

2011-08-02

# Benefits of Physical Activity on Depression and Functional Quality of Life During Treatment for Breast Cancer: Psychosocial Mechanisms.

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UNIVERSITY OF MIAMI

BENEFITS OF PHYSICAL ACTIVITY ON DEPRESSION AND FUNCTIONAL  
QUALITY OF LIFE DURING TREATMENT FOR BREAST CANCER:  
PSYCHOSOCIAL MECHANISMS

By

Jamie M. Stagl

A THESIS

Submitted to the Faculty  
of the University of Miami  
in partial fulfillment of the requirements for  
the degree of Master of Science

Coral Gables, Florida

August 2011

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Benefits of Physical Activity on Depression  
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Treatment for Breast Cancer:  
Psychosocial Mechanisms.

(M.S., Psychology)  
(August 2011)

Abstract of a thesis at the University of Miami.

Thesis supervised by Professor Michael H. Antoni.  
No. pages in text. (102)

Women who are post surgery for breast cancer (BCa) experience distressing side effects that negatively influence Quality of Life (QoL). Physical activity (PA) following a BCa diagnosis is associated with decreased mortality, reduced recurrence, increased functional capacity, less fatigue, and may improve depression and QoL. Furthermore, evidence suggests that a combined PA and psychotherapy intervention may reduce physically and emotionally distressing side effects associated with diagnosis and treatment. The purpose of the study is to examine relationships among PA, fatigue, clinician-rated depression, depressed mood, and QoL in women after undergoing surgery for BCa and to assess the continuity of these relationships as they move through adjuvant treatment. In addition, the study investigates whether fatigue is an underlying psychosocial mechanism accounting for the effects of PA on study outcomes. Finally, given prior evidence that participation in a Cognitive-Behavioral Stress Management (CBSM) intervention was associated with reduced fatigue, the study assesses whether women who were physically active showed less fatigue above and beyond the effects of CBSM. Women (N=240) with non-metastatic stage 0-III BCa were recruited 2-10 weeks post-surgery and randomized to either a CBSM intervention group or a psycho-educational control group. Physical activity, fatigue, functional QoL, rated depression,

and depressed mood were assessed at the baseline and 3-month post intervention time points. Structural equation modeling was used to test hypotheses. At baseline, results revealed that greater PA was associated with less fatigue-related daily interference (FRDI), and that less FRDI was associated with greater functional QoL, lower rated depression, and less depressed mood. Furthermore, lower FRDI was a pathway by which greater PA was associated with greater functional QoL, less rated depression, and less depressed mood. These relationships were similar at the 3-month post intervention time point and when difference scores were used in the model. Finally, PA contributed significantly to the change in FRDI above and beyond the effects of participation in CBSM. A combined PA and CBSM intervention may be effective in reducing FRDI, and improving depressive symptoms and QoL for women after surgery for BCa and during adjuvant treatment, and should be investigated in future studies.

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## CHAPTER 1: Summary

Background: Women who have recently undergone surgery for non-metastatic breast cancer experience distressing side effects associated with treatment that negatively affect Quality of Life (QoL). These symptoms, such as fatigue, pain, sleep difficulties, anxiety, and depression, may be managed or alleviated through enhanced physical activity (PA) and psychosocial interventions. Evidence suggests that PA following a diagnosis of breast cancer is associated with decreased mortality, reduced risk of recurrence, increased functional capacity, less fatigue, and may improve mental health outcomes related to depression and QoL. As a result, recent research has moved towards investigating the benefits of a PA intervention for women with breast cancer and exploring potential biopsychosocial mechanisms by which PA improves QoL. Furthermore, some evidence suggests that a combined PA and psychosocial intervention may be beneficial in reducing both physically and emotionally distressing side effects associated with diagnosis and treatment.

Objective: The purpose of the study was to examine the relationships between PA, fatigue, clinician-rated depression (rated depression), depressed mood, and QoL in women who recently completed surgery for breast cancer and to assess the continuity of these relationships as they move through treatment. The study aimed to evaluate these causal relationships in a statistical path model based on prior theory. An additional objective of the study was to identify plausible psychosocial mechanisms, by determining whether level of fatigue is a pathway by which PA, depression, and QoL are associated. Finally, given prior evidence that participation in the Cognitive-Behavioral Stress

Management (CBSM) intervention group was associated with reduced fatigue, the study aimed to assess whether women who were physically active showed less fatigue above and beyond the effects of CBSM.

Methods: Women (N=240) with non-metastatic stage 0-III breast cancer were recruited 2-10 weeks post-surgery and randomized to either the CBSM intervention group or the psycho-educational control group. Women were assessed prior to randomization and 3-months post intervention. Measures included a Seven Day Physical Activity Recall Questionnaire, Fatigue Symptom Inventory, Affects Balance Scale, Hamilton Rating Scale for Depression, and the Functional Assessment of Cancer Therapy for Breast Cancer. Structural Equation Modeling was used to test study hypotheses at the baseline and 3-month post intervention assessment time points as well as changes between these time points.

Results: At baseline, tests of the model revealed that there was a direct association such that greater PA was associated with less fatigue-related daily interference (FRDI), and that lower FRDI was associated with greater functional QoL, less rated depression, and less depressed mood. Furthermore, there was an indirect association between greater PA and greater functional QoL, less rated depression, and less depressed mood via lower FRDI. The relationships in this model were consistent at the 3-month post intervention time point. Furthermore, the model was stable when baseline to 3-month change scores were used in place of the cross-sectional variables. Finally, PA contributed significantly to the change in FRDI above and beyond what was accounted for by participation in the CBSM group.

Conclusions: Physical activity is related to reduced cancer-related fatigue interference, improved depressive symptoms and increased QoL for women after surgery for breast cancer. In addition, PA may continue to be beneficial as women move through adjuvant treatment. Furthermore, reduced FRDI is a potential mechanism by which PA improves QoL and attenuates depression. A combined PA and CBSM intervention may have added benefit, and should be investigated in future studies.

Keywords: Physical activity, Quality of Life, Fatigue, Depression, Breast Cancer

## CHAPTER 2: Introduction

According to the Centers for Disease Control and Prevention (CDC, 2005), breast cancer is the second most common type of cancer found in women. The most recent report from the United States Cancer Statistics (2005) revealed that 186,467 women were diagnosed with breast cancer in 2005 alone. Due to medical and scientific advances, survival rates have increased, although risk for recurrence remains high (Dixon & Montgomery, 2008). The etiology of cancer can be associated with a multitude of factors, including, but not limited to lifestyle choices, genetic predispositions, and environmental exposure (Hoffman-Goetz et al., 1998). The International Agency for Research on Cancer has estimated that 25% of all cancer cases can be linked to an inactive lifestyle (Cambell & McTiernan, 2007). An increased risk for breast cancer is associated with lack of physical activity (PA), but this risk factor can be modified (Friedenreich, 2001). In 1999, the U.S. Surgeon General's Report stated that over 60% of women in the U.S. do not meet the recommended guidelines for PA. In fact, the report showed that more than 25% of women were physically inactive, and a sedentary lifestyle is more common in women than in men. Accordingly, the American Cancer Society (ACS, 2009) has established exercise guidelines to help reduce risk for cancer, advising adults to engage in a minimum of 30 minutes of moderate or vigorous exercise on at least 5 days per week. The ACS guidelines are in conjunction with those of the American College of Sports Medicine (ACSM, 2007), which outline that 30 minutes of exercise per day, 5 days a week will reduce risk for chronic disease in adults. Despite evidence that a physically active lifestyle may be protective and beneficial, research has shown that PA levels drop drastically following a breast cancer diagnosis (Courneya & Friedenreich, 2007) and

decline from pre-diagnosis to active treatment (Courneya & Friedenreich, 1997). One study in particular demonstrated that women newly diagnosed with ductal carcinoma-in-situ (DCIS) were mostly inactive, with majority of women engaging in vigorous activity infrequently, and only half engaging in exercise more than twice per week (Ligibel et al., 2009). Moreover, the largest decrease in PA has been noted in women treated with both radiation and chemotherapy, as opposed to women who received radiation alone or only underwent surgery (Irwin et al., 2003), suggesting that the decline in activity may be due to side effects of treatment. In turn, researchers have begun to investigate exercise interventions in breast cancer populations in an effort to establish safety, feasibility, and mental and physical health outcomes. This study will contribute to the growing research base by examining relationships among PA, fatigue, Quality of Life (QoL), and depression after breast cancer diagnosis and during active treatment.

The rationale for studying PA as it relates to psychological outcomes in women with breast cancer is supported by studies investigating relationships between: a) physiological and psychological benefits of PA and b) physiological and psychological benefits of PA in breast cancer. More specifically, literature is discussed that outlines relationships in breast cancer between: c) PA and fatigue, d) PA and depression/QoL, and e) fatigue and depression/QoL. Finally, research is presented that examines whether PA in addition to a group-based psychosocial intervention is beneficial for women undergoing active treatment for breast cancer.



