations should be interpreted with caution as the parallel mediator model did not fit the data according to all fit indices. Results are shown in Table 12, Figure 17.

To further test the robustness of the intervention effects, the parallel mediator model was analyzed with baseline fatigue severity as an additional covariate (Table 13, Figure 18). The direct effect of group on 5M fatigue severity was no longer significant (b=0.16, se= 0.34, p= 0.65); however, the effect of change in depression remained significant (b=0.06, se=0.02, p<0.01).

CDC CFS Symptom Severity (5M)

The total effect of Group on CFS symptom severity was examined with only age and BMI as covariates (the parallel mediators not included). The model fit the data and was just identified (RMSEA= 0.00, CFI= 1.00, SRMR= 0.00, χ^2 (0)= 0.00, p<0.01). Group had an effect on CFS symptom severity (b=0.27, se= 0.12, p=0.02) such that those assigned to the HP group experienced greater CFS symptom severity at 5 months (T2). Age and BMI did not have a significant direct effect (all p's>0.05).

Next, the parallel mediator model was tested and the model partially fit the data (RMSEA= 0.16, CFI= 0.63, SRMR= 0.04, χ^2 (1)= 4.61, p= 0.03). The direct effect of Group on fatigue severity was significant (b= 0.27, se=0.12, p=0.02), such that participants assigned to the control condition (HP) experienced greater CFS symptom severity, even with age, BMI, and the mediators in the model. The direct effect of change in depression was marginally significant (b= 0.01, se= 0.01, p=0.06), such that greater magnitude of change in depression severity scores (becoming more depressed between T1 and T2) predicted greater fatigue severity at 5M. Additionally, the direct effect of change in PSDS was significant (b= -0.02, se= 0.01, p=0.02), such that greater magnitude of decline in PSDS scores (decreasing satisfaction with communication about symptoms between T1 and T2) predicted greater fatigue severity at 5M. Group assignment, age, and BMI did not significantly predict change in depression severity or PSDS from T1 (baseline) to T2 (5 months) or CFS symptoms severity at 5 months (all p's<0.05).

The sum of the indirect effects were not significant (b = -0.00, se = 0.04, p = 0.99). Again, the specific indirect effect of Group on CFS symptom severity by way of change in depression was not significant (a_1b_1= -0.01, se=0.04, p=0.99), nor was the specific indirect

effect of Group on CFS symptom severity by way of change in PSDS (a_2b_2= 0.01, SE=0.03, p=0.75). The lack of indirect effects of change in depression or PSDS was due to the lack of a significant effect of Group on change in depression or PSDS. Spontaneous change in PSDS (independent of Group assignment) significantly predicted fatigue severity at 5M (b= -0.02, se= 0.01, p=0.02). These estimations should be interpreted with caution as the parallel mediator model did not fit the data according to all fit indices. Results are shown in Table 14, Figure 19.

To further test the robustness of the intervention effects, the parallel mediator model was analyzed with baseline CFS Symptom severity as an additional covariate (Table 15, Figure 20). The direct effect of group and change in PSDS on 5M CFS symptom severity was no longer significant (b= 0.16, se= 0.09, p= 0.22; b= -0.01, se= 0.01, p= 0.11, respectively).

Evening Cortisol (5M)

The direct effect of Group on evening cortisol was examined with only age and BMI as covariates (the parallel mediators not included). The direct effect model fit the data and was just identified (RMSEA= 0.00, CFI= 1.00, SRMR= 0.00, $\chi^2(0)$= 0.00, p < 0.01). Group assignment, age and BMI did not have a significant direct effect on evening cortisol at 5 months (all p's>0.05).

Next, the parallel mediator model was tested and the model poorly fit the data (RMSEA= 0.15, CFI= 0.00, SRMR= 0.04, χ^2 (1)=4.56, p = 0.03). The total direct effect of Group on evening cortisol at 5 months was not significant (b= -0.01, se=0.02, p=0.56). Neither was the effect of the mediators or covariates (all p's>0.05, Table 16). Group

assignment, age, and BMI did not significantly predict change in depression severity or PSDS from T1 (baseline) to T2 (5 months) or evening cortisol at 5 months (all p's<0.05).

The sum of the indirect effects were not significant (b = -0.00, se = 0.01, p = 0.78), nor was the indirect effect of change in depression (b = 0.00, se = 0.00, p = 0.88) or that of the change in PSDS (b = -0.00, se = 0.01, p = 0.82). Caution is warranted in interpreting the estimates, as the model poorly fit the data.

Interleukin (IL)-6 (5M)

The direct effect of Group on circulating serum IL-6 was examined with only age and BMI as covariates (the parallel mediators not included). The direct effect model fit the data and was just identified (RMSEA= 0.00, CFI= 1.00, SRMR= 0.00, χ^2 (0)= 0.00, p < 0.01). Group assignment, age and BMI did not have a significant direct effect on serum IL-6 at 5 months (all p's>0.05).

Next, the parallel mediator model was tested and the model poorly fit the data (RMSEA= 0.16, CFI= 0.00, SRMR= 0.04, χ^2 (1)=4.65, p= 0.03). The total direct effect of Group on IL-6 at 5 months was not significant (b= -0.06, se=0.13, p=0.67). Neither were the effects of the mediators or covariates (all p's>0.05, Table 17). Group assignment, age, and BMI did not significantly predict change in depression severity or PSDS from T1 (baseline) to T2 (5 months) or IL-6 at 5 months (all *p*'s<0.05).

The sum of the indirect effects were not significant (b = 0.00, se = 0.02, p = 0.95), nor was the indirect effect of change in depression (b = 0.00, se = 0.02, p = 0.80) or that of the change in PSDS (b = -0.00, se = 0.02, p = 0.86). Caution is warranted in interpreting the estimates, as the model poorly fit the data.

Tumor Necrosis Factor (TNF)-α (5M)

The direct effect of Group on circulating serum TNF-α was examined with only age and BMI as covariates (the parallel mediators not included). The direct effect model fit the data and was just identified (RMSEA= 0.00, CFI= 1.00, SRMR= 0.00, χ^2 (0)= 0.00, $p < 0.01$). Group assignment, age and BMI did not have a significant direct effect on serum TNF-α at 5 months (all p's>0.05).

Next, the parallel mediator model was tested and the model partially fit the data (RMSEA= 0.16, CFI= 0.00, SRMR= 0.04, χ^2 (1)= 4.64, p= 0.03). The total direct effect of Group on TNF-α at 5 months was not significant (b= 0.03, se=0.18, p=0.86). Neither were the effects of the mediators or covariates (all p's>0.05, Table 18). Group assignment, age, and BMI did not significantly predict change in depression severity or PSDS from T1 (baseline) to T2 (5 months) or TNF-α at 5 months (all p's<0.05).

The sum of the indirect effects were not significant (b = -0.00, se = 0.02, p = 0.94), nor was the indirect effect of change in depression (b = 0.00, se = 0.02, p = 0.92) or that of the change in PSDS (b = -0.00, se = 0.02. p = 0.85). Caution is warranted in interpreting the estimates, as the model poorly fit the data.

CHAPTER 4: DISCUSSION

The present dissertation study involved an analysis of the effects of relationship satisfaction, depression, and patient symptom disclosure satisfaction (PSDS) on fatigue severity, overall CFS symptom severity, salivary evening cortisol, and serum pro-inflammatory cytokines in women with CFS who were enrolled, with their caregiving partner, into an intervention testing the efficacy of a 10-week remotely-delivered group cognitive behavioral stress management (CBSM) program versus an attention-matched health promotion (HP) control program. Depression and PSDS were examined as mediators of the hypothesized effects of relationship satisfaction on CFS-related outcomes (Aim 1). These effects were studied cross-sectionally at study entry (baseline-T1). In Aim 2, the intervention effects on the change in the mediators (T2-T1) and on the 5 M outcomes (T2) were examined using repeated measures analysis of covariance (ANCOVA) and path analysis using structural equation modeling (SEM). Parallel multiple mediation modeling was used to test the indirect effects of the two mediators simultaneously. Direct effects were also examined.

Specific Aim 1

The first aim of this study was to look at the direct effect of relationship satisfaction and indirect effects of depression and patient symptom disclosure satisfaction (PSDS) on fatigue severity, CFS symptom severity, salivary evening cortisol, and serum pro-inflammatory cytokines interleukin (IL)-6 and tumor necrosis factor (TNF)-α in patients with CFS. These effects were estimated simultaneously using structural equation modeling (SEM), with age and BMI as covariates in all models.

Relationship satisfaction, as measured by the composite Dyadic Adjustment Scale (DAS) score, showed no total or direct effects on baseline fatigue severity, CFS symptom severity, evening cortisol, TNF-α and IL-6. Greater relationship satisfaction was associated with more TNF-α.

The direction of the association between PSDS and inflammation (positive correlation) was not what would be expected, as I would expect greater communication satisfaction to relate to less inflammation. The positive relationship between PSDS and TNF-α could be reflective of CFS patients being more communicative and partners being more responsive to the CFS patients' presumed worse condition (brought on by increased TNF-α). However, this same pattern was not seen for fatigue severity or CFS symptom severity. Relevant literature in pain and in CFS implies that partners can be more sympathetic and responsive to more physical versus more somatic complaints. Hypothetically, this supposed selective attention towards the CFS patients' physical versus somatic issues could explain the findings here, showing a significant effect of communication satisfaction on TNF-α, but not fatigue severity or CFS symptom severity.

It is also interesting that we did not observe a similar pattern for the related pro-inflammatory cytokine, IL-6. Previous research in our lab shows that TNF-α does not directly load onto CFS symptoms, as measured by the same questionnaire used in this study. CFS patients who endorsed more severe CFS symptoms and fatigue may seem different to their respective partners (i.e., showing subjective symptoms) and evoke different responses from them, as compared to those who have increased serum TNF-α, (i.e., showing objective laboratory-based signs) but do not endorse high somatic symptom severity. It is also not uncommon for CFS patients to know their inflammatory cytokine

levels, and these results may be shared with their partners. Partners who receive "hard evidence" of increased inflammation (e.g. laboratory results showing elevated TNF-α levels) may be more sympathetic to their partners suffering from CFS than are those who only report symptoms. Also, patients will likely rate higher relationship satisfaction if they felt their partners were more sensitive about their symptoms. The significant positive correlation seen in this study between increased relationship satisfaction and increased PSDS lends itself well to this argument.

Additionally, PSDS is the CFS patient's own assessment of communication satisfaction. It is possible that patients who have high TNF-α may appraise partners' responses differently than those who have more severe fatigue and/or overall CFS symptoms. Importantly, these results are cross-sectional and may not adequately capture the constructs and behaviors that might account for these direct and indirect effects. Experimental research is needed to further clarify this apparent mechanism.

In all models, relationship satisfaction related to less depression and greater PSDS, as expected theoretically (S. S. Goodwin, 1997; Sheila S Goodwin, 2000; Romano et al., 2009). With regards to the indirect variables (PSDS and depression) relating to outcomes, both PSDS and depression related to greater fatigue severity, only depression related to greater CFS symptom severity, and only PSDS related to greater TNF-α. The indirect variables were not associated with IL-6 or evening cortisol.

Depression and CFS symptoms (including fatigue) are positively related in many patient populations, including CFS patients (Janssens et al., 2015); therefore, the finding that depression related to greater CFS symptom severity, and fatigue severity was in line with the study hypothesis and extant literature. However, it is interesting to note that PSDS

(as well as depression) related to greater fatigue severity, and that only PSDS related to greater TNF-α, even when depression was included in the model. Further research is needed to fully ascertain the clinical significance of these findings, especially with regard to possible CFS phenotypes.

The positive relationship between PSDS and fatigue severity and TNF-α was not congruent with one longitudinal study, which showed that perceived negative interactions and decreased social support among dyads predicted greater fatigue severity in patients diagnosed with CFS and chronic fatigue (Prins et al., 2004). As such, I would expect a negative relationship between PSDS and fatigue and inflammation, which was not seen in the present study. Importantly, Prins et al. did not measure perceived satisfaction about couples' communications about symptoms, but instead used a more global measure encompassing 6 types of social support using the Social Support List, which has similarities to the Dyadic Adjustment Scale (DAS) used in this study, which was not significantly related to fatigue severity.

The patients' perceived valence and quality of the partner responses (i.e. solicitous versus supportive) and fatigue-related disability was not analyzed as part of this study. Extant literature showed that relationship satisfaction moderated the positive relationship between partners' solicitous responses and fatigue-related disability, and fatigue severity in the context of CFS/ME, such that the effect was stronger for those dyads with the highest level (low, average, high) of relationship satisfaction (Schmaling et al., 2000). Solicitous responses may be perceived as positive by the patient and may be reflected in a higher PSDS score and/or solicitous responses and PSDS may be positively correlated; therefore, my study results may be in line with those of Schmaling et al. The present study was

similarly cross-sectional, therefore causative claims cannot be made, especially the implication that partner responses perpetuate fatigue severity or fatigue-related disability (operant theory) in CFS. Instead, the present study's results, in combination with extant literature findings, suggested that the relationship between greater PSDS and greater fatigue and inflammation (TNF-α) may be reflective of the fact that partners were being (appropriately) attentive to their partners with CFS, at times when they have more severe somatic and physical signs and symptoms (e.g. increased fatigue severity, increased TNF-α). This study also used a sample who reported relatively high relationship satisfaction and symptom disclosure satisfaction. The results might differ if a sample of patient-partner dyads with low relationship satisfaction was used.

Specific Aim 2 Repeated Measures

An assessment of time and intervention effects showed that the two intervention arms had no significant differential effects on depression, PSDS, fatigue severity, CFS symptom severity, evening cortisol, or pro-inflammatory IL-6 and TNF-α. However, depression severity scores decreased over time in both treatment arms, and the depression score for the CBSM group was less elevated at T2. Additionally, PSDS increased over time for both treatment arms. Fatigue severity was significantly greater for the HP group (vs CBSM) at both time points; fatigue severity decreased over time in the HP group, but this was not significant and remained worse in severity as compared to the CBSM group at T2. Similarly, the HP group showed significantly worse CFS symptom severity than CBSM at each time point, but there were no significant time or intervention effects for either treatment arm. Evening cortisol slightly increased in the CBSM arm, but this was not significant. Serum IL-6 levels slightly decreased in the HP group, but this was not

significant. Serum TNF-α levels slightly increased in both treatment arms between time points, but again this was not a statistically significant change.

The lack of significant treatment effects on the outcomes measured in this study were not in line with the hypotheses that the CBSM condition should exert significantly more powerful, beneficial effects on biological and psychological outcomes in this patient population. There are many possible reasons why there was no apparent intervention effect seen in this analysis. CFS patients in both groups started the interventions clinically depressed, and clinically fatigued, which could have prevented the intervention(s) modules from enacting their intended effect (i.e. too fatigued to practice progressive muscle relaxation (PMR), or too depressed to implement cognitive restructuring). On the other hand, both groups had relatively high relationship satisfaction, with those randomized to the CBSM group reporting significantly higher relationship satisfaction than those in HP. The CBSM intervention may have had a stronger impact on patient-partner dyads who had started the study with lower relationship satisfaction, as patient-partner dyads enrolled in this study could have already been reaping the biopsychosocially-relevent benefits that come from being in a more functional relationship (Sheila S Goodwin, 2000; Martire et al., 2010), and would conceivably affect the outcomes of interest in this study. If true, CBSM's modules dedicated to improving relationship functioning and communication may not have been as applicable to couples in this study as compared to distressed couples. The effect of relationship satisfaction on outcomes within the context of this intervention should be studied further, potentially using moderated mediation analyses. Relatedly, there was slight variation in the types of relationships included as part of this study (married vs monogamous), though the percentage of each type of committed relationship was not

significantly different between treatment arms. Future iterations of this intervention in CFS patient-partner dyads might benefit from having more uniformly coupled dyads in the sample.

Previous research using this intervention with CFS patients has shown that a live, in-person CBSM group reported improvements in perceived stress, total mood disturbance, and quality of life as compared to a one-day psychoeducation control group (Lopez et al., 2011). That "live" study reported significant but small to medium Cohen's D effect sizes for total CFS symptom severity (d= -0.20) and fatigue severity (d= -0.31), as measured by the Profile of Mood States (POMS)(Lopez et al., 2011). For comparison, the Cohen's D comparing the two groups in this study at 5 months are d= -0.40 for depression, d= -0.41 for CFS symptom severity, and d= -0.37 for fatigue severity, which were all significant (all p's <0.05). However, the control group (HP) started this study with initially worse relationship satisfaction, depressive symptom severity, CFS symptom severity, and fatigue severity, as compared to the CBSM group at baseline, which may have obscured the comparative effectiveness of the two treatment arms on the randomized patient-partner samples.

Importantly, that study was a pilot study and was introduced to participants "live," which would presumably have more robust effects as compared to telephone or videophone/tablet-delivered CBSM. Indeed, the "live" version was more effective than the telephone-delivered CBSM at improving the CFS-symptom-related outcomes such as post-exertional malaise, chills, fever, and restful sleep, though both live and telephone versions of the intervention successfully decreased perceived stress (Daniel L Hall et al., 2017). Possibly, the videophone/tablet-delivered CBSM tested in the present study was similarly

not as effective as the live version, due in part to any additional challenges and impediments to connection that are unique to remote, technological interventions (Banbury et al., 2018). Additionally, perceived stress was not examined in the present study; therefore, the videophone/tablet version of CBSM may very well significantly improve perceived stress but not depression.

The videophone/tablet version of CBSM tested in the present study was delivered to patients and their partners, whereas the prior iterations of this intervention (live, telephone-delivered) were delivered to patients only. Therefore, the addition of the partner in the present study might have changed the dynamics of the intervention's effectiveness or mechanism of action. Potentially, uncoupled patients with CFS (enrolled in the other studies) showed more benefit from CBSM because the intervention provided those patients with added social support, whereas the coupled patients who were enrolled in the present study were already reaping the benefits of emotional support from their partner (for example), so there was not as much need or room for improvement, in that respect, among other benefits that the partners provide. Alternatively, partners could have negatively impacted the effectiveness of the techniques introduced in the intervention in the present study (i.e. assertiveness training) or the intervention could have precipitated or exacerbated relationship problems that would impede and overshadow improvements in psychological and/or physical outcomes due to stress management skills training. It remains unclear whether a patient-only remotely delivered CBSM intervention would be more efficacious than a patient-partner remote CBSM venue as was tested here. Online or remote interventions that are more specifically aimed at improving couples' communication skills and relationship satisfaction (e.g. OurRelationship program (Doss et al., 2016)) may have

worked more effectively in this context. Additionally, CBSM may have been more effective if delivered to one dyad, and not in a group venue.

A major difference between the present study and the "live" CBSM study, which was the most effective version of CBSM for CFS patients tested to date (Lopez et al., 2011), is that the present study used an attention-matched Health Promotion (HP) control condition that was designed to be informative and beneficial to the patient's and partner's health. The control condition included modules on nutrition, sleep, and doctor-patient relationships, while it excluded the presumably more psychologically-relevant stress management-specific "active ingredients" such as the modules related to cognitive behavioral therapy, stress management, assertiveness training, cognitive reappraisal, acceptance, guided imagery, and progressive muscle relaxation. The health-related modules in the HP condition could have changed the patients' health behaviors and improved mental and physical wellbeing synergistically (or protected against their symptoms worsening over time, spontaneously) to such an extent that their improvements were equal in magnitude to those improvements seen in CFS patients enrolled in the CBSM group. For example, participants randomized to the HP intervention could have decreased their BMI and/or improved their sleep quality (i.e. through change in nutrition and other healthy lifestyle behaviors), which could have theoretically improved depression, evening cortisol, fatigue, CFS symptom severity, and inflammation. Thus the richness of the HP control condition may have made it more like an active therapeutic condition.

Beyond the richness of its content, the HP control condition was delivered to the patient and partner directly, and was not delivered to a group of patient-partners, as the CBSM condition was. The patient and partner in the HP condition missed out on the

(intended) increased social support afforded by being in a group of patients and partners who have similar experiences and can relate during the CBSM sessions. On the other hand, the patient (and partner) in the HP condition could have been able to generate a deeper connection to the therapist since the HP therapist's attention was not divided among the other dyads in the group, but instead, was focused on that couple alone. In stark contrast to the present study's attention-matched, potentially holistically beneficial HP control condition, the live version of the intervention was previously compared to a single-day psychoeducational seminar in a previously published study (Lopez et al., 2011). That study's control condition was not attention-matched, but was a group format, and it is likely that the therapeutic connection between therapist and patient was not developed in the span of one day, especially in comparison to the CBSM intervention condition spanning multiple weeks. This is significant, as attention and therapeutic connection between the healthcare provider and the patient in and of itself, irrespective of the type of treatment offered, can improve treatment outcomes (Krupnick et al., 1996).

In conclusion, the CBSM intervention was not differentially effective at ameliorating the outcomes in the study as compared to the HP control condition; however, there were many factors that can explain the lack of significant differences in treatment effects on outcomes: (1) CFS symptoms may relapse and remit over time, for no apparent reason or due to various stressors, and the timeframe of this study might not have been adequately timed to capture these changes; (2) The interventions were delivered via tablet/videophone, which could have rendered each non-effective; (3) The design compared the effects of the CBSM intervention delivered to a group of dyads versus an HP control condition delivered to a singular dyad; (4) both interventions were delivered to

couples, irrespective of baseline relationship functioning, which may impact the uptake and effectiveness of the treatment's therapeutic contents; and (5) the control condition was attention-matched (for time) and was designed to be informative and beneficial, and thus was too potent. The unique characteristics of this study make a comparison to the more effective "live" study of CBSM in CFS difficult. It remains plausible that both of the conditions tested in this trial were effective, but achieved their effects in different ways. A more thorough examination into the mechanism by which the treatment conditions exerted an effect on the outcomes is discussed next.

Specific Aim 2 Direct and Indirect Effects

Examination of the interventions' differential effects on mediators (T2-T1 change in PSDS and depression) and 5-month outcomes (fatigue severity, CFS symptom severity, evening cortisol, IL-6, and TNF-α) was conducting using structural equation modeling. The total effects and parallel mediation modeling showed that group assignment had a direct effect on fatigue severity, such that those assigned to the HP group experienced greater fatigue severity than those in CBSM at 5 months (T2). Indirect effect analysis showed that greater magnitude of change in depression severity scores (becoming more depressed between T1 and T2) predicted greater fatigue severity at 5M. However, condition did not predict change in depression (T2-T1); instead, depression changed in both conditions, changed spontaneously, or changed as a result of something other than intervention assignment. When baseline fatigue severity was added to the model, the group effects were no longer significant but the effect of change in depression remained. Therefore, there is no evidence in the present study that change in depression (due to intervention assignment) mediated the relationship between condition and fatigue severity.

This corroborated the repeated measures analysis showing no significant differences in fatigue severity between treatment arms. This result lends more support to the argument that both interventions might have been beneficial and effective, as well as the possibility that neither intervention was beneficial or effective.

For CFS symptom severity outcomes, change in PSDS played a more significant role than change in depression in explaining the variance. Like fatigue severity outcomes, the total effects and parallel mediation modeling showed that group assignment had a direct effect on CFS symptom severity, such that those assigned to the HP group experienced greater CFS symptom severity at 5 months (T2), though as noted previously there were no intervention effects on the magnitude of the T1 –T2 change. Indirect effect analysis showed that greater magnitude of change in PSDS scores (becoming more satisfied with communication between T1 and T2) predicted less fatigue severity at 5M. The indirect effect for change in depression was marginally significant. In sum, condition did not predict change in depression or PSDS (T2-T1); instead, independent of group assignments, the mediators in both conditions changed spontaneously, or as a result of something other than intervention assignment. When the mediation analyses include baseline CFS symptom severity as a covariate, both the effect of group and change in PSDS became non-significant.

The intial results of the analyses of PSDS and depression changes are in line with the hypothesis that mental well-being and perceived social support from the patients' partners could have a significant impact on CFS-related outcomes (Band et al., 2015; Brooks et al., 2014; Dickson et al., 2007; Porter et al., 2008; Prins et al., 2004; Stephens et al., 2006). The fact that depression exerted a significant effect on fatigue severity while

PSDS exerted a significant effect on CFS symptom severity is a potentially noteworthy distinction in the biopsychosocial pathogenesis and experience of CFS. The CDC CFS Symptom Inventory was used to examine overall CFS symptom severity, and therefore, captured more all-encompassing symptoms associated with CFS than did the Fatigue Symptom Inventory. Because of that, increased or decreased satisfaction with communicating about symptoms (PSDS) might have been more relevant to and sensitive to changes in the CFS symptom severity measures, since there are more different types of symptoms that patients and partners could be communicating about. In the case of fatigue severity it is possibly that item overlap in the depression and fatigue questionnaires could have accounted for the association between these variables. Importantly, the group effects were no longer significant when adding baseline fatigue and CFS symptom severity to the model. Only change in depression remained significant in its effect on fatigue severity at 5 months. Therefore, changing depression may be more salient in improving fatigue severity in CFS, and future intervention development and research should target this mechanism further.