## **Physiological and Psychological Benefits of Physical Activity**

Although the terms ‘physical activity’ and ‘exercise’ are used interchangeably in the literature, they are defined differently. PA is “any bodily movement produced by skeletal muscles that results in energy expenditure... PA in daily life can be categorized into occupational, sports, conditioning, household, or other activities.” Alternatively, exercise is a “subset of PA that is planned, structured, and repetitive and has a final or an intermediate objective in the improvement or maintenance of physical fitness” (Caspersen, Powel, & Christenson, 1985). In research, both PA and exercise are measured in terms of duration, frequency, intensity (low, moderate, vigorous/high), chronicity, and mode (Woods, Davis, Mayer, Ghaffar, & Pate, 1993).

The effects of both PA and exercise have been studied in detail, and beneficial outcomes have been noted for both healthy and chronically ill populations. Leon (1985) discusses the well-supported finding that cardiovascular functioning is improved by exercise and PA, and increased exercise is associated with decreased risk for coronary heart disease (as cited in LaPerriere et al., 1994, p. 182). According to the ACSM, it has been established that people who are physically active live healthier and longer lives than those who are sedentary. Regular PA contributes significantly to weight loss, diet maintenance, lower blood pressure, improved lipid profiles, denser, stronger bones, and glucose regulation (ACSM, 2005). Studies evaluating behavioral mechanisms to complement HIV treatment have increased, with some providing evidence for a delay in immune decrements due to a moderate exercise routine (LaPerriere et al., 1994). PA is important in aging populations, specifically for joint flexibility, aerobic endurance, and

muscle strength (Fletcher et al., 1996). Literature describes the benefits of PA as protective against disease, referring to the increase in activity and quantity of innate immune cells, such as macrophages, cytotoxic T-lymphocytes, and natural killer (NK) cells, following bouts of exercise (Moldoveanu & Shepard, 1995). However, more research is needed to determine to what extent these contribute to disease and health outcomes.

Evidence is strong for associations of PA and exercise with improvements in mental health and psychological functioning (Morgan, 1984; Morgan & Goldston, 1987). Cross-sectional studies have shown that individuals who lead active lifestyles exhibit less anxiety and depressive symptoms (LaFontaine et al., 1992; Lobstein, Mosbacher, & Ismail, 1983) and have better overall life adjustment (Eysenck, Nias, & Cox, 1982). Longitudinal intervention studies have demonstrated that an active lifestyle can alleviate depressive symptoms in healthy men (Blumenthal, Emery, Madden, & George, 1989), cardiac patients with depression (Kavanagh, Shephard, Tuck, & Qureshi, 1977), and individuals with major depressive disorder (Martinsen, Medhus, & Sandvik, 1985; Martinsen, 1987). Both cross-sectional and longitudinal studies have found that physically active individuals show an attenuated cardiovascular response when exposed to mental stress (Crews & Landers, 1987, Blumenthal et al., 1990). Exercise has been shown to improve self-esteem, body image (Ginsberg, 2010), and self-confidence (McAuley, Blissmer, Katula, Duncan, & Mihalko, 2000; Nelson, 1991; Folkins & Sime, 1981). Interestingly, Berlin and colleagues (2006) conducted a study that examined changes in psychological well-being upon exercise withdrawal. Results revealed that

regular exercisers who decreased exercise frequency experienced increased fatigue, elevated depression, and increased negative mood (Berlin, Kop, & Deuster, 2006).

### **Role of Physical Activity in Breast Cancer**

Among the most prevalent and intense symptoms associated with breast cancer treatment are fatigue, sleep difficulties, pain, anxiety, and depression (Mock et al., 1997; Badger et al., 2004; Thornton, Andersen, & Blakely, 2010). Intervention research has shown that PA may ameliorate physical and psychological symptoms associated with cancer diagnosis and treatment (Courneya & Friedenreich, 1999; Pinto, Clark, Maruyama, & Feder, 2003; Pinto & Maruyama, 1999; Daley et al., 2007). In addition, strong epidemiological studies support the relationship between PA and decreased risk of cancer, particularly for colorectal cancer and postmenopausal breast cancer (Friedenreich & Orenstein, 2002). In addition, PA intervention studies have evaluated outcomes of established biomarkers for cancer risk, and randomized controlled trials have targeted those biomarkers that relate specifically to breast cancer (Campbell & McTiernan, 2007). Furthermore, observational studies have shown that exercise at a moderate intensity is associated with reduced breast cancer recurrence and mortality in women with previous diagnoses of invasive breast cancer (Harris, 2009). Overall, evidence is mounting in support of reduced risk of death from breast cancer for women who were physically active following diagnosis (Irwin et al., 2008, Holmes, Chen, Feskanich, Kroenke, & Colditz, 2005; Holick et al., 2008). Research has shown that PA can affect biological processes associated with preventing the initiating and progressive events in cancer. For instance, exercise has been shown to reduce pro-inflammatory components and attenuate

chronic inflammation. Furthermore, the innate immune response is enhanced through exercise by way of increased natural killer cell and macrophage activity (Rogers, Colbert, Greiner, Perkins, & Hursting, 2008). As a result of this increasing support for considering the role of PA in oncology, the ACS (2009) has put forth a list of benefits to encourage cancer patients to engage in moderate exercise. ACS states that exercise will help cancer patients by preventing muscles from wasting, decreasing symptoms of fatigue, enhancing QoL, maintaining balance, and lowering risk of heart disease (ACS, 2009).

More specifically, a structured exercise program for women with stage I and II breast cancer found that exercise provided protective effects against the usual loss of physical functioning during treatment (Segal et al., 2001). In addition, studies have found increased physical functioning and decreased fatigue and emotional distress in women undergoing radiation therapy who participated in an exercise or home-based walking program (Mock et al., 1997). Furthermore, a study for older women with breast cancer revealed that participants in the exercise intervention group showed significantly improved sleep quality, as compared with the usual care control group (Payne, Held, Thorpe, & Shaw, 2008).

Although further investigation is needed to determine whether the inverse relationship between cancer risk and PA is brought about by increased immune function, studies have demonstrated immunostimulatory effects in breast cancer patients following bouts of exercise (Lee, 1995). Women undergoing treatment for breast cancer who participated in an exercise intervention showed greater proliferation and activation of CD4 and CD69+ T-helper cells (Hutnick et al., 2005), and elevated NK cell and

monocyte cell counts (Peters, Lötzerich, Niemeier, Schüle, & Uhlenbruck, 1994). Researchers suggest that these immunostimulatory responses may have a protective effect against secondary infections, metastasis, and recurrence, following treatment-induced immunosuppression. Many studies suggest that exercise may be influential in increasing survival post-cancer treatment, as a result of improved immune function (Pinto & Floyd, 2007).

PA is beneficial for breast cancer survivors as well, who often continue to experience physical and emotional distress following treatment (Basen-Engquist, Hughes, Perkins, Shinn, & Taylor, 2008). In these women, exercise interventions have been shown to improve physical performance, functional capacity (Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997) and fatigue (Mock et al., 1997; Courneya et al., 2003). In addition, findings support positive effects from PA on body image (Pinto et al., 2003), psychological adjustment (Mock et al., 1997; Daley et al., 2007), pain (Basen-Engquist et al., 2006), and QoL in breast cancer survivors (Basen-Engquist et al., 2006; Daley et al., 2007). A systematic review of randomized controlled trials for both breast cancer survivors and patients provided strong support for improved cardiorespiratory fitness, QoL, physical functioning, and fatigue (McNeely et al., 2006). To elaborate on the most prevalent treatment-related symptoms, the following sections outline specific relationships among PA, fatigue, depression, and functional QoL.

## Physical Activity and Fatigue

Cancer-related fatigue is among the most frequent and intense of symptoms reported by women undergoing treatment for breast cancer (Mock et al., 1997; Jacobsen et al., 1999; Wagner & Cella, 2004; Longman, Braden, & Mishel, 1996). The National Comprehensive Cancer Network Cancer-Related Fatigue Clinical Practice Guidelines in Oncology defines cancer-related fatigue as a “distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” (Mock et al., 2007). The severity of a woman’s fatigue influences her ability to engage in daily tasks and activities (Berger, 1998) and is not alleviated with rest (Glaus, Crow, & Hammond, 1996). Clinical practice guidelines endorse activity enhancement as a category 1 recommendation to alleviate fatigue in individuals undergoing cancer treatment, stating that exercise as a non-pharmacological treatment for fatigue has the strongest supporting evidence (Mustian, Katula, & Gill, 2002; Mitchell, Beck, Hood, Moore, & Tanner, 2007; Conn, Hafdahl, Porock, McDaniel, & Nielsen, 2006). Specifically, a systematic review and meta-analysis of PA intervention research revealed statistically significant reductions in fatigue for women with breast cancer (McNeely et al., 2006). In fact, Goedendorp and colleagues (2008) conducted research examining factors contributing to fatigue after diagnosis and prior to and during cancer treatment (Goedendorp, Gielissen, Verhagen, Peters, & Bleijenberg, 2008). Results revealed that level of PA was the primary contributing factor to levels of fatigue both prior to and during treatment. Given the strong evidence,

researchers have stated that therapeutic aerobic activity for cancer patients should be treated as a prescription for primary fatigue (Dimeo, Rumberger & Keul, 1998).