As noted previously, the change in depression and PSDS observed over time could not be attributed to intervention assignment. Instead, depression decreased and PSDS increased from baseline to the 5-month follow-up period either spontaneously or as a result of participating in either one of the interventions. The latter is plausible because dyads participating in either CBSM or HP experienced the intervention as a couple, and going through that experience jointly, in and of itself, may have improved mental health and perceived social support. This study did not use a wait-list control, or otherwise inactive

control group, so the effectiveness of either intervention as compared to no treatment cannot be discussed conclusively here.

Group assignment did not exert any effects on evening cortisol, IL-6, or TNF-α, nor were there any significant indirect effects on the biological outcomes, due to change in depression or PSDS. This result ran counter to the hypothesis in the study that CBSM would improve CFS-relevant biological outcomes, by way of reduced depression and/or increased PSDS as compared to the HP condition. CBSM has previously been shown to increase benefit finding, reduce serum cortisol levels, and improve *in vitro* lymphocyte functioning (Antoni et al., 2001; Cruess et al., 2000; McGregor et al., 2004); however, that was demonstrated among women with breast cancer, not CFS, and measured different indices of hypothalamic-pituitary-adrenal (HPA) axis and neuroimmune functioning. Similar beneficial psychological and biological outcomes were seen in a CBSM trial of men and women in HIV+, but again, the measures and control group differed greatly from that used in the present study (Antoni, Cruess, Cruess, Lutgendorf, et al., 2000; Antoni, Cruess, Cruess, Kumar, et al., 2000; Cruess et al., 1999). It is possible that CBSM positively impacted other biological and psychological outcomes that are not analyzed and represented in the present study.

Limitations and Future Directions

Though the analyses performed in this study were adequately powered to detect a small-medium effect, the relatively small sample size of this study used to detect direct and indirect baseline and longitudinal effects limited the use of more covariates (i.e. education, gender) and might not have been sensitive enough to detect a smaller effect that was evident. Missing data was an issue in this study, as was overlap between mediator and

outcome measures (e.g. CES-D and FSI) . Structural equation modeling in Mplus utilized full information maximum likelihood (FIML) to maximize power, and was able to detect a small group effect, whereas repeated-measures ANCOVA using listwise deletion did not show any significant time or treatment effects. Additionally, many of the structural equation models did not fit the data according to all fit indices, and Mplus was not able to generate modification indices that would help improve model fit. More robust time and/or intervention effects could have been detected if analyses included the final follow-up time point at 9 months post-baseline, especially if the beneficial skills learned in the intervention (i.e. cognitive restructuring, assertiveness training) need more time to be practiced and implemented consistently in order to exert their desired effects on psychological and biological outcomes in CFS patients. This remains to be examined further in subsequent analyses of this intervention trial using the 9-month follow-up data, especially using latent growth modeling. Because of the significant differences at baseline between groups, and the significant differences in attendance among intervention groups, among other reasons, a sensitivity analysis is suggested for further analysis of this and subsequent CBSM trials (Thabane et al., 2013). Additionally, subsequent studies should test whether the results from limiting the analyses to only those participants who completed 80-90% of the intervention would differ from the results outlined in this study, which was an intent-to-treat analysis(Thabane et al., 2013).

Evening cortisol and pro-inflammatory cytokines IL-6 and TNF-α were chosen as indices of HPA and neuroimmune functioning because of their relation to CFS and depression; however, there are many other measures of neuroimmune functioning that could be analyzed in further studies, which might be more sensitive to the direct and

indirect predictors at baseline, and as a result of the CBSM or HP intervention. Cytokines were only measured once per time-point and di-urnal cortisol was measured twice per time-point. A myriad of factors, including sleep quality, wake-time, daily stressors, food, among others can affect neuroimmune variable measurement or can be reflective of processes unrelated to this study (O'Connor et al., 2009).

Results show that the videophone/tablet-delivered CBSM intervention was not effective at ameliorating the outcomes outlined in the study as compared to the HP control condition; however, there are many factors that can explain the lack of significant effects. These include the timing of the study measurements, and intervention-specific factors. This is the first study to test CBSM delivered via tablet/videophone and it is plausible that this venue is not as powerful as when administered in-person, which we know is more effective than CBSM delivered by telephone in this patient population (Daniel L Hall et al., 2017). Other design factors that may have obscured differences between CBSM and HP were the group dyadic format used in CBSM vs the singular dyadic format in HP, and the possibility that differences in couple's baseline relationship status (e.g. dyadic consensus) could have interacted with intervention assignment. Therefore, further study of the moderating effects of relationship quality on intervention effects in a design with both conditions being either group dyads or singular dyads is warranted. Furthermore, this area of research would benefit from using more specific indices of relationship functioning and communication satisfaction in subsequent analyses, and would benefit from deeper examination of other mechanisms not specified in this dissertation (e.g. moderated mediation).

The results of this study suggested that communication satisfaction and/or depression can relate to CFS-relevant outcomes at baseline, and that changes in these mediators might also affect changes in the outcomes specified, irrespective of intervention assignment. Intuitively, designing patient-partner interventions aimed at improving both mediators seem like they would hypothetically be beneficial for any couple, especially those coping with a chronic illness such as CFS. However, some patients within a dyad, who are in relationships that are characteristically different than others', may benefit more from interventions that are specifically targeted to improving their idiosyncratic needs. Various modules in each intervention arm might be more or less applicable to certain sub-populations within a CFS patient-partner sample. Interventions targeting relationship and communication-related mediators should be compared against those targeting stress and depression-related mediators, especially comparing their effectiveness at improving CFS-related outcomes (including but not limited to ones specified in this study). Additionally, these interventions should be tested in samples composed of couples who are are distressed in their relationships. Information provided by these subsequent analyses and targeted interventions will not only inform mechanism-based research, but also foster the field of personalized medicine in a psychosocially-relevant treatment context.

Conclusions

This study demonstrated the direct effects of relationship satisfaction, and indirect effects of depression and patients' satisfaction of communicating about their symptoms to their partner (PSDS) on fatigue and CFS symptom severity, and showed these factors to be unrelated or inconsistently related to neuroimmune processes. There was no evidence of differential effects of a remotely-delivered 10-week cognitive behavioral stress

management (CBSM) program versus a 10-week health promotion (HP) control condition on the outcomes measured at 5 months. Further research in this area would benefit from measuring the outcomes at later time-points, testing the moderating effect of relationship quality, matching conditions for group vs individual dyad delivery, and considering other indices of HPA-axis and neuroimmune functioning. Participants may have benefitted from both remotely-delivered conditions, as depressive symptoms decreased and patient communication satisfaction about symptoms increased in both CBSM and HP, though this was not significant. These findings may aid the design of subsequent remote interventions that have the opportunity to improve mental and physical well-being for CFS patients and possibly a wide variety of individuals and couples dealing with chronic illness.

TABLES

Table 1a. Demographic Characteristics of Sample (In Total and Within Groups)

	CBSM		HP		Total		Chi-Square	p
	M	SD	M	SD	M	SD		
Age in years	48.0	11.4	47.9	10.5	48.0	10.9	35.83	0.86
	N	%	N	%	N	%		
Gender							0.54	0.46
Male	8	10.7	11	14.7	19	12.7		
Female	67	89.3	64	85.3	131	87.3		
Ethnic Identification							7.36	0.19
Caucasian (non-Hispanic)	51	68.0	47	62.6	98	65.3		
Black/African American	2	2.6	0	0	2	1.3		
Caribbean Islander	0	0	3	4.0	3	2.0		
Hispanic	21	28.0	24	32.0	45	30.0		
Asian/Asian American	0	0	1	1.3	1	0.7		
Other	1	1.3	0	0	1	0.7		

Table 1b. Demographic Characteristics of Sample (Continued)

	CBSM		HP		Total		Chi-Square	p
	M	SD	M	SD	M	SD		
Employment status							9.31	0.23
Full-Time	17	22.7	15	20.0	32	21.3		
Part-Time	4	5.3	12	16.0	16	10.7		
Student	4	5.3	1	1.3	5	3.3		
On Disability	21	28.0	17	22.7	38	25.3		
Retired	3	4.0	5	6.7	8	5.3		
Unemployed	10	13.3	17	22.7	27	18.0		
Volunteer Worker	1	1.3	1	1.3	2	1.3		
Other	14	17.3	6	8.0	20	12.7		
Education Level							7.26	0.30
Some high school	2	2.7	1	1.3	3	2.0		
High school graduate	1	1.3	4	5.3	5	3.3		
GED			4	5.3	4	2.7		
Trade school	3	4.0	3	4.0	6	4.0		
Some college	20	26.7	16	21.3	36	24.0		
College graduate	30	40.0	25	33.3	55	36.7		
Graduate degree	18	24.0	21	28.0	39	26.0		

Table 2. Descriptive Statistics on Baseline Mediator and Outcome Variables

	CBSM		HP		χ^2	p-value
	%	N	%	N		
Withdrawal (5M)	8	6	10.7	8	0.32	0.58
Some Missing Data (5M)	22.7	17	22.7	17	0.00	1.00
	Mean	Standard Deviation	Mean	Standard Deviation	t (df)	p-value
Attendance*	9.31	2.45	8.19	2.81	2.53 (134.9)	**0.01**
DAS Total	114.73	19.98	106.49	22.03	2.20 (124)	**0.03**
Depression	20.15	10.19	24.10	11.81	-2.16 (144)	**0.03**
PSDS	208.78	79.547	200.68	74.20	.64 (146)	0.52
CFS Symptom Severity	2.29	0.81	2.55	0.77	-2.03 (147)	**0.04**
Fatigue Severity	5.66	2.03	6.60	1.71	-2.96 (139)	**<.01**
Evening Cortisol (ug/ dL)*	0.08	0.13	0.09	0.11	-.41 (139)	0.69
IL-6 (pg/mL)*	2.16	1.99	2.54	4.23	.53 (143)	0.60
TNF-α (pg/mL)*	11.49	12.50	11.57	12.50	.21 (143)	0.83

* Levene's Test for Equality of Variances was significant for Attendance; therefore, the adjusted t-statistic was used

**Cortisol and cytokine raw values are presented here, but were log-transformed as such for analyses: ln (x+1)

Table 3. Correlations among Baseline Predictor, Mediator, and Outcome Variables (Total Sample)

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13
1. GROUP		-.21 *	.05	-.00	.05	-.05	**.18***	**-.19***	**.17***	**.24****	.03	-.05	-.02
2. Attendance			-.44**	.03	.01	**.18***	-.16	.09	**-.18***	-.01	.00	-.12	.03
3. 5M Withdrawal				.07	.01	.07	-.02	-.01	.11	.06	-.00	.02	.07
4. Age					.12	**.18***	-.13	.12	-.06	.02	.05	.09	.02
5. BMI						.04	**.24****	.12	.14	.14	-.04	.04	.10
6. PSDS							**-.29****	**.50****	.04	.13	-.05	.04	**.18***
7. Depression								**-.38****	**.31****	**.26****	.15	-.00	.02
8. DAS Total									-.00	-.00	-.11	-.01	-.03
9. CFS Sx* Severity										**.39****	**.26****	.06	.14
10. Fatigue Severity											.13	.08	-.01
11. Evening Cortisol												.05	.04
12. IL-6													-.03
13. TNF-α													

*Sx is symptom

Table 4. Correlations among Attendance, Mediator, and Outcome Variables at 5 Months (Total Sample)

Variables	1	2	3	4	5	6	7	8
1. Attendance		-.14	0.02	-.12	-.06	.09	-05	.04
2. ΔDepression			**-.19***	**.31****	**.18***	.01	-.09	-.03
3. ΔPSDS				-.16	**-.23***	.13	.08	.07
4. F.S.*					**.52****	.06	.05	.07
5. CFS S.S.**						-.07	-.14	.07
6. E.C.							-.10	-.03
7. IL-6								-.11
8. TNF-α								

*F.S. is Fatigue Severity

**CFS S.S. is CFS Symptom Severity

Table 5. Correlations among Attendance, Mediator, and Outcome Variables at 5 Months (CBSM/HP)

Variables	1	2	3	4	5	6	7	8
1. Attendance		-.04/ **-.26***	.03/ -.00	.02/ -.16	.21/ -.22	.09/ .06	-.03/ .12	.13/ -.14
2. ΔDepression			-.12/ **-.28***	**.46**/ .18	.21/ .17	-.06/ .12	-.08/ -.10	.01/ -.06
3. ΔPSDS				-.18/ -.14	-.23/ -.23	.24/ -.06	.03/ .15	-.08/ .21
4. F.S.					**.50**/ **.52**	-.03/ .22	.13/ -.02	-.00/ .12
5. CFS S.S.						-.12/ .02	-.17/ -.08	.20/ -.05
6. E.C.							-.08/ -.16	.15/ -.25
7. IL-6								-.06/ -.15
8. TNF-α								

Table 6. Direct Effects of Relationship Satisfaction, Parallel Mediators and Covariates on Fatigue Severity at Baseline.