The literature suggests that while toxic treatments and decreased activity can lead to a decrease in physical performance, functional capacity can be increased or maintained through an exercise training program (Mock et al., 2005). This increase, in turn, leads to less effort expenditure in daily tasks and decreased subjective fatigue (ACSM, 2005; Mock et al., 2005). There have been an increasing number of studies conducted in women undergoing active treatment for breast cancer that evaluate the effects of PA on fatigue. An individual, home-based, self-paced walking program illustrated increased physical functioning and decreased fatigue in women undergoing radiation therapy (Mock et al., 1997). Another home-based aerobic exercise program for women undergoing chemotherapy treatment revealed reduced fatigue and maintenance of functional ability. In fact, these researchers illustrated that there was a dose-dependent relationship such that as the number of minutes spent exercising increased, fatigue levels decreased (Schwartz, Mori, Gao, Nail, & King, 2001). In addition, women receiving high dose chemotherapy who participated in a hospital exercise program experienced decreased fatigue and an improvement in psychological distress (Dimeo, Stieglitz, Novelli-Fischer, Fetscher, & Keul, 1999). To clarify the mechanism by which exercise improves cancer-related fatigue, Courneya and colleagues purport that biopsychosocial processes related to coping ability and self-efficacy are enhanced during exercise and PA. This, in turn, may lead to participation in daily activities and lower subjective experience of fatigue (Courneya, 2003). Overall, exercise interventions and PA, whether home-based

or group-based, have been shown to positively influence fatigue levels in breast cancer survivors and in women undergoing active breast cancer treatment.

### **Physical Activity and Quality of Life**

The concept of QoL is defined as “an appraisal of and satisfaction with one’s current level of functioning compared to what one believes is possible or ideal” (Cella & Cherin, 1988). In order to measure QoL in terms of life satisfaction and overall well-being, the construct is conceptualized in multiple domains of functioning: physical, functional, emotional, and social (Cella & Tulsky, 1990). Interestingly, the domain of functional QoL has been shown to have the strongest association with overall life satisfaction (Courneya & Friedenreich, 1997). Studies have shown that cancer treatment significantly affects QoL and impairs functional capacity (Courneya & Friedenreich, 1999). The ACS (2009) asserts that the evidence base is growing in support for exercise as an accepted intervention for QoL in cancer survivors.

Research suggests that exercise and PA are potentially beneficial in increasing QoL during and after treatment for breast cancer (Kirshbaum, 2007). A combined aerobic and resistance training intervention was found to improve QoL in breast cancer survivors (Milne, Wallman, Gordon, & Courneya, 2008a, 2008b). A study of breast cancer survivors, which compared an exercise therapy group to a usual care control group, found significant improvements in the women in the exercise group in QoL domains including social/family well-being, functional well-being, and the breast cancer subscale of the Functional Assessment of Cancer Therapy-Breast scale. Moreover, maintenance of PA



following a breast cancer diagnosis has been strongly associated with QoL (Pinto & Maruyama, 1999; Kramer et al., 2000; Chang et al., 1998). Studies have increasingly tested the effects of exercise interventions for women undergoing active breast cancer treatment, finding that PA sustains and increases functional capacity and improves QoL (Mock et al., 2005, Holmes et al., 2005; McNeely et al., 2006). A retrospective study, which questioned breast cancer survivors about their exercise patterns during treatment, found that exercising during active treatment was linked to better QoL and life satisfaction. Furthermore, this group found that women who maintained their activity levels at pre-diagnosis, active treatment, and post-treatment had better QoL and life satisfaction than those who were inconsistent in their exercise routine (Courney & Friendenreich, 1997). An exercise trial examining aerobic and resistance exercise during active chemotherapy in breast cancer patients found that those who reported regular continued exercise at the follow-up assessment also reported better QoL (Courneya, et al., 2007). However, a paucity of research exists in the area of PA and QoL in breast cancer survivors and especially in breast cancer patients undergoing active treatment.

### **Physical Activity and Depression**

Depression is among the most frequent and intense symptoms reported by women undergoing treatment for breast cancer (Mock et al., 1997). Depressive symptoms experienced as a result of cancer diagnosis and treatment include lowered mood, low self-esteem, hopelessness, loss of appetite, loss of weight, loss of energy, and constant tiredness (Tait, 1991). A review of the literature showed that breast cancer patients develop psychological distress that relates to depression, and this distress contributes

directly to lower QoL (Montazeri, 2008). In fact, previous work has demonstrated that more depressed breast cancer patients have worse health outcomes overall related to QoL and disease progression (Spiegel & Giese-Davis, 2003).

Some work has attempted to use PA interventions to minimize depression in other populations. Reviews and studies have documented significant improvements in depressive symptoms following increased PA and exercise among healthy volunteers (Ernst, Rand, & Stevinson, 1998; Byrne & Byrne, 1993; Mutrie, 2000). A meta-analysis found that depression improved in healthy adults whether they were engaged in a supervised or unsupervised PA intervention (Conn, 2010). In a sample of individuals who were clinically depressed, an inverse relationship was found between the level of PA and depression (Pelham et al., 1993). In addition, a review demonstrated the effects of both acute and chronic exercise in relation to reduction in depression, independent of the chosen mode of exercise (North et al., 2008). A systematic review reported that PA is effective in alleviating depressive symptoms in older, depressed individuals (Blake, Mo, Malik & Thomas, 2009; Pinquart, Duberstein, & Lyness, 2007). Observational studies have demonstrated that greater PA is associated with fewer depressive symptoms in obese breast cancer survivors (Yeter et al., 2006). Furthermore, research has suggested that PA may improve overall mood, and levels of fitness may be inversely related to depression (Kirshbaum, 2005). Segar and colleagues (1998) showed that breast cancer survivors who participated in an aerobic exercise program had significantly less depression over time, as compared to the usual care control group. An additional study revealed that breast cancer survivors who were regular exercisers reported significantly

less depression and total mood disturbance (Pinto & Trunzo, 2004). Daley and colleagues (2007) demonstrated that women who participated in an exercise therapy group had significantly less depression compared to the usual care group at both the post-intervention and 6-month follow-up assessments (Daley et al., 2007).

Although the literature is expanding with regard to PA interventions for breast cancer survivors, researchers suggest more evidence is needed to support these effects in women following breast cancer surgery (Segar et al., 1998). A Cochrane review concluded that more research is needed to determine the influence of PA on mood disturbances in women receiving adjuvant therapy for breast cancer (Markes, Brockow, & Resch, 2006). Moreover, little research has investigated the possible mechanisms by which depressive symptoms may be reduced through PA (Conn, 2010). Authors have suggested that the mechanisms which may account for reduced depression in response to exercise are likely an interaction of many neurobiological and psychological factors (Ströhle, 2009; Conn, 2010). In part, the exercise-induced mood elevation is due to an increased release of endogenous opiates such as  $\beta$ -endorphin (LaPerriere et al., 1994). Interestingly, research suggests that the endogenous opiates which are elevated during exercise have positive effects on immune function (LaPerriere et al., 1994). Other proposed physiological mechanisms include brain neurotransmitters, cerebral blood flow, anti-inflammatory cytokines, and hypothalamic-pituitary-adrenal axis function (Deslandes et al., 2009; Daley, 2008). Proposed psychological explanations include improved self-efficacy, self-esteem, behavioral activation, self-determination, and sense of achievement/mastery (Martinsen, 2008; Daley, 2008; Lawlor & Hopler, 2001). With

cancer specifically, it has been hypothesized that the lack of participation in meaningful activities adversely affects QoL and functional capacity, thereby influencing depressive symptoms (Pinto et al., 2003). Overall, more research is needed to delineate the processes by which PA may reduce depressive symptoms.

### **The Role of Fatigue in QoL and Depression**

Cancer-related fatigue interferes with daily functioning and causes severe emotional distress for patients prior to, during, and after cancer treatment (Mock et al., 2007; Jacobsen et al., 1999). Research provides evidence for a relationship between fatigue and depressive symptoms (Patrick et al., 2003). In fact, depression and fatigue are commonly grouped together in a symptom cluster related to cancer and cancer treatment (Thorton et al., 2010; Cleeland et al., 2003). Clinical practice guidelines from the National Comprehensive Cancer Network state that elevated fatigue levels may be a causal factor of high emotional distress, especially when functional status is impaired and participation in valued roles is lessened (Mock et al., 2007). The Fatigue Coalition reported that patients who experienced fatigue on a daily basis were significantly more likely to report depressive symptoms than those who experienced fatigue less frequently. As a result of fatigue, these patients reported decreased interest in daily activities, feelings of sadness, difficulty concentrating, and increased irritability (Curt et al., 2000). A study specifically in patients with lung cancer found that approximately one-third of the sample reported depression. Furthermore, this study found fatigue to be a significant independent predictor of depression (Hopwood & Stephens, 2000). A cross-sectional study in women undergoing treatment for breast cancer reported a symptom cluster in

which fatigue and depression were highly correlated. Furthermore, this group found that QoL was influenced by fatigue indirectly (via depression) and directly (So et al., 2009). Thus, while research has documented the prevalence of fatigue in cancer patients, an increasing amount of research has studied the specific effects of fatigue on QoL (Curt et al., 2000; Barsevick, Whitmer, & Walker, 2001). A systematic review illustrated that psychological distress contributes significantly to decreased overall QoL in breast cancer patients (Montazeri, 2008). Many studies in women with primary breast cancer have suggested that fatigue has the strongest and largest influence on overall QoL (Byar, Berger, Bakken, & Cetak, 2006; Arndt, Stegmaier, Ziegler, & Brenner, 2006; Janz et al., 2007). Given the role of fatigue in QoL, the Fatigue Coalition supports further investigation of approaches to reduce fatigue with an end result of improving QoL (Curt et al., 2000).

### **Psychosocial Interventions for Fatigue, Depression, and QoL**

The National Cancer Policy Board of the Institute of Medicine Studies advocates for the implementation of psychosocial services for women with breast cancer, based on randomized controlled trials that have demonstrated that psychological interventions are efficacious in decreasing stress and managing symptoms and side effects from treatment (Herdmann, & Holland, 2004). Psychosocial interventions for women undergoing treatment include psycho-educational groups, cognitive-behavioral methods, individual and group psychotherapy, and complementary interventions. A review of the literature provided support for the positive effects of psychosocial interventions on the psychological outcomes of cancer patients (Andersen, 1992). A meta-analysis conducted

by Meyer and Mark (1995) provided further support for this finding, reporting strong effect sizes for all categories of psychosocial interventions for cancer patients, including cognitive-behavioral therapy, relaxation training, and counseling.

The National Comprehensive Cancer Network reported that psychosocial interventions are a category 1 non-pharmacological intervention to reduce fatigue for patients during active cancer treatment (Mock et al., 2007). Psychosocial interventions found to reduce cancer-related fatigue have addressed stress management and coping techniques (Jacobsen, 2002; Vargas et al: submitted for publication). In addition, one study found that cancer patients experienced a reduction in their levels of fatigue following supportive educational and informational groups (Ream et al., 2006). Specifically, a group-based educational intervention for women with breast cancer undergoing adjuvant chemotherapy was found to reduce fatigue in the short-term (Yates, et al., 2005). Furthermore, individual psychotherapy has been shown to be effective in reducing levels of fatigue in cancer patients during radiation treatment (Forester, Kornfeld, Fleiss, & Thompson, 1993). Preliminary pilot studies have collected evidence in support of Mindfulness-Based Stress Reduction (MBSR) as an approach to reduce fatigue and improve QoL in breast cancer outpatients (Carlson, Speca, Patel, & Goodey, 2003; Carlson, Speca, Patel, & Goodey, 2004) and in cancer patients in general (Carlson & Garland, 2005).

Naaman and colleagues (2009) conducted 3 meta-analyses examining outcomes of psychological interventions for depression and QoL in breast cancer patients (Naaman, Radwan, Fergusson, & Johnson, 2009). Findings illustrated moderate to strong effects of

group therapy for reducing depression and moderate effects on improving QoL. Researchers concluded that psychological interventions focused on coping and social support were most efficacious in improving emotional and psychological well-being (Naaman et al., 2009). Group-based cognitive-behavioral stress management (CBSM) aims to increase relaxation, decrease tension, alter cognitions, enhance coping strategies, and help individuals maintain social support networks (Antoni, 2003). CBSM positively affects mood states and depression (Trijsburg, van Knippenberg, & Rijpma, 1992) and improves QoL (Antoni et al., 2001; 2006) in cancer patients. In addition, a multi-component psychological intervention aimed to reduce stress and enhance social support was found to alleviate depressive symptoms in women undergoing active breast cancer treatment (Thornton et al., 2009). This psychosocial intervention was also found to improve QoL, fatigue, and emotional distress in breast cancer patients (Andersen et al., 2004; 2007). Furthermore, a telephone-delivered psychosocial intervention that used interpersonal counseling to address adjustment and coping with stressors and social support behaviors was found to decrease symptoms of depression in women with breast cancer (Badger et al., 2007). An additional study demonstrated the importance of psychosocial interventions that address coping skills. This study found that women with breast cancer who had a lower coping ability reported higher levels of distress, greater symptomatology, worse perceived health, and in turn had impaired QoL (Kenne et al., 2007). Overall, various psychosocial interventions have the potential to attenuate cancer-related symptoms, such as fatigue, and to improve psychological well-being, as indicated by depression and overall QoL.

## PA and CBSM

The National Comprehensive Cancer Network labels psychosocial interventions as an additional category 1 non-pharmacological intervention for fatigue reduction during active cancer treatment (Mock et al., 2007). As category 1 interventions, PA and psychosocial interventions have the strongest supporting evidence base, while other non-pharmacological interventions, such as dietary management and sleep therapy, follow as category 2 recommendations (Mustian et al., 2007). Exercise has been shown to have stress management type effects, such that individuals who exercise are better equipped to cope with unpredictable and unmanageable stressors (Roth & Holmes, 1985; LaPerriere et al., 1991). In fact, a review of the literature (Martinsen, 1987) found that exercise was as effective as placebo or no treatment in reducing depressive symptoms. Furthermore, this review reported that exercise was just as effective as group-psychotherapy, individual psychotherapy, and meditation-relaxation for adults with depression. While many studies have investigated PA or psychosocial therapy as interventions to improve QoL, only a few have addressed the question of whether a combination therapy including both interventions would strengthen the effects on well-being. A review of the literature by Weyerer and Kupfer (1994) revealed two studies that compared a counseling intervention to an aerobic exercise plus counseling intervention in reducing depression. Results showed that aerobic exercise in addition to counseling was more effective in reducing depression than counseling on its own.

Researchers are beginning to examine the possibilities of combining cognitive behavioral therapy (CBT) and exercise for cancer patients. Literature identifies links



between maladaptive coping techniques in response to stressful life events and chronic illness, which can be explained by elevated biomarkers of stress, including increased neuroendocrine levels and decreased immune functioning (McEwen et al., 2003; Yehuda & McEwen, 2004). As a result, researchers have advocated for integrative approaches for cancer care. One such proposal identifies an integrative stress management and exercise intervention, both of which have been used in previous cancer research and may complement one another. Based on this theoretical approach, investigators are examining the effects of a Mindfulness-Based Exercise Program on QoL in women with breast cancer (Tacón & McComb, 2009). This intervention will combine Mindfulness-Based Stress Reduction with PA, including hatha yoga and walking meditation. In addition, another current study is looking into a combination CBT and exercise intervention for women with breast cancer treatment-induced menopause (Dujits et al., 2009).

One randomized controlled trial examined the effects of group psychotherapy alone compared to group psychotherapy plus moderate exercise on well-being in cancer survivors (Courneya et al., 2003). The study aimed to assess whether participation in the exercise component in addition to the group psychotherapy would produce results such that cancer survivors would show improvement in both physical and emotional dimensions of QoL. As hypothesized, results revealed significant effects such that cancer survivors in the combined group psychotherapy and exercise intervention experienced less fatigue and greater functional well-being than those in the group psychotherapy alone. In addition, borderline significant trends favored the combined exercise and

psychotherapy group on outcomes of satisfaction with life and physical well-being (Courneya et al., 2003).

Evidence suggests that a potential psychosocial mechanism by which increased PA improves fatigue in women with breast cancer is through an increase in self-efficacy (McAuley et al., 2010; Courneya, 2003; Ströhle 2009). If women are able to perform daily functions, partially as a result of a greater confidence in their ability to do so, this may trigger appraisals of lower fatigue, heightened daily functioning, and less depression. On the other hand, improvements in psychological well-being following CBT are explained through mechanisms such as cognitive restructuring and acquisition of stress management techniques (Duijts, Oldenburg, van Beurden, & Aaronson, 2009), as well as more realistic appraisal of stressors, increased self-efficacy related to coping with stressors, and enhanced sense of control (Andersen, 1992). In summary, psychosocial interventions may affect self-efficacy and self confidence through coping techniques and cognitive restructuring. PA addresses stress management and also increases task self-efficacy and confidence in functional capacity. While group psychotherapy and exercise combined have enhanced effects on QoL and fatigue (Courneya et al., 2003), further research needs to be conducted to replicate and validate these results using other psychosocial interventions that have proven efficacious in breast cancer patients (e.g., CBSM and MBSR).