Antecedent		Depression (M₁)				PSDS (M₂)				Fatigue Severity (Y)		
		b	SE	p		B	SE	p		b	SE	p
DAS Total (X)	a_1	-.20	.05	.00	a_2	.17	.03	.00	c'	.00	.01	.74
Depression (M₁)									b_1	.06	.02	.00
PSDS (M₂)									b_2	.05	.03	.03
Age		-.13	.08	.10		.09	.05	.06		.00	.01	.92
BMI		.47	.14	.00		-.02	.09	.79		.01	.03	.61
Constant	i_{M1}	37.57	6.55	.00	i_{M2}	-2.07	4.46	.64	i_y	2.99	1.23	.02

Table 7. Direct Effects of Relationship Satisfaction, Parallel Mediators and Covariates on CFS Symptom Severity at Baseline

		Consequent										
		Depression (M$_1$)				PSDS (M$_2$)				CDC Symptom (Y)		
Antecedent		b	SE	p		B	SE	p		b	SE	p
DAS Total (X)	a$_1$	-.21	.05	.00	a$_2$	.17	.03	.00	c'	.00	.01	.55
Depression (M$_1$)									b$_1$	.03	.01	.00
PSDS (M$_2$)									b$_2$	.01	.01	.25
Age		-.13	.08	.10		.09	.05	.06		.00	.01	.55
BMI		.47	.14	.00		-.02	.09	.78		.01	.01	.48
Constant	i$_{M1}$	37.83	6.53	.00	i$_{M2}$	-2.04	4.46	.65	i$_y$	1.30	.55	.02

Table 8. Direct Effects of Relationship Satisfaction, Parallel Mediators and Covariates on Evening Cortisol at Baseline

		Consequent									
		Depression (M$_1$)				PSDS (M$_2$)				Evening Cortisol (Y)	
Antecedent		b	SE	p		B	SE	p		b	SE	p
DAS Total (X)	a$_1$	-.02	.05	.00	a$_2$	.17	.03	.00	c'	.00	.00	.90
Depression (M$_1$)									b$_1$	.00	.00	.07
PSDS (M$_2$)									b$_2$	.00	.00	.91
Age		-.12	.08	.11		.09	.05	.06		.00	.00	.40
BMI		.47	.14	.00		-.03	.09	.77		-.00	.00	.27
Constant	i$_{M1}$	37.35	6.47	.00	i$_{M2}$	-2.03	4.44	.65	i$_y$	.06	.08	.46

Table 9. Direct Effects of Relationship Satisfaction, Parallel Mediators and Covariates on Interleukin (IL)-6 at Baseline

		Consequent									
		Depression (M₁)				PSDS (M₂)				Interleukin (IL)-6 (Y)		
Antecedent		b	SE	p		b	SE	p		b	SE	p
DAS Total (X)	a₁	-.20	.05	.00	a₂	.17	.03	.00	c'	-.00	.00	.81
Depression (M₁)									b₁	.00	.00	.96
PSDS (M₂)									b₂	.00	.01	.71
Age		-.12	.08	.11		.09	.05	.06		.00	.01	.46
BMI		.47	.14	.00		-.02	.09	.78		.00	.01	.72
Constant	i₍M1₎	34.47	6.54	.00	i₍M2₎	-2.00	4.38	.65	i₍y₎	.72	.51	.15

Table 10. Direct Effects of Relationship Satisfaction, Parallel Mediators and Covariates on Tumor Necrosis Factor (TNF)-α at Baseline

		Consequent										
		Depression (M$_1$)				PSDS (M$_2$)				TNF-α (Y)		
Antecedent		b	SE	p		B	SE	p		b	SE	p
DAS Total (X)	a$_1$	-.20	.05	.00	a$_2$	.17	.03	.00	c'	-.01	.01	.18
Depression (M$_1$)									b$_1$	-.00	.01	.88
PSDS (M$_2$)									b$_2$	.03	.01	.02
Age		-.13	.08	.10		.09	.05	.06		-.00	.01	.81
BMI		.47	.14	.00		-.03	.09	.77		.02	.01	.19
Constant	i$_{M1}$	37.36	6.57	.00	i$_{M2}$	-2.10	4.46	.64	i$_y$	2.04	.59	.00

Table 11. Mean Differences Between CBSM and HP at T1 and T2

	CBSM		HP		F	*p*-curve	Partial η²
	T1 Mean (SD)	T2 Mean (SD)	T1 Mean (SD)	T2 Mean (SD)			
Depression	19.17 (9.57)	18.67 (11.16)	24.02 (11.21)	22.66 (10.77)	0.63	0.54	0.01
PSDS	21.18 (7.84)	22.34 (6.49)	20.20 (7.70)	20.98 (8.42)	1.00	0.37	0.01
Fatigue Severity	5.51 (2.06)	5.51 (2.16)	6.54 (1.68)	6.20 (2.11)	0.26	0.77	0.01
CFS Symptom Severity	2.32 (0.92)	2.65 (0.74)	2.78 (0.77)	2.92 (0.59)	1.23	0.30	0.02
Evening Cortisol	0.07 (0.12)	0.09 (0.11)	0.08 (0.10)	0.08 (0.09)	0.26	0.77	0.01
IL-6	0.97 (0.50)	1.00 (0.69)	1.03 (0.62)	0.91 (0.61)	0.62	0.54	0.01
TNF-α	2.10 (0.85)	2.17 (0.85)	2.08 (0.71)	2.15 (1.06)	0.63	0.54	0.01

Table 12. Direct Effects of Relationship Satisfaction, Parallel Mediators and Covariates on Fatigue Severity at 5 Months (T2)

			Consequent								
		ΔDepression (M$_1$)				ΔPSDS (M$_2$)				Fatigue Severity (5M) (Y)	
Antecedent		b	SE	p		B	SE	p		b	SE	p
Group	a$_1$	-.83	1.89	.66	a$_2$	-.43	1.18	.72	c'	**.84**	**.36**	**.02**
ΔDepression (M$_1$)									b$_1$	**.07**	**.02**	**.00**
ΔPSDS (M$_2$)									b$_2$	-.03	.03	.23
Age		.00	.08	.96		-.01	.05	.85		-.02	.01	.21
BMI		-.15	.14	.30		-.04	.09	.65		.02	.03	.46
Constant	i$_{M1}$	4.32	6.11	.48	i$_{M2}$	3.24	3.75	.39	i$_y$	4.99	1.12	.00

Table 13. Direct Effects of Relationship Satisfaction, Parallel Mediators and Covariates on Fatigue Severity at 5 Months with Baseline Fatigue Severity as Covariate (T2)

		Consequent									
		ΔDepression (M₁)				ΔPSDS (M₂)				Fatigue Severity (5M) (Y)		
Antecedent		b	SE	p		B	SE	p		b	SE	p
Group	a_1	-.59	2.1	.78	a_2	.18	1.27	.89	c'	.16	.40	.65
ΔDepression (M₁)									b_1	**.06**	**.02**	**.00**
ΔPSDS (M₂)									b_2	-.01	.02	.79
Age		-.01	.08	.91		-.02	.06	.77		-.01	.01	.24
BMI		-.14	.15	.36		-.02	.09	0.79		.00	.03	.91
B.L. F.S.		-.11	.51	.84		-.46	.34	.18		**.59**	**.11**	**.00**
Constant	i_{M1}	5.06	6.38	.43	i_{M2}	4.85	3.80	.20	i_y	2.68	1.03	.01

B.L. F.S. is baseline fatigue severity

Table 14. Direct Effects of Intervention, Parallel Mediators and Covariates on CFS Symptom Severity at 5 Months (T2)

		Consequent										
		ΔDepression (M$_1$)				ΔPSDS (M$_2$)				CFS Symptom Sev. 5M (Y)		
Antecedent		b	SE	p		B	SE	p		b	SE	p
Group	a$_1$	-.84	1.88	.65	a$_2$	-.42	1.18	.72	c'	**.27**	**.12**	**.02**
ΔDepression (M$_1$)									b$_1$	.01	.01	.06
ΔPSDS (M$_2$)									b$_2$	**-.02**	**.01**	**.02**
Age		.01	.08	.95		-.01	.05	.85		-.00	.01	.67
BMI		-.14	.14	.32		-.04	.09	.65		.01	.01	.52
Constant	i$_{M1}$	4.01	6.08	.51	i$_{M2}$	42.61	6.38	.00	i$_y$	2.37	.33	.00

Table 15. Direct Effects of Intervention, Parallel Mediators and Covariates on CFS Symptom Severity at 5 Months with Baseline CFS Symptom Severity as Covariate (T2)

Antecedent		ΔDepression (M$_1$)				ΔPSDS (M$_2$)				CFS Symptom Sev. 5M (Y)		
		b	SE	p		B	SE	p		b	SE	p
GROUP	a$_1$	-1.2	1.8	.51	a$_2$	-.03	1.2	.98	c'	.12	.09	.22
ΔDepression (M$_1$)									b$_1$	.01	.01	.10
ΔPSDS (M$_2$)									b$_2$	-.01	.01	.11
Age		.01	.08	.88		-.02	.05	.74		.00	.00	.90
BMI		-.16	.14	.26		-.02	.09	.81		-.00	.01	.77
B.L. CFS Sx		1.10	1.57	.49		-1.25	.83	.13		**.49**	**.06**	**.00**
Constant	i$_{M1}$	2.13	7.25	.77	i$_{M2}$	5.39	4.10	.19	i$_y$	.27	.04	.00

B.L. CFS Sx is Baseline CFS Symptom Severity

Table 16. Direct Effects of Intervention, Parallel Mediators and Covariates on Evening Cortisol at 5 Months (T2)

		Consequent									
		ΔDepression (M₁)				ΔPSDS (M₂)				Evening Cortisol (Y)	
Antecedent		b	SE	p		B	SE	p		b	SE	p
Group	a₁	-.84	1.91	.66	a₂	-.37	1.18	.75	c'	-.01	.02	.56
ΔDepression (M₁)									b₁	.00	.00	.68
ΔPSDS (M₂)									b₂	.00	.00	.27
Age		.00	.08	.96		-.01	.05	.80		-.00	.00	.09
BMI		-.14	.14	.33		-.04	.09	.68		.00	.00	.47
Constant	i_M1	4.01	6.12	.51	i_M2	3.33	3.75	.38	i_y	.16	.08	.04

Table 17. Direct Effects of Intervention, Parallel Mediators and Covariates on Interleukin (IL)-6 at 5 Months (T2)

		Consequent									
		ΔDepression (M₁)				ΔPSDS (M₂)				Interleukin (IL)-6 (Y)	
Antecedent		b	SE	p		B	SE	p		b	SE	p
Group	a_1	-.88	1.88	.64	a_2	-.40	1.18	.73	c'	-.06	.13	.67
ΔDepression (M₁)									b_1	-.01	.01	.48
ΔPSDS (M₂)									b_2	.01	.01	.53
Age		.01	.08	.95		-.01	.05	.84		-.00	.01	.38
BMI		-.14	.14	.33		-.04	.09	.64		.01	.01	.54
Constant	i_{M1}	4.00	6.11	.51	i_{M2}	3.27	3.74	.38	i_y	1.11	.46	.02

Table 18. Direct Effects of Intervention, Parallel Mediators and Covariates on Tumor Necrosis Factor (TNF)-α at 5 Months (T2)

		Consequent										
		ΔDepression (M₁)				ΔPSDS (M₂)				TNF-α (Y)		
Antecedent		b	SE	p		B	SE	p		b	SE	p
Group	a_1	-.87	1.88	.65	a_2	-.42	1.18	.72	c'	.03	.18	.86
ΔDepression (M₁)									b_1	-.00	.01	.80
ΔPSDS (M₂)									b_2	.01	.01	.47
Age		.00	.08	.96		-.01	.05	.85		-.01	.01	.36
BMI		-.14	.14	.32		-.04	.09	.66		-.00	.01	.93
Constant	i_{M1}	4.06	6.11	.51	i_{M2}	3.24	3.75	.00	i_y	2.48	.51	.00

Figure 1. Randomized-Controlled VideoHealth Trial Timeline

| Baseline | Randomization | 10 Week Intervention | 5 Month Follow Up | 9 Month Follow Up |

Figure 2. Parallel Multiple Mediator Model from Hayes (2017)
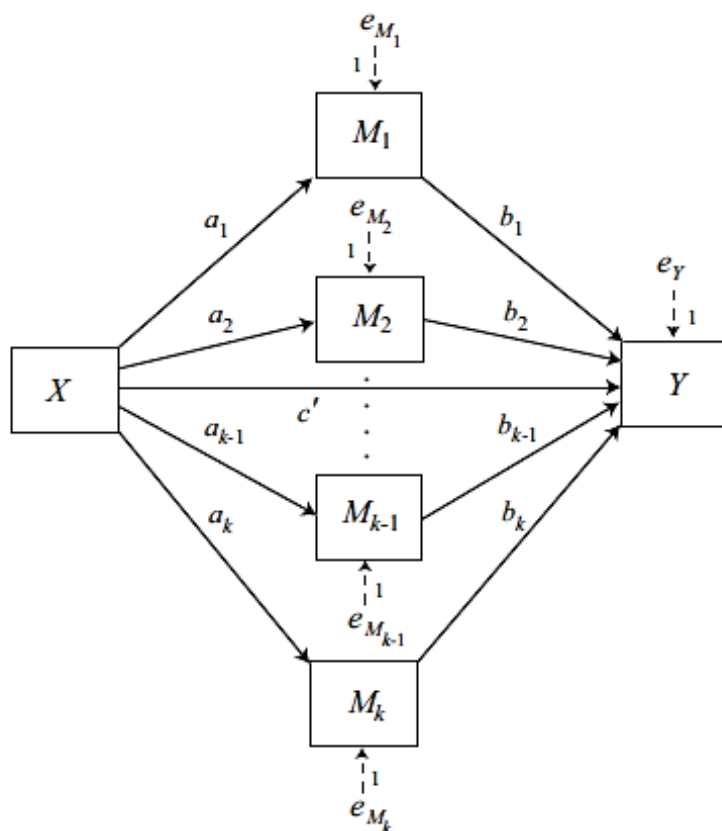
Figure 3. Parallel Multiple Mediator Model (Specific Aim 1)
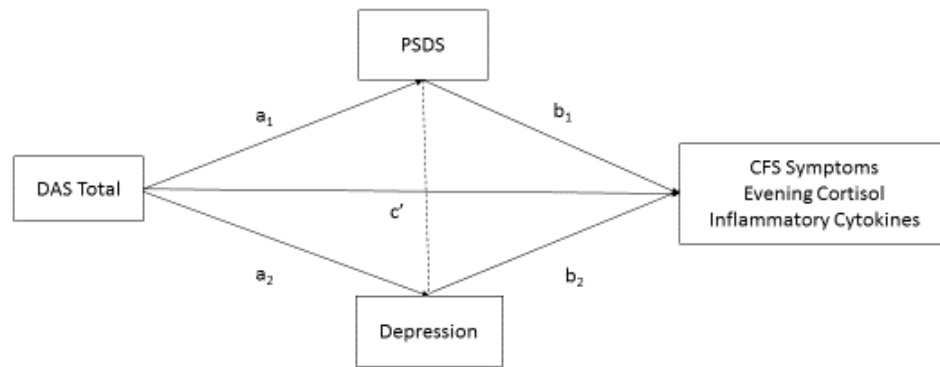
Figure 4. CONSORT Diagram for the VideoHealth Study
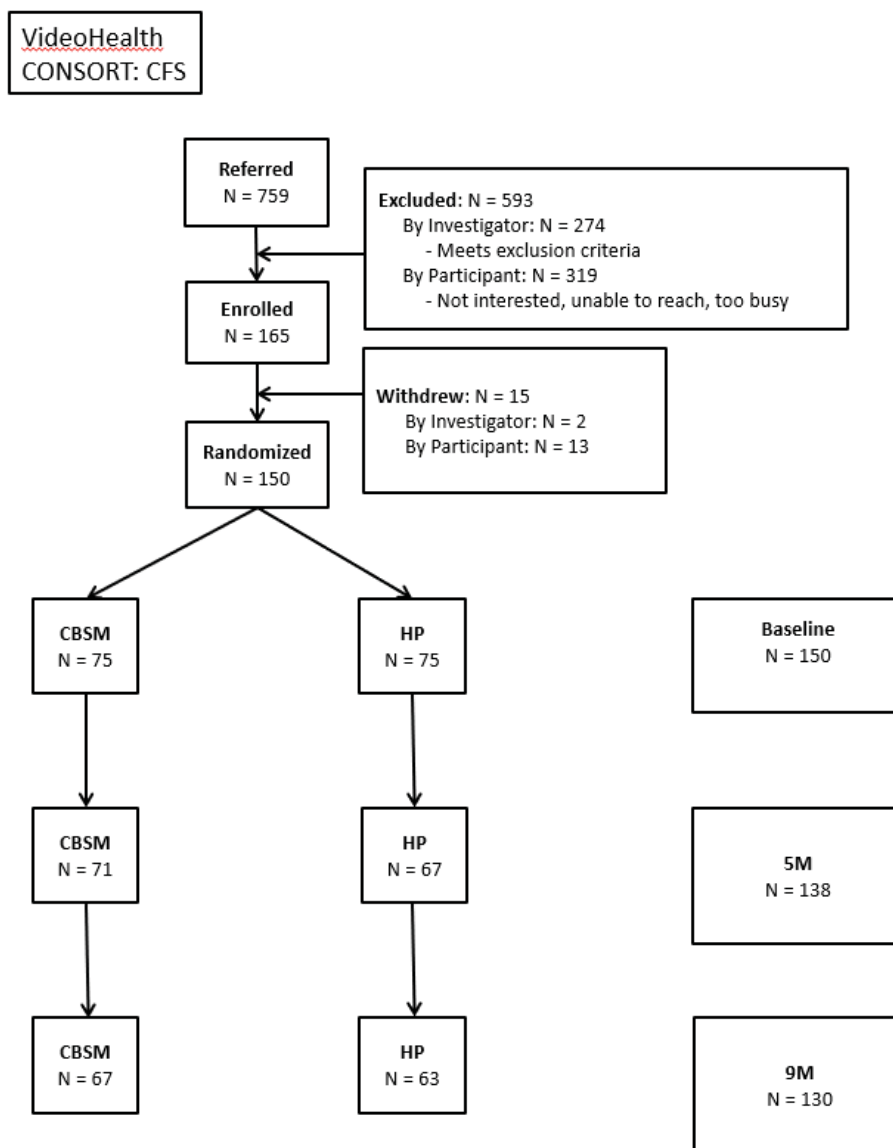
Figure 5. Specific Aim 1 Model

Figure 6. Specific Aim 2 Model
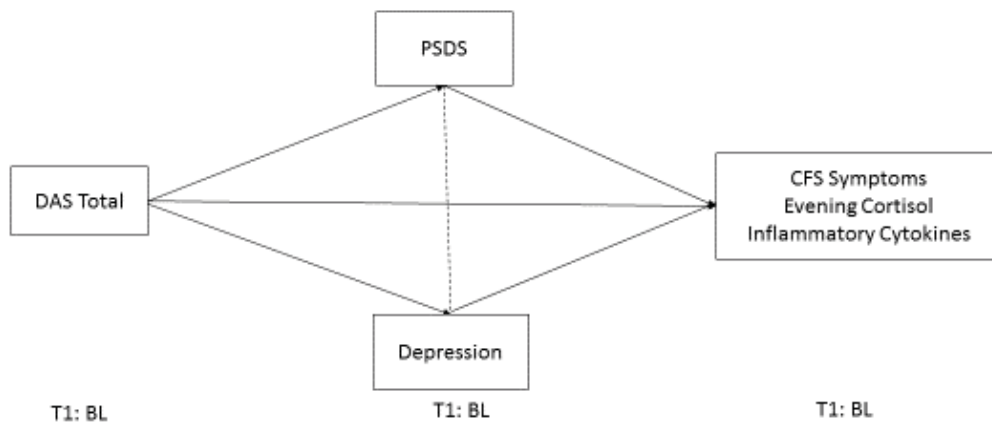
Figure 6. Specific Aim 2 Model
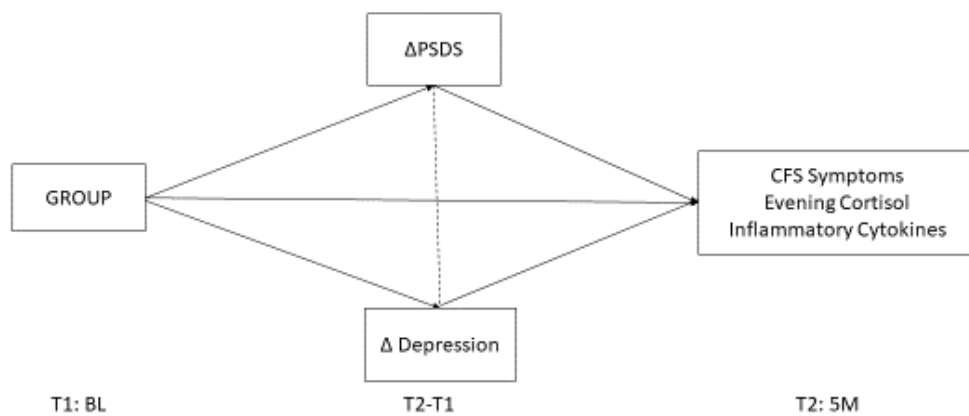
Figure 7. Structural Equation Model of Direct and Indirect Effects on Fatigue Severity at Baseline (Aim 1)
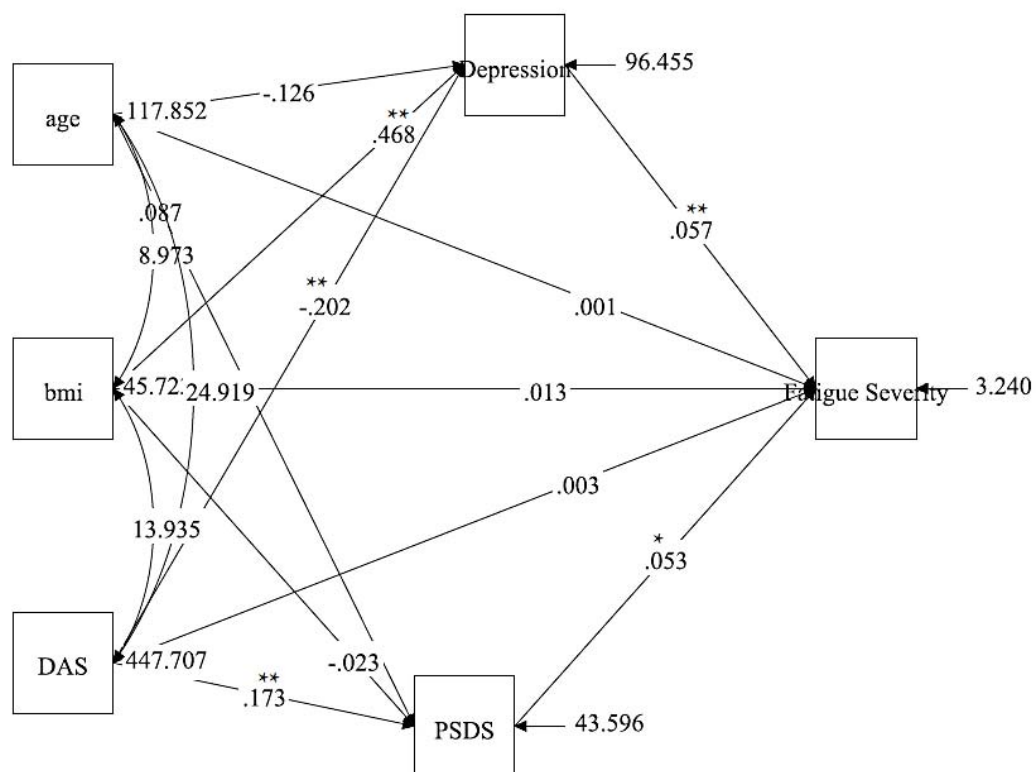
Beta weights are shown within the path arrows
*p<0.05; **p<0.01