## Study Objectives

Despite the breadth of research on PA and cancer prevention and symptom management, scientific and medical communities have yet to fully acknowledge and embrace the benefits of exercise as a complementary behavioral approach *during* cancer treatment (Kolden et al., 2002). The purpose of this study was to address these gaps by examining the association between duration of PA, rated depression, depressed mood, and functional QoL in women undergoing treatment for breast cancer. Another objective of the study was to delineate possible fatigue-associated mechanisms by which PA relates to improved functional QoL, depressed mood, and rated depressive symptoms. In addition, analyses examined these relationships post-surgery as well as during active treatment, thereby addressing the paucity of literature at these specific points along the cancer spectrum. Furthermore, these models test the theoretically hypothesized relationship among these variables put forth by Pinto and colleagues (2003). This theory suggests that PA leads to a reduction in fatigue as a result of increased functional capacity, and that women who are less fatigued are able to participate in daily activities that make life meaningful, therefore leading to greater QoL and ultimately fewer depressive symptoms.

Previous research by our group has found that women undergoing treatment for breast cancer who were assigned to the CBSM intervention experienced a reduction in Fatigue-Related Daily Interference (FRDI). Therefore, an additional objective of this study was to test whether engagement in PA was associated with FRDI reductions above and beyond the effects of the CBSM intervention at the post-intervention time point. In

sum, the proposed research will examine whether: a) PA is associated with functional QoL, fatigue, rated depression, and depressed mood prior to breast cancer treatment, b) these effects are stable post-intervention while women are undergoing active breast cancer adjuvant treatment, c) change in PA is associated with change in fatigue, depressed mood, rated depression, and change in functional QOL, and d) PA has an additive effect on fatigue above and beyond the effect of CBSM.

### **Specific Study Aims.**

1. To examine potential direct and indirect pathways by which PA relates to fatigue (as measured by three indicators: FRDI, fatigue intensity, and number of days fatigued per week), functional QoL, rated depression, and depressed mood in women recently diagnosed with breast cancer who are post-surgery and pre-adjuvant treatment. To determine whether fatigue is an intermediate pathway by which PA is related to functional QoL, rated depression, and depressed mood.
2. To examine whether the direct and indirect pathways examined in aim 1 are similar at the post-intervention follow-up assessment, when women are undergoing active treatment for non-metastatic breast cancer.
3. To determine whether the change in PA from pre- to post-intervention is associated with the change in fatigue, as well as change in functional QOL, rated depression, and depressed mood from pre-to post-intervention.

4. To assess whether there is an additive effect of change in PA on change in fatigue above and beyond the effect of CBSM on fatigue, such that the combination of PA and CBSM may lead to a larger reduction in fatigue. To determine if the relationship between condition, PA and FRDI can be explained using moderation, such that the association between condition and FRDI is moderated by the amount of PA engaged in each week.

## CHAPTER 3: Methods

### Participants

Women diagnosed with non-metastatic stage 0-III breast cancer were recruited for the current study through physician referrals and community advertising. Participants were required to have had surgery for primary breast cancer in the past 2-10 weeks. Exclusion criteria included prior cancer diagnosis and treatment, prior psychiatric treatment for serious mental disorder, and lack of fluency in English. Initial assessments took place at approximately 4 to 10 weeks post-surgery (lumpectomy, mastectomy, or bilateral mastectomy) and prior to initiation of adjuvant cancer treatment (chemotherapy and/or radiation). These baseline assessments consisted of blood samples and psychosocial questionnaires measuring PA, depressed mood, fatigue, and QoL. All assessments took place prior to randomization to study intervention or control group. Women in the intervention group attended weekly group sessions of CBSM for a period of 10 weeks. The control condition consisted of a 1-day psycho-educational seminar that was within the 10-week period. In addition to the initial assessment pre-intervention, women were assessed 3 months post-intervention (Time 2), 6 months after the second assessment (Time 3), and 6 months after the third assessment (Time 4). Again, assessments consisted of blood samples and psychosocial questionnaires measuring PA, rated depression, depressed mood, fatigue, and functional QoL. Of interest in this sub-study are the psychosocial measures at the pre- and 3 months post-intervention time points. A more detailed description of the parent study design is provided elsewhere (Antoni et al., 2006).

## **Intervention**

The CBSM group met two hours per week for ten consecutive weeks. The structured, manualized CBSM (Antoni, 2003) is a psychosocial intervention that combines relaxation techniques, such as muscle relaxation and imagery, with cognitive behavior therapy (CBT) techniques, such as cognitive restructuring to modify negative or distorted cognitive appraisals, coping skills training, interpersonal assertiveness, and anger management skills. The intervention aims to increase relaxation, decrease tension, replace negative cognitions, enhance coping strategies, and maintain social support networks. Stress reduction techniques focus on cancer- and treatment-related issues. Interventionists were trained in the protocol and sessions were videotaped and monitored for fidelity by two clinical psychologists.

## **Control seminar**

Participants assigned to the control group received an abbreviated classroom lecture format of the information from the intervention that lasted 5-6 hours and took place one weekend during the corresponding 10-week intervention. This psycho-educational group received information related to breast cancer. The seminar was void of the opportunity to practice any of the techniques or to do at home exercises.

## **Measures**

**Demographics.** Information regarding demographics, socioeconomic status, medical condition, and cancer treatment was collected at baseline and at the follow-up assessment via self-reports. Variables included age, ethnicity, employment status, marital

status, income, education, stage of disease, type of surgery (lumpectomy or mastectomy), time from surgery to baseline assessment, and type of adjuvant treatment (chemotherapy, radiation, and/or hormonal).

**Physical Activity.** Intensity and duration of PA was measured using a brief version of the Seven-Day Physical Activity Recall Questionnaire (Blair et al., 1985). The activity log asks participants to record the total time engaged in vigorous and/or moderate activity each day of the previous week. Vigorous intensity includes activities that require substantial energy expenditure and increased heart rate (e.g., jogging, running, sustained swimming, aerobic dancing, strenuous sports). However, moderate intensity includes activities in which the heart rate is increased yet conversation is still possible (e.g., yard work, heavy housecleaning, brisk walking for the purpose of exercise). Previous research suggests that moderate to vigorous intensity activity is most beneficial for health outcomes (Sallis et al., 1985), therefore moderate and vigorous activity will be combined into one continuous variable to represent the duration of all PA in minutes per week.

**Fatigue.** Fatigue outcomes were measured using the Fatigue Symptom Inventory (FSI; Hann et al, 1998). The FSI is a 12-item self-report instrument assessing fatigue intensity, duration, and interference/disruption of fatigue on daily function. The FSI has 4 items that measure fatigue intensity, 1 item that measures duration of fatigue in the previous week (total number of days fatigued), and 7 items that measure interference or Fatigue-Related Daily Interference (FRDI). FRDI is the extent to which the fatigue has impacted QoL and functional capacity (e.g., “Rate how much, in the past week, fatigue has interfered with your normal work activity”). These items are rated from 1 (no



interference) to 9 (extreme interference). Items on each scale were averaged, and the alpha averages for the intensity and interference subscale were .83 and .93, respectively, for this sample.

**Rated Depression.** Depressive symptomatology was measured using the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). The HRSD is a 17-item interviewer-administered measure assessing for symptoms of depression. The measure uses a Likert-type scale with both 3-point and 5-point responses depending on the item. Items fall under categories of depressed mood, suicide, work and loss of interest, retardation, agitation, gastro-intestinal symptoms, hypochondriasis, insight, and loss of weight. A final score is obtained by simple summation of individual item responses, and the average alpha for this sample was .66.

**Depressed Mood.** Depressed Mood was measured using the Depression subscale of the Affect Balance Scale (ABS; Derogatis, 1975). The ABS is a 40-item self-report measure assessing positive and negative affect and mood states. The measure uses a Likert-type rating scale with 5-point responses asking participants to indicate how often they experience a list of emotions (1=never to 5= always). The 5 items in the depressed mood subscale include the following emotions: sad, hopeless, worthless, miserable, and unhappy. A final score is obtained by averaging the responses for each item, and the average alpha for the depression subscale from this sample was .80.

**Quality of Life: Functional Well-Being.** The Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B; Cella and Tulsky, 1990; Brady et al., 1997) was

used to assess QoL of the participants. The FACT-B is a 36-item self-report instrument containing 5 subscales representing dimensions of QoL: physical, emotional, social, functional well-being, and breast cancer. Participants rate each item on a Likert-type scale from 0 (not at all) to 4 (very much). Better functional status is indicated by higher scores. Subscale scores for each domain of QoL are calculated, as well as a total well-being score. Of interest in this study is the dimension of functional well-being. Items are summed, and the alpha for the functional well-being subscale was .84.