Figure 8. Structural Equation Model of Direct and Indirect Effects on CFS Symptom Severity at Baseline (Aim 1)
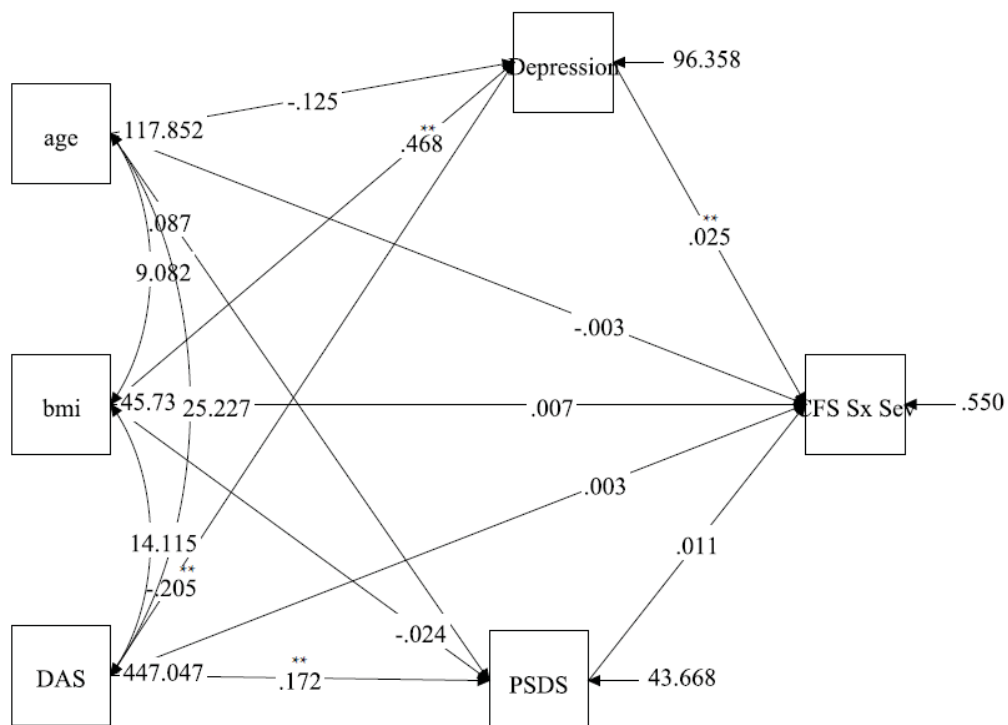
Beta weights are shown within the path arrows
*p<0.05; **p<0.01

Figure 9. Structural Equation Model of Direct and Indirect Effects on TNF-α at Baseline (Aim 1)
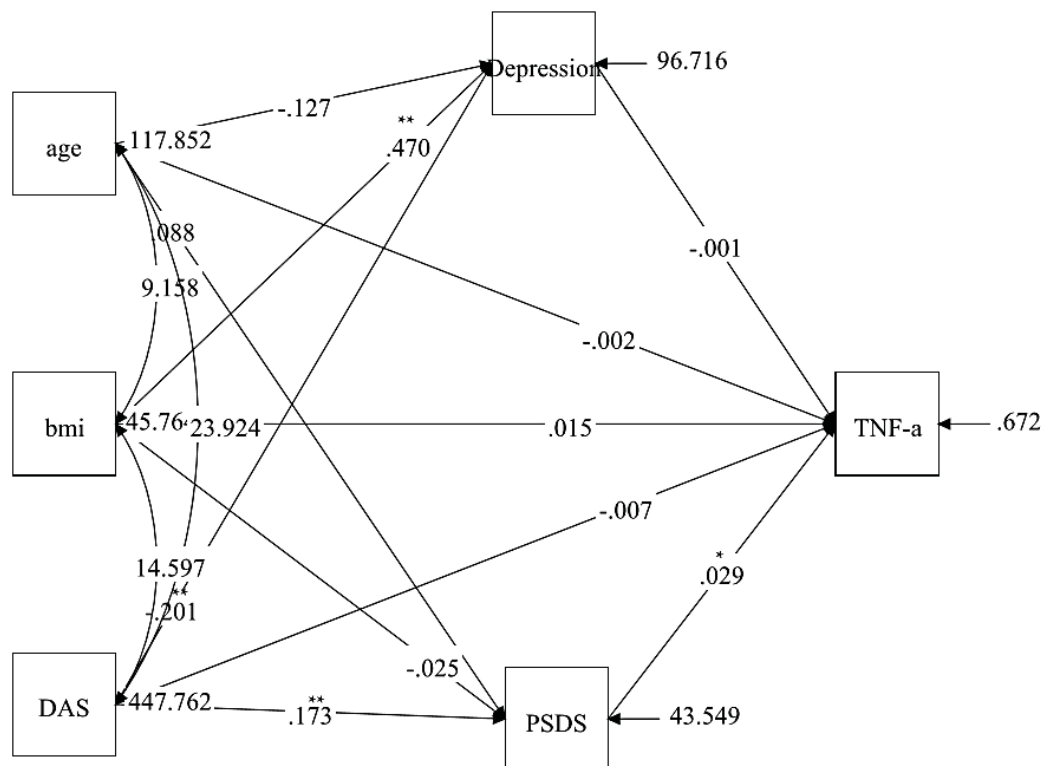
Beta weights are shown within the path arrows
*p<0.05; **p<0.01

Figure 10. Repeated Measures Analysis of Variance comparing Depression scores at Baseline vs 5-month Follow-up by Condition (CBSM vs HP) (Aim 2)
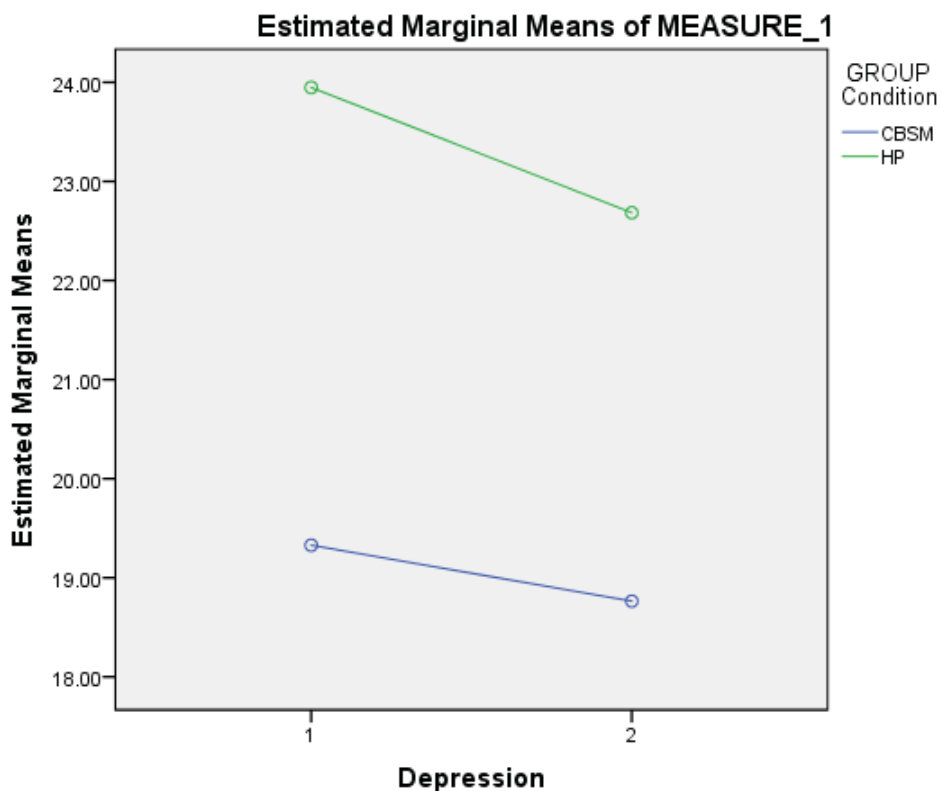
Multivariate Tests
Depression*Group*Age*BMI F(2, 111)=.31, p=.73, partial η^2= 0.01
Within-Subject Effects
Depression*Group*Age*BMI
F(2, 111)= .31, p=.73, partial η^2= 0.01
Between-Subject Effects
F(2,111)=0.63, p=.54, partial η^2= 0.01
Pairwise Comparison (CBSM vs HP)
Mean Difference= -4.27, F(1, 111)=6.28, p=0.01, partial η^2= 0.05
Repeated Measures Depression Per Condition

Figure 11. Repeated Measures Analysis of Variance comparing Patient Symptom Disclosure Satisfaction (PSDS) scores at Baseline vs 5-month Follow-up by Condition (CBSM vs HP) (Aim 2)
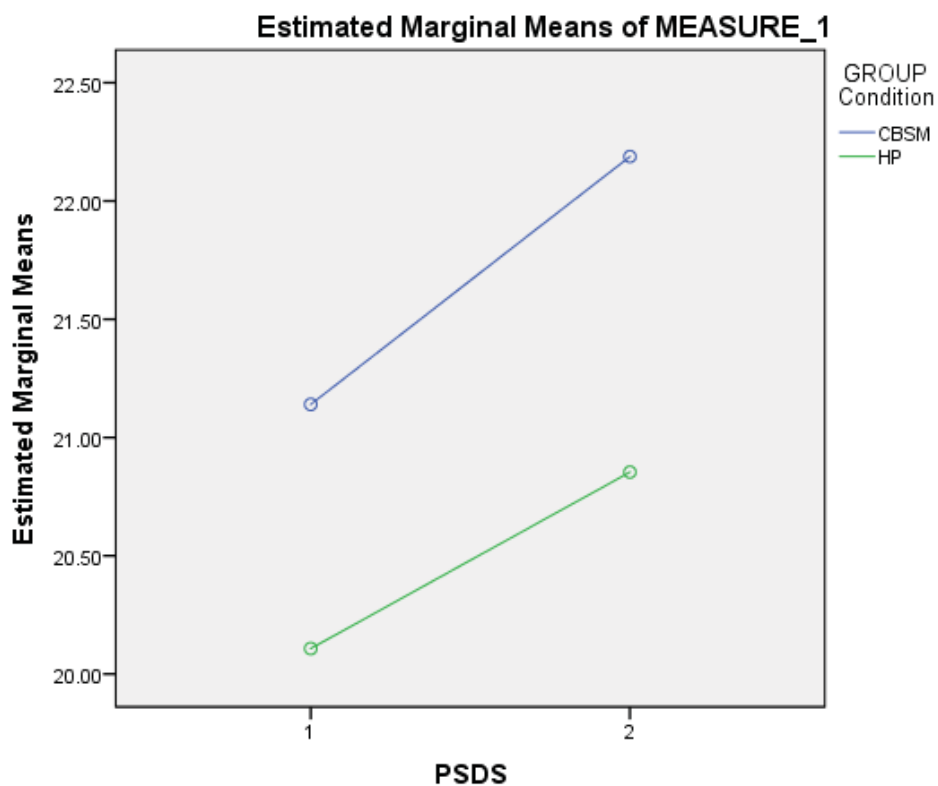
Multivariate Tests
PSDS*Group*Age*BMI $F_{(2, 114)}=1.04$, p=.36, partial $\eta^2= 0.02$
Within-Subject Effects
PSDS*Group*Age*BMI
$F_{(1, 114)}= 47.35$, p=.36, partial $\eta^2= 0.02$
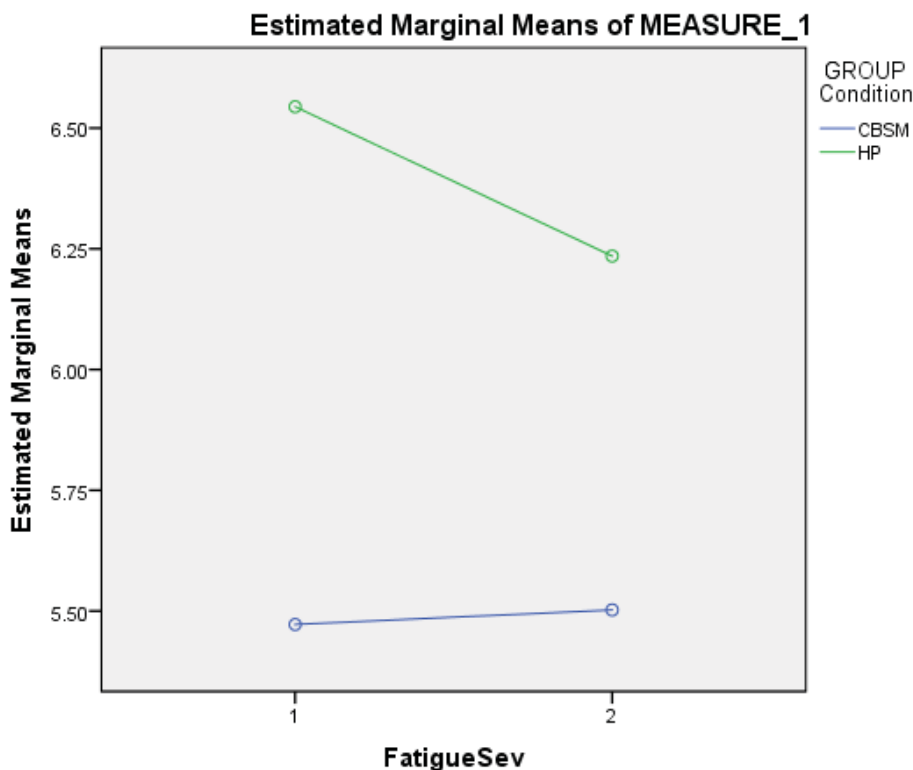Between-Subject Effects
$F_{(2, 114)}=1.00$, p=.37, partial $\eta^2= 0.01$
Pairwise Comparison (CBSM vs HP)
Mean Difference= -1.18, $F_{(1, 114)}=.88$, p=0.35, partial $\eta^2= 0.01$