### **Analytic Strategy**

**Preliminary Analyses and Data Screening.** Preliminary analyses were conducted with analysis of variance (ANOVA) and Pearson chi-square tests to evaluate group differences at the baseline data collection. Prior to analyses, the data was screened for outliers. One high value for PA at T1, and two high values for PA at T2 were Winsorized to fall within three standard deviations of the mean. Descriptive statistics were examined to determine whether variables were highly skewed or kurtotic. The PA seven-day recall was originally measured in minutes per week, and therefore had a large variance. In order for the Mplus program to converge, the ratio of the largest variance to the smallest variance must be less than 10 units. To meet this criteria, the PA seven-day recall was transformed into hours by dividing by 60.

**Tests of Aim 1 Hypotheses.** To test the hypothesis of the first aim, data were analyzed from the baseline assessment (T1). At study entry, women ages 23-70 years old had been diagnosed with different stages of breast cancer and had recently received some

type of surgical intervention between 4 -10 weeks prior to the T1 assessment. Therefore, analyses at this time point controlled for participants' age, stage of disease (0-III), and surgery type (lumpectomy or mastectomy) (Winters-Stone, Bennett, Nail, & Schwartz, 2008; Thorton et al., 2010; Golden-Kreutz & Andersen, 2004). In addition, due to between-group differences in amount of elapsed time from their surgery date to the T1 assessment ( $p < .05$ ), analyses controlled for time since surgery. The model was estimated with and without adjustments based on these covariates.

First, structural equation modeling (SEM; Bollen, 1989; Kline, 2005) was used to test the measurement component of the model. The model was estimated to determine whether three indicators: fatigue intensity, FRDI, and the number of days fatigued over the past week, share a common variance that can be explained by the underlying construct of fatigue. The full information maximum likelihood method (FIML) was used to estimate missing data values by estimating missing information from relations among variables in the full sample. The use of FIML, as conducted in Mplus (Muthén & Muthén, 1998-2010, Version 6.0), ensures that each participant is represented in the analyses. Indices of model fit were examined, including the overall chi-square value, comparative fit index (CFI), root-mean-square error of approximation (RMSEA), and the standardized root mean square residual (SRMR). Values indicating good fit for each of these indices are as follows: a non-significant chi-square, a CFI  $> .95$ , a RMSEA  $< .06$ , and a SRMR  $< .10$ , respectively (Kline, 2005). The unstandardized coefficients, or loadings, were examined to determine whether these indicators significantly load on the latent fatigue construct. The model was re-specified and re-estimated consistent with

suggested modification indices provided by Mplus, which were correspondingly theoretically supported. The measurement model was not found to be a good fit for the data (as described in the results section), and therefore the observed variable, FRDI, was used in subsequent model testing.

Next, the structural component of the model was tested to determine the relationships among the observed variables (PA, FRDI, functional QoL, rated depression, and depressed mood). The model was specified with the observed variable FRDI regressed on PA, and functional QoL, rated depression, and depressed mood regressed on FRDI. A path was specified to include an association of functional QoL with rated depression, rated depression with depressed mood, and functional QoL with depressed mood. The model also specified indirect paths from PA to rated depression via FRDI, PA to functional QoL via FRDI, and PA to depressed mood via FRDI. Additional indirect paths were specified via the unknown associations between the three dependent variables, functional QoL, rated depression, and depressed mood. Control variables were included as possible covariates if they were theoretically supported (Babyak, 2004). The model was estimated both independent of covariates and adjusted for covariates. Indices of model fit (Chi-square, CFI, RMSEA, SRMR as described above) and the specific direct and indirect effects were interpreted by examining the  $z$  statistic at a two-tailed significance level of .05. Alternative models were tested to assess reverse directionality, and the final model was chosen according to best model fit, and interpretation of unstandardized coefficients of the direct and indirect effects. The final baseline model is referred to as Model T1.

**Tests of Aim 2 Hypotheses.** For tests of Aim 2 hypotheses, data from the 3-month post-intervention time point (T2) was used. Given that these women were in the midst of treatment, several covariates were considered in the analyses. While some women were undergoing adjuvant treatment, others were not; therefore treatment type (chemotherapy, radiation, and/or endocrine therapy) was examined as a possible confounder in addition to age, time since surgery, and procedure type (lumpectomy or mastectomy) (Thorton et al., 2010; Golden-Kreutz & Andersen, 2004). To determine whether the established baseline model, Model T1, is stable over time, this second model was estimated in the same manner as Model T1, with the additional adjuvant treatment-related covariates. Alternative models were estimated to test reverse directionality and determine the best fit for the data. Model fit indices, direct effects, and indirect effects were interpreted, and this post-intervention model is referred to as Model T2.

**Test of Hypothesis 3.** Aim 3 hypotheses tested whether change in PA was associated with change in FRDI, and subsequently, change in functional QOL, change in rated depression, and change in depressed mood. For these analyses, difference scores were computed. Difference scores for each variable reflect the change from the baseline assessment (T1) to the 3-month post-intervention assessment (T2). The model was then estimated in a similar fashion to the T1 and T2 final models, including age, time since surgery, and adjuvant treatment (chemotherapy, radiation, and/or endocrine), and type of surgical procedure (lumpectomy or mastectomy) as covariates. Alternative models were estimated to determine the best fit for the data with difference scores. Model fit indices,

direct effects, and indirect effects were interpreted, and the final model is referred to as T1-T2 Change Model.

**Tests of Hypothesis 4.** Due to previous work by this group, which has demonstrated that women assigned to the CBSM group experience significantly larger reductions in FRDI than women in the control group, tests of hypotheses for Aim 4 assessed whether PA added to the effect of CBSM on FRDI in women undergoing treatment for non-metastatic breast cancer. In order to test this hypothesis, the T1-T2 change model was estimated with the categorical variable, condition (CBSM, control), in place of PA in the model. Next, PA was added back into the model and main effects were interpreted to determine whether PA significantly accounted for variability in FRDI, above and beyond that which was accounted for by the treatment condition, CBSM. Finally, a plausible explanation for the relationships between condition, PA, and FRDI, may be that the benefits of CBSM for FRDI is dependent on how much time is spent in PA at the post-intervention assessment, such that women who engage in CBSM subsequently engage in more health behaviors. Tests of moderation were conducted in order to determine whether this hypothesis is plausible. First, the model was estimated regressing FRDI on condition and PA at T2, and was adjusted for covariates, including the amount of PA at T1. Next, an interaction term was created using the predictor (condition) and moderator (PA at T2) variables. This interaction term was added to the model as a predictor to determine whether there was a significant association between the interaction and FRDI above and beyond that which was explained by condition and PA at T2. A significant association would indicate that moderation existed.

## CHAPTER 4: Results

### Participant Characteristics

Participants were 240 women with stage 0-III primary breast cancer who were 2-10 weeks post surgery. Participants were an average of  $50.3 \pm 9.0$  years of age, with more than 50% completing college or advanced degrees, and 36.3% being of a racial or ethnic minority. Participants were randomly assigned to either the 10-week CBSM group ( $n=120$ ) or the 1-day Psycho-educational control group ( $n=120$ ) (see CONSORT diagram, Figure 1). A significant difference was found between the intervention and control group on the amount of time elapsed from surgery to the baseline assessment,  $F(229) = 5.84$ ,  $p < .05$ , and therefore this was controlled for in the analyses. No significant differences were found between the intervention and control group on any other demographic, socio-economic, or medical/treatment-related variables. Demographic and medical characteristics of the sample according to condition (CBSM or control) are presented in Table 1. At the pre-intervention assessment, women reported an average of 158 minutes ( $SD= 285$ ) of moderate intensity and 24 minutes ( $SD = 150$ ) of vigorous intensity PA per week. At the post-intervention assessment, women reported an average of 275 minutes ( $SD = 489$ ) of moderate intensity and 55 minutes ( $SD = 130$ ) of vigorous intensity PA per week. An intent-to-treat approach was used to conduct all outcome analyses, wherein all participants were included in the analyses.

## Results of Hypothesis 1

First, the measurement component of the model was estimated to determine whether the three measures of fatigue ('FRDI, 'fatigue intensity', and 'number of days fatigued') shared common variance explained by the underlying construct of fatigue. The model was not a good fit for the data, as indicated by the overall significant chi-square value,  $\chi^2(1) = 4.27$ ,  $p = .039$  and RMSEA = .12. As a result, the latent fatigue variable was not included in further analyses. Rather, FRDI was used in further analyses as an observed variable, due to previous work by this group demonstrating intervention effects on FRDI (Vargas et al: submitted for publication) and preliminary analyses suggesting a relationship between PA and FRDI (Stagl et al., 2010).