Figure 12. Repeated Measures Analysis of Variance comparing Fatigue Severity scores at Baseline vs 5-month Follow-up by Condition (CBSM vs HP) (Aim 2)

Covariates appearing in the model are evaluated at the following values: What is your age? = 47.64, BMI = 27.6287

Multivariate Tests
Fatigue Severity*Group*Age*BMI $F(2, 106)$=.36, p=.70, partial η^2= 0.01
Within-Subject Effects
Fatigue Severity*Group*Age*BMI
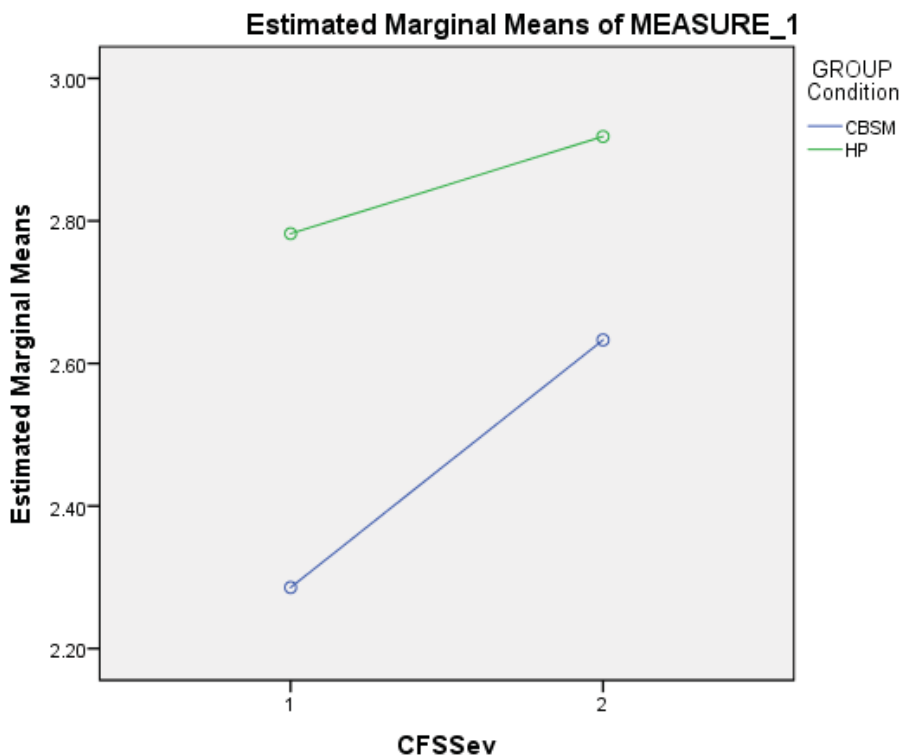$F(2, 106)$= .36, p=.70, partial η^2= 0.01
Between-Subject Effects
$F(1,106)$= .26, p=.77, partial η^2= 0.01
Pairwise Comparison (CBSM vs HP)
Mean Difference= -0.902, $F(1, 106)$=7.17, p=0.01, partial η^2= 0.06

Figure 13. Repeated Measures Analysis of Variance comparing CFS Symptom Severity scores at Baseline vs 5-month Follow-up by Condition (CBSM vs HP) (Aim 2)

Multivariate Tests
CFS Symptom Severity*Group*Age*BMI F(2, 116)=.90, p=.41, partial η^2= 0.02
Within-Subject Effects
CFS Symptom Severity*Group*Age*BMI
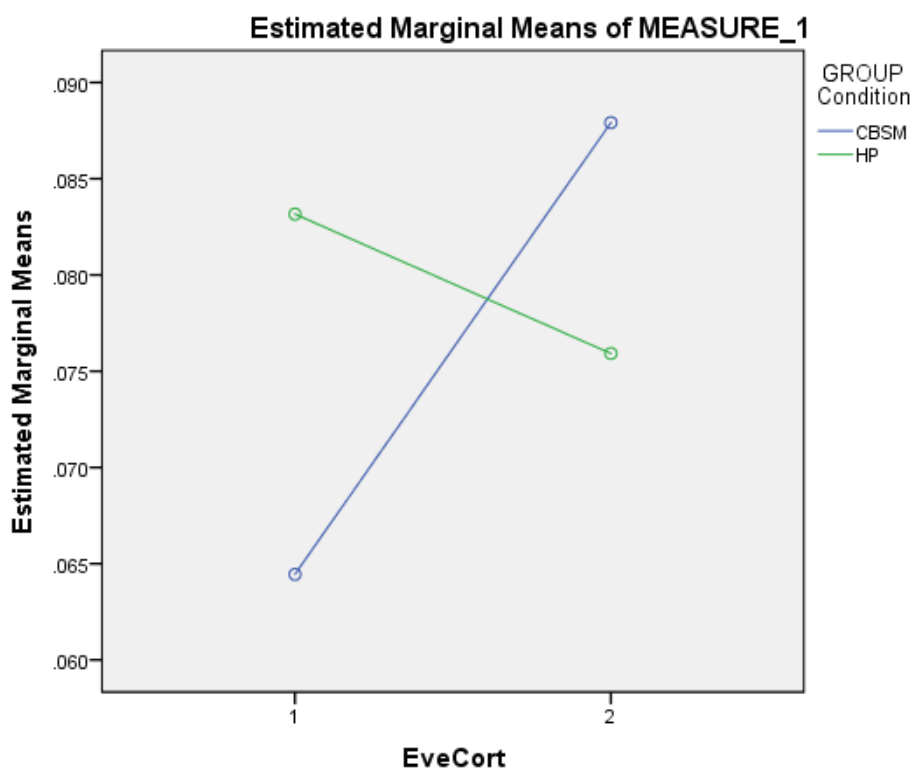F(2, 116)= .90, p=.41, partial η^2= 0.02
Between-Subject Effects
F(2,116)=1.23, p=.30, partial η^2= 0.02
Pairwise Comparison (CBSM vs HP)
Mean Difference= -0.39, F(1, 116)=9.90, p=.00, partial η^2= 0.058

Figure 14. Repeated Measures Analysis of Variance comparing Evening Cortisol levels at Baseline vs 5-month Follow-up by Condition (CBSM vs HP) (Aim 2)

Covariates appearing in the model are evaluated at the following values: What is your age? = 47.03, BMI = 27.6262

*Evening cortisol is ug/dL and log-transformed ln(x+1)
Multivariate Tests
Evening Cortisol*Group*Age*BMI F(2, 99)=.02, p=.98, partial η^2= 0.00
Within-Subject Effects
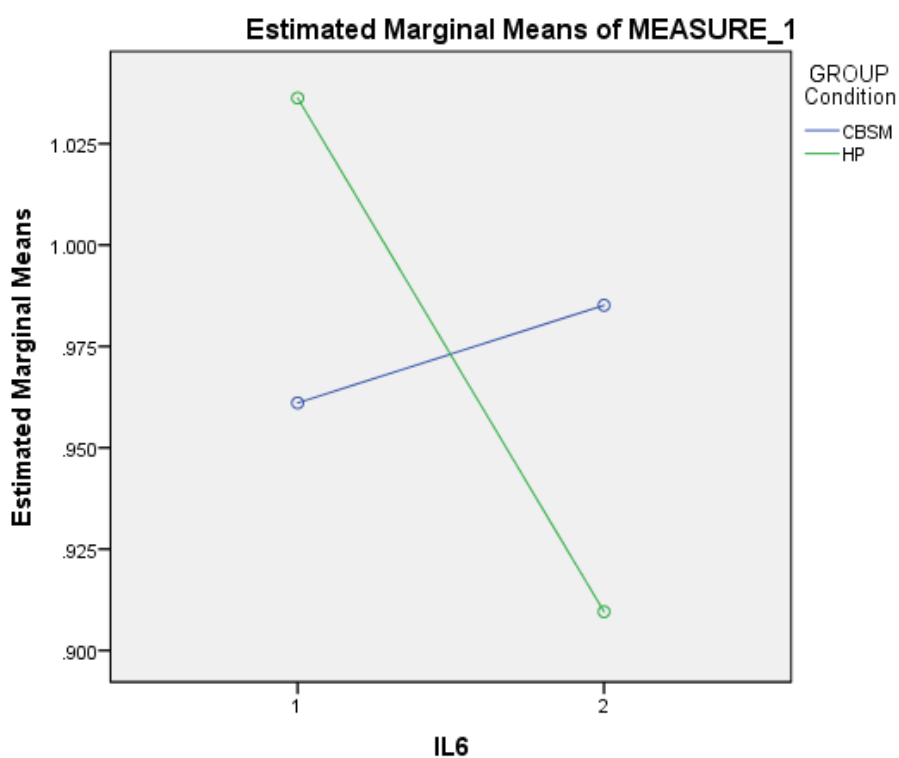Evening Cortisol*Group*Age*BMI
F(2, 99)= .02, p=.98, partial η^2= 0.00
Between-Subject Effects
F(2,99)=0.26, p=.77, partial η^2= 0.01
Pairwise Comparison (CBSM vs HP)
Mean Difference= -.003, F(1, 99)=.04, p=0.83, partial η^2= 0.00

Figure 15. Repeated Measures Analysis of Variance comparing Interleukin (IL)-6 levels at Baseline vs 5-month Follow-up by Condition (CBSM vs HP) (Aim 2)

IL-6 is pg/mL and log-transformed ln(x+1)
Multivariate Tests
IL-6*Group*Age*BMI F(2, 102)=.03, p=.97, partial η^2= 0.00
Within-Subject Effects
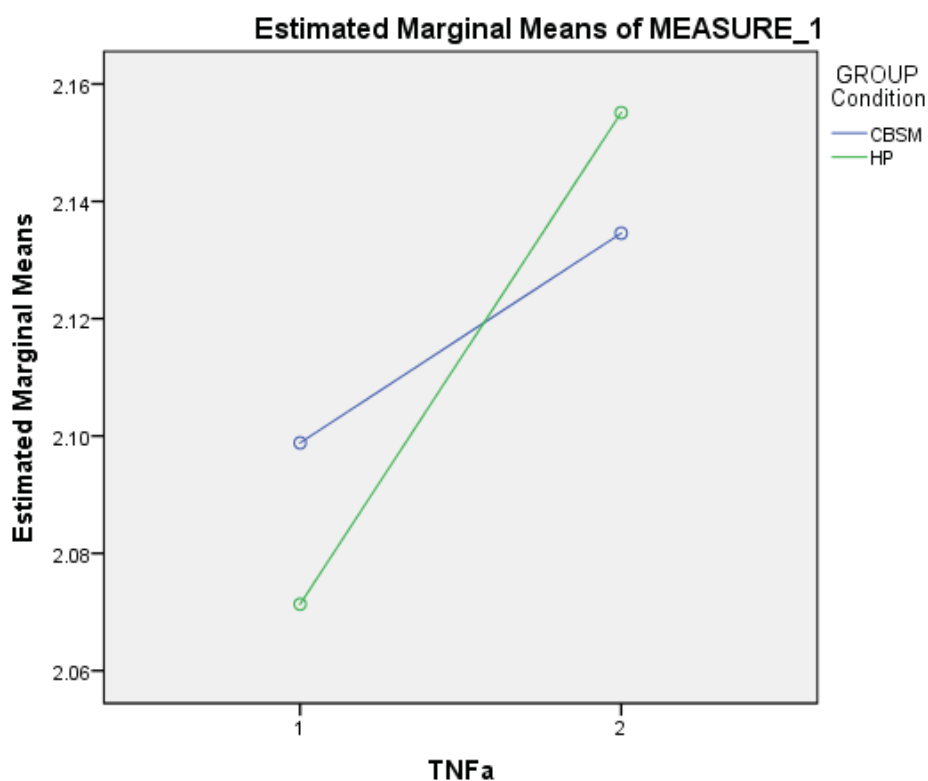IL-6*Group*Age*BMI
F(2, 102)= .03, p=.97, partial η^2= 0.00
Between-Subject Effects
F(2, 102)=0.62, p=.54, partial η^2= 0.01
Pairwise Comparison (CBSM vs HP)
Mean Difference= 0.00, F(1, 102)=0.00, p=1.00, partial η^2= 0.00