Next, the structural component of the model was estimated using data from the baseline assessment. First, the model was estimated unadjusted for control variables. Results indicated that the model was consistent with the data as indicated by the non-significant overall chi-square value,  $\chi^2(3) = 3.65$ ,  $p = 3.02$ , a CFI greater than .95 (CFI = .99), a RMSEA value less than .06 (RMSEA = .03), and a SRMR less than .10 (SRMR = .02). Examination of the direct effects showed that all paths were statistically significant. The path from PA to FRDI was significant, such that a greater number of hours of moderate and strenuous PA was associated with less FRDI ( $\beta = -.09$ ,  $z = -3.41$ ,  $p < .01$ ). Next, the path from FRDI to functional QoL was significant, such that women who reported less FRDI showed greater functional QoL ( $\beta = -.167$ ,  $z = -10.49$ ,  $p < .01$ ). Third, the path from FRDI to rated depression was significant, such that women who had less FRDI reported fewer depressive symptoms ( $\beta = 1.17$ ,  $z = 6.93$ ,  $p < .01$ ). In addition,



the path from FRDI to depressed mood was significant, such that women who reported less FRDI reported a less depressed mood ( $\beta = .76, z = 7.99, p < .01$ ). Finally, the specified associations between functional QoL and rated depression ( $\beta = -.60, z = 3.79, p < .01$ ), functional QoL and depressed mood ( $\beta = -4.43, z = -4.75, p < .01$ ), and rated depression with depressed mood ( $\beta = 4.58, z = 4.72, p < .01$ ) were all significant. All indirect paths were significant.

Next, the model was re-estimated with each control variable added individually in the model. The final model was estimated adjusting for the following covariates: age, time since surgery, stage of disease (0-III), and type of procedure (lumpectomy, mastectomy). This analysis was conducted with 229 women, due to 11 missing data values for the control variables. The model, adjusted for these covariates, was a good fit for the data,  $\chi^2(3) = 3.02, p = .39, CFI = 1.00, RMSEA = .005, SRMR = .01$ . All adjusted direct paths were significant. First, the path from PA to FRDI was significant, such that a greater duration of hours of moderate and strenuous PA was associated with less FRDI ( $\beta = -.08, z = -2.84, p < .01$ ). Second, the path from FRDI to functional QoL was significant, such that women who reported less FRDI showed greater functional QoL ( $\beta = -1.60, z = -9.8, p < .01$ ). Next, the path from FRDI to rated depression was significant, such that women who had less FRDI reported fewer depressive symptoms ( $\beta = 1.13, z = 6.61, p < .01$ ). In addition, the path from FRDI to depressed mood was significant, such that women who reported less FRDI reported a less depressed mood ( $\beta = .70, z = 7.06, p < .01$ ). Finally, the specified associations between functional QoL and rated depression ( $\beta = -.557, z = 3.66, p < .01$ ), functional QoL and depressed mood ( $\beta = -4.01, z = -4.37, p$

<.01), and rated depression with depressed mood ( $\beta = 3.78, z = 4.07, p <.01$ ) were all significant. Examination of the indirect paths in the model revealed that all were significant. Specifically, the indirect path from PA to rated depression via FRDI was significant ( $\beta = -.09, z = -2.6, p <.01$ ). In addition, the indirect path from PA to functional QOL via FRDI was significant ( $\beta = 1.11, z = 6.61, p <.01$ ). Furthermore, the indirect path from PA to depressed mood via FRDI was significant ( $\beta = -.05, z = -2.64, p <.01$ ).

Alternative models were estimated to determine whether the above model is the best representation of the relationships between PA, FRDI, functional QOL, rated depression, and depressed mood. First, a multiple group analysis was conducted to determine any differences in the model based on ethnicity of the women (Caucasian,  $n=148$ ; Hispanic,  $n=57$ ). A grouping variable was specified when estimating the model. Although this model was a good fit for the data as indicated by the chi-square and CFI indices ( $\chi^2 (6) = 8.64, p = .195, CFI = .99$ ), the RMSEA value greater than .06 (RMSEA = .07) indicated that the model may not be the best fit for the data. A chi-square difference was conducted to determine whether the model in which Caucasians and Hispanics estimated separately was a significantly better fit for the data than the model in which they were estimated to be equal. The chi-square difference test was not significant,  $\chi^2 \Delta (3) = 5.61, p = .13$ , therefore the model in which Caucasians and Hispanics were estimated to be the same was retained for further testing. Next, an alternative model was tested in which paths were specified to estimate a direct effect from PA to rated depression and from PA to functional QoL. The model was a good fit for the data,  $\chi^2 (1)$

=.00,  $p = .99$ , CFI = 1.00, RMSEA = .000, SRMR = .00, however the unstandardized coefficients for the direct paths from PA to rated depression ( $\beta = -.04$ ,  $z = -.52$ ,  $p = .60$ ) and from PA to functional QoL ( $\beta = .11$ ,  $z = 1.73$ ,  $p = .084$ ) were not significant. Therefore, this model was not retained, as the relationships between PA and rated depression and PA and functional QOL are more accurately represented by indirect associations. Third, alternative models were tested in which the positions of the variables in the model were switched, so that each was tested as a predictor (FRDI, depressed mood, rated depression, and functional QoL) and each was tested as the intermediate variable (PA, depressed mood, rated depression, and functional QoL). These analyses adjusted for the established covariates. Results revealed one model that was a good fit for the data. The model estimated with indirect effects from PA to FRDI, rated depression and depressed mood, via functional QOL as an intermediate pathway revealed a good fit for the data,  $\chi^2 (3) = 2.41$ ,  $p = .49$ , CFI = 1.00, RMSEA = .000, SRMR = .01. Interpretation of the direct and indirect effects revealed significant paths. Therefore, this was considered as a plausible alternative to the T1 model such that it may be that functional QOL determines FRDI rather than that FRDI determines functional QOL. Follow-up analyses were conducted in the T2 Model and T1-T2 Change Model to determine whether the models were comparable at these time points, and these results are discussed in the following sections. However, the model with functional QOL as the intermediate path did not retain direct and indirect paths in subsequent hypotheses testing (T1 and T1-T2 Change Model) and therefore was not considered to be an optimal representation of the data. No other alternative model was a good fit for the data, when

substituting each variable as the predictor variable and intermediate variable. As a result, the originally described, adjusted model was retained for the tests of Aim 1 hypotheses, due to the consistent fit of the model for the data and the significant direct and indirect pathways. This model will be referred to as Model T1 (see Figure 1). The covariance matrix for the data at this time point is reported in Table 2 and relevant descriptive statistics are reported in Table 3.

## Results of Hypothesis 2

In order to test whether Model T1 was stable after intervention, Model T2 was specified in an identical fashion to Model T1. Without adjusting for covariates, results revealed that the model was a good fit for the data,  $\chi^2 (3) = 1.32$ ,  $p = .73$ , CFI = 1.00, RMSEA = .00, SRMR = .02. All direct effects were found to be statistically significant. Next, the model was adjusted for the following covariates, which were added individually to the model: age, time since surgery, type of procedure (lumpectomy or mastectomy), and adjuvant treatment (chemotherapy, radiation, and/or endocrine). The adjusted model when all covariates were included was a good fit for the data,  $\chi^2 (3) = 1.25$ ,  $p = .75$ , CFI = 1.00, RMSEA = .00, SRMR = .01. Examination of the unstandardized coefficients revealed that the regression of FRDI on PA was borderline significant, such that greater duration of PA was associated with lower FRDI ( $\beta = -.04$ ,  $z = -1.87$ ,  $p = .06$ ). All other direct paths in the model were significant. Functional QoL was significantly associated with FRDI, such that women who reported less FRDI showed greater functional QoL ( $\beta = -2.07$ ,  $z = -11.98$ ,  $p < .01$ ). In addition, rated depression was significantly associated with fatigue, such that women who had less FRDI reported fewer depressive symptoms

( $\beta = 1.59, z = 7.65, p < .01$ ). Furthermore, depressed mood was significantly related to FRDI, such that women who reported less FRDI also reported less depressed mood ( $\beta = .65, z = 5.85, p < .01$ ). The specified associations between functional QoL and rated depression ( $\beta = -4.99, z = -3.89, p < .01$ ), functional QOL and depressed mood ( $\beta = -2.78, z = -3.99, p < .01$ ), and rated depression and depressed mood ( $\beta = 2.68, z = -3.21, p < .01$ ) were all significant. Finally, examination of the indirect effects revealed a borderline significant effect from PA to rated depression via fatigue ( $\beta = -.06, z = -1.81, p = .07$ ), a borderline significant indirect effect from PA to functional QOL via fatigue ( $\beta = .07, z = 1.84, p = .065$ ) and a borderline significant indirect effect from PA to depressed mood ( $\beta = -.02, z = -1.78, p = .075$ ).