Figure 16. Repeated Measures Analysis of Variance comparing Tumor Necrosis Factor (TNF)-α scores at Baseline vs 5-month Follow-up by Condition (CBSM vs HP) (Aim 2)

TNF-α is pg/mL and log-transformed ln(x+1)
Multivariate Tests
TNF-α *Group*Age*BMI $F_{(2, 102)}$=.43, p=.65, partial η^2= 0.01
Within-Subject Effects
TNF-α *Group*Age*BMI
$F_{(2, 102)}$= .43, p=.65, partial η^2= 0.01
Between-Subject Effects
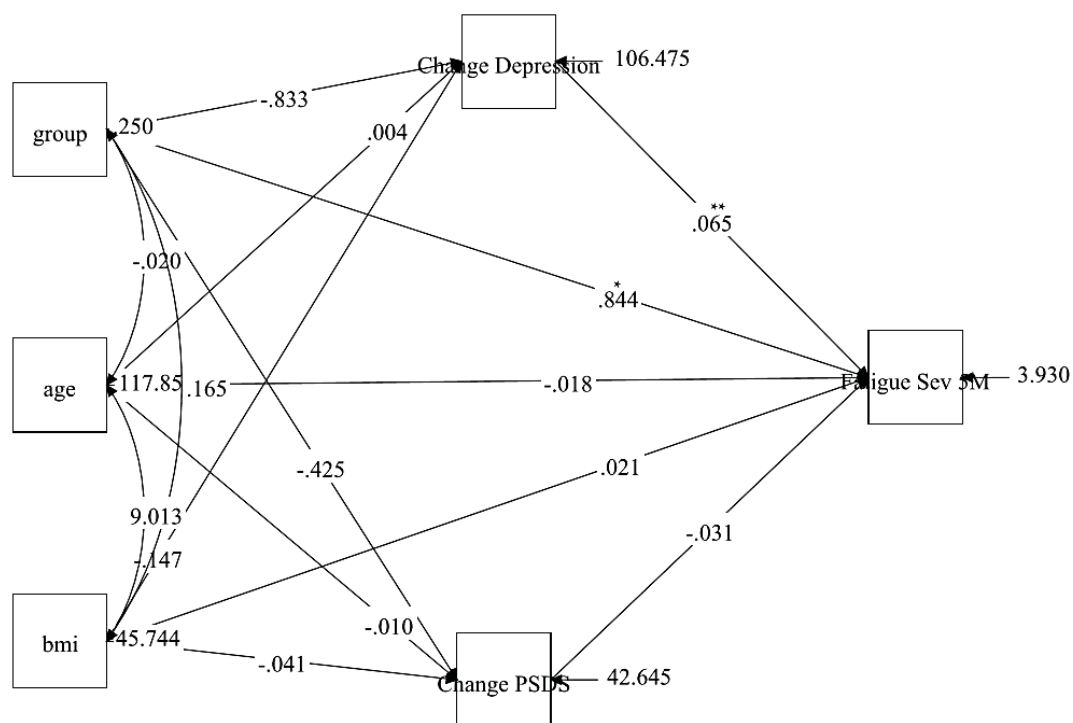$F_{(2,111)}$=0.63, p=.54, partial η^2= 0.01
Pairwise Comparison (CBSM vs HP)
Mean Difference= 0.00, $F_{(1, 102)}$=.001, p=0.97, partial η^2= 0.00
Repeated Measures TNF-α Per Condition

Figure 17. Structural Equation Model of Direct and Indirect Effects on Fatigue Severity at 5 Months (Aim 2)

Beta weights are shown within the path arrows
*p<0.05; **p<0.01

Figure 18. Structural Equation Model of Direct and Indirect Effects on Fatigue Severity
at 5 Months with Baseline Fatigue Severity as Covariate (Aim 2)

Beta weights are shown within the path arrows
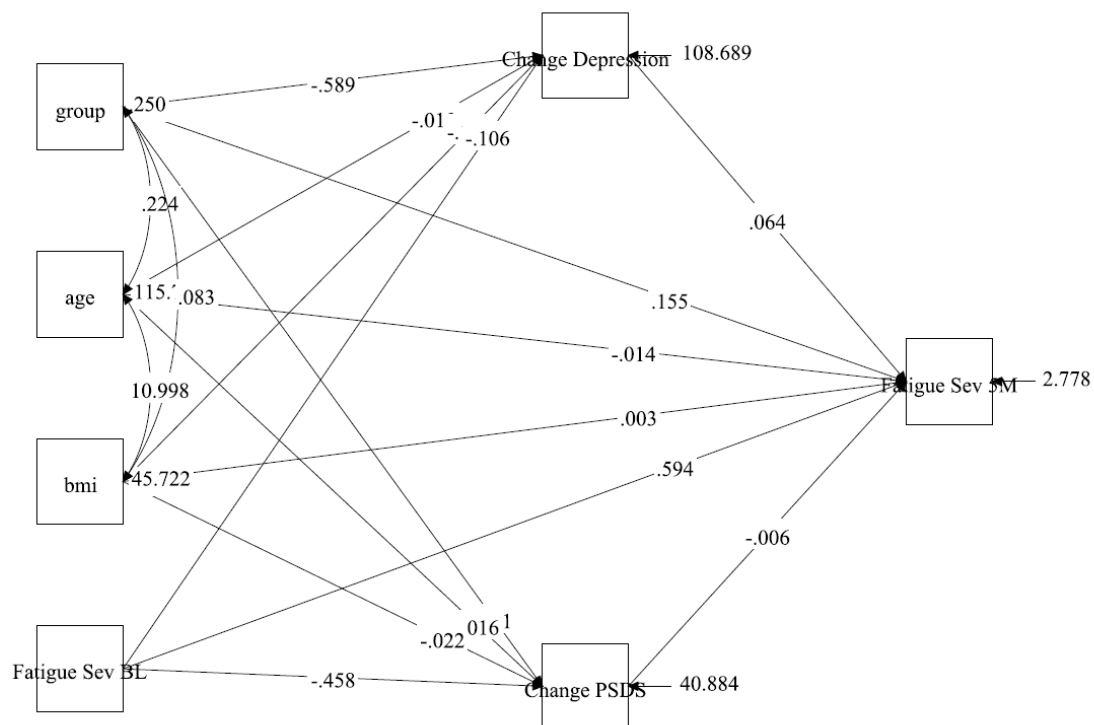*p<0.05; **p<0.01

Figure 19. Structural Equation Model of Direct and Indirect Effects on CFS Symptom
Severity at 5 Months (Aim 2)

Beta weights are shown within the path arrows
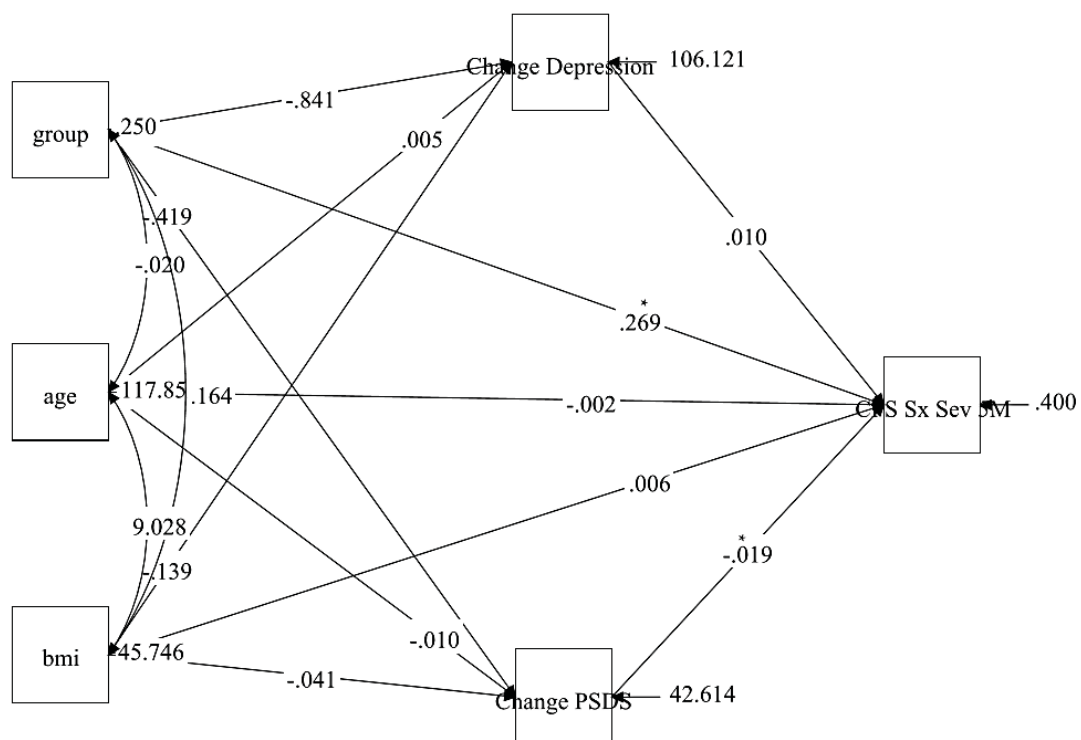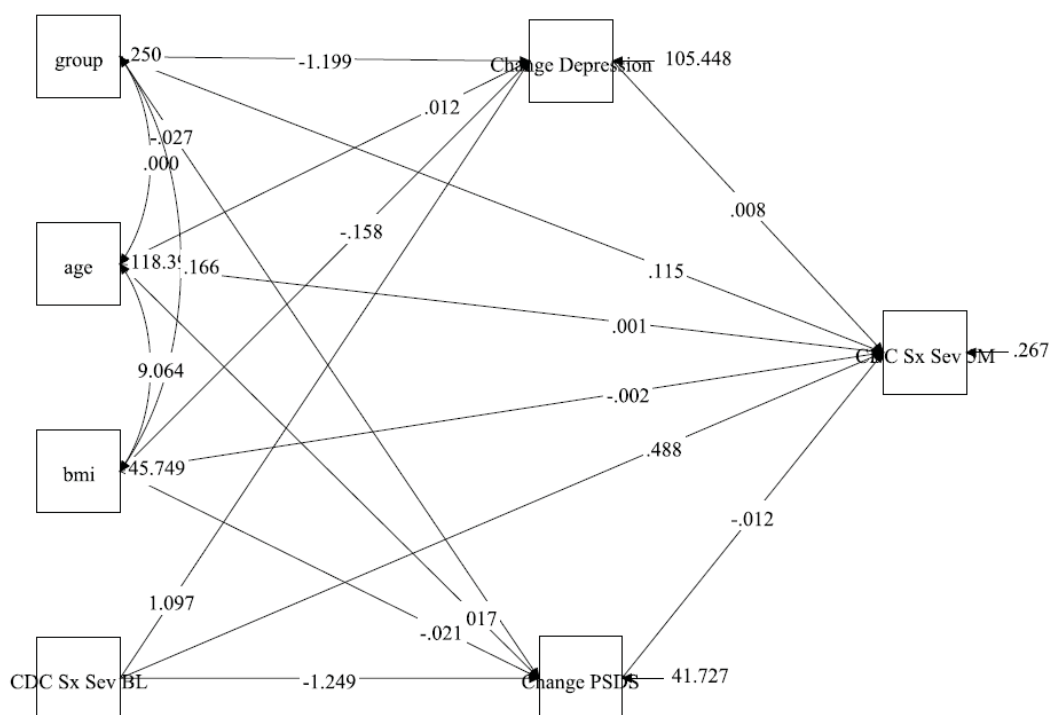*p<0.05; **p<0.01

Figure 20. Structural Equation Model of Direct and Indirect Effects on CFS Symptom
Severity at 5 Months with Baseline CFS Symptom Severity as Covariate (Aim 2)

Beta weights are shown within the path arrows
*p<0.05; **p<0.01

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