Alternative models were estimated to determine whether the model specified above was the best representation of the relationships between PA, FRDI, functional QOL, rated depression, and depressed mood at the post-intervention assessment time point (T2). First, a multiple group analysis was conducted to determine any differences in the model based on ethnicity of the women (Caucasian,  $n=124$ ; Hispanic,  $n=42$ ). A grouping variable was specified when estimating the model. Although this model was a good fit for the data as indicated by the chi-square and CFI ( $\chi^2 (6) = 4.94, p = .55, CFI = 1.0, RMSEA = 0.00, SRMR = .015$ ), a chi-square difference was conducted to determine whether the model in which Caucasians and Hispanics estimated separately was a significantly better fit for the data than the model in which they were estimated to be equal. The chi-square difference test was not significant,  $\chi^2 \Delta (3) = 3.69, p = .30$ , therefore the model in which Caucasians and Hispanics were estimated to be the same

was retained for further testing. Next, an alternative model was tested in which paths were specified to estimate a direct effect from PA to rated depression and PA to functional QOL. The model was not a good fit for the data, and the unstandardized coefficients for these direct paths were not significant. Third, alternative models were tested in which the positions of the variables in the model were switched, so that each was tested as a predictor (FRDI, depressed mood, rated depression, and functional QoL) and each was tested as the intermediate variable (PA, depressed mood, rated depression, and functional QoL). These analyses adjusted for the established covariates. Of these models tested for reverse directionality, three were considered plausible based on the fit indices. However, further examination of the direct and indirect effects revealed that they were not good representations of the data. The first of those tested was a model that estimated direct effects from PA to functional QOL and indirect effects from PA to FRDI, rated depression and depressed mood, via functional QOL as an intermediate pathway. The model revealed a good fit for the data,  $\chi^2(3) = 3.13$ ,  $p = .37$ , CFI = 1.0, RMSEA = .02, SRMR = .01. However, interpretation of the direct and indirect effects revealed that the path from PA to functional QOL was not significant ( $\beta = .07$ ,  $z = 1.25$ ,  $p = .21$ ). Furthermore, examination of the indirect effects from PA to FRDI, PA to rated depression, and PA to depressed mood, via functional QOL, were not significant (all  $p$ 's  $> .05$ ). Although this model with functional QOL as an intermediate pathway was a plausible alternative model at T1, it was no longer considered to be comparable at the T2 time point due to these non-significant direct and indirect effects. The second model which fit the data included direct effects from PA to rated depression, with indirect

effects from PA to FRDI, functional QOL, and depressed mood via rated depression as an intermediate pathway. Although this was a good fit for the data,  $\chi^2(3) = 3.04$ ,  $p = .39$ , CFI = 1.0, RMSEA = .01, SRMR = .01, the direct path from PA to rated depression was not significant ( $\beta = .08$ ,  $z = 1.28$ ,  $p = .20$ ). Therefore, this model was not considered to be a plausible alternative. The third model included a direct path from PA to depressed mood, with indirect paths from PA to rated depression, functional QOL, and FRDI, via depressed mood as an intermediate pathway. Although this model was a good fit for the data,  $\chi^2(3) = 4.68$ ,  $p = .20$ , CFI = .99, RMSEA = .055, SRMR = .02, the direct path from PA to depressed mood was not significant ( $\beta = .002$ ,  $z = .08$ ,  $p = .94$ ). Of the other models tested for reverse directionality, none was a good fit for the data. As a result, the originally described, adjusted post-intervention model was retained for the tests of Aim 2 hypotheses, due to the consistent fit of the model for the data and the significant direct and marginally-significant indirect pathways. This model is referred to as Model T2. Furthermore, the model was specified in the same way as was Model T1, therefore showing consistency across time of the relationships among PA, FRDI, rated depression, depressed mood, and functional QoL. Model T2 is illustrated in Figure 2. Table 4 contains the covariance matrix for the data at this time point, and Table 5 displays the means and standard deviations for these variables.

### Results of Hypothesis 3

In order to test whether the change in PA from pre- to post-intervention was associated with changes in: (1) FRDI, (2) rated depression, (3) depressed mood, and (4) functional QOL, the model was estimated in a similar fashion to the T1 and T2 models,

yet with difference scores. First, the model was estimated unadjusted for covariates (n=193). Results showed that the model was a good fit for the data,  $\chi^2(3) = 4.68$ ,  $p = .20$ , CFI = .98, RMSEA = .054, SRMR = .04. All paths estimating the direct effects were significant, except for the path regressing rated depression change on FRDI change ( $\beta = .30$ ,  $z = 1.42$ ,  $p = .16$ ). Next, the model was estimated adjusting for the following covariates relevant to the T2 time point: age, time since surgery, type of procedure (lumpectomy or mastectomy), and type of adjuvant treatment (chemotherapy, radiation, and/or endocrine treatment). Covariates were entered individually into the model, and the final estimation, adjusted for all covariates, revealed that the model was a good fit for the data,  $\chi^2(3) = 4.21$ ,  $p = .24$ , CFI = .99, RMSEA = .05, SRMR = .02. In addition, all direct effects were found to be statistically significant. Examination of the unstandardized coefficients revealed that the regression of FRDI change on PA change was significant, such that an increase in PA was associated with a decrease in FRDI ( $\beta = -.05$ ,  $z = -2.41$ ,  $p = .016$ ). Next, functional QoL change was significantly associated with FRDI change, such that women who reported a decrease in FRDI showed improved functional QoL ( $\beta = 1.18$ ,  $z = -6.18$ ,  $p < .01$ ). In addition, rated depression change was significantly associated with FRDI change, such that women who had reduced FRDI reported a decrease in depressive symptoms ( $\beta = .43$ ,  $z = 1.97$ ,  $p < .05$ ). Furthermore, depressed mood change was significantly related to FRDI change, such that women who reported decreased FRDI also reported a decrease in depressed mood ( $\beta = .49$ ,  $z = 4.19$ ,  $p < .01$ ). The specified association between functional QoL change and rated depression change was not significant ( $\beta = -1.35$ ,  $z = -.74$ ,  $p = .46$ ), the association between rated depression change



and depressed mood change was borderline significant ( $\beta = 1.97, z = 1.73, p = .08$ ), and the association between functional QOL change and depressed mood change was significant ( $\beta = -4.2, z = -4.08, p < .01$ ). Finally, examination of the indirect effects revealed a significant effect from PA change to functional QOL change via FRDI change ( $\beta = .05, z = 2.25, p = .025$ ), and a significant indirect effect from PA change to depressed mood change via FRDI change ( $\beta = -.02, z = -2.09, p = .036$ ). However, the indirect path from PA change to rated depression change showed only a tendency toward significance ( $\beta = -.02, z = -1.53, p = .13$ ).

Alternative models were estimated to determine whether the model specified above was the best representation of the relationships between the changes in PA, FRDI, functional QOL, rated depression, and depressed mood from the pre- to post-intervention assessment time points. First, a multiple group analysis was conducted to determine any differences in the model based on ethnicity of the women (Caucasian,  $n=124$ ; Hispanic,  $n=42$ ). A grouping variable was specified when estimating the model. This model was not a good fit for the data, as indicated by the CFI:  $\chi^2 (6) = 10.66, p = .10, CFI = .94, RMSEA = 0.10, SRMR = .03$ . This suggests that the model in which parameters for Caucasians and Hispanics were estimated separately was not a good representation of the data. Therefore, the model in which Caucasians and Hispanics were estimated to be the same was retained for further testing. Next, an alternative model was tested in which paths were specified to estimate a direct effect from PA change to rated depression change, PA change to depressed mood change, and PA change to functional QOL change. The model was not a good fit for the data, and the unstandardized coefficients for

the direct paths were not significant. Third, alternative models were tested in which the positions of the variables in the model were switched, so that each was tested as a predictor (FRDI, depressed mood, rated depression, and functional QoL change) and each was tested as the intermediate variable (PA, depressed mood, rated depression, and functional QoL change). These analyses adjusted for the established covariates. Results revealed that the model estimated with direct effects from rated depression change to FRDI change and indirect effects from rated depression change to PA change, functional QoL change, and depressed mood change, via FRDI change as an intermediate pathway, revealed a good fit for the data,  $\chi^2(3) = 4.19$ ,  $p = .24$ , CFI = .99, RMSEA = .05, SRMR = .02. In addition, interpretation of the direct effects revealed that the paths were significant. As a result, this model was seen as comparable to the originally estimated model. However, unlike the originally estimated model, this model with rated depression as the predictor variable is not a good fit for the data at either the pre- or post-intervention time point. Given that the original model is a good fit at both the pre- and post-intervention time points and when estimated with difference scores, it is a more plausible and consistent representation of the data. No other alternative model was a good fit for the data, when substituting each variable as the predictor variable and intermediate variable. Furthermore, correlations were run to determine whether the change in PA from T1 to T2 was significantly associated with reported FRDI at study entry (T1). These were not significantly correlated ( $r = .097$ ,  $p = .19$ ), indicating that reported levels of FRDI at T1 are independent of changes in PA from T1-T2. As a result, the originally described, adjusted T1-T2 change model was retained for the tests of Aim 3 hypotheses, due to the

consistent fit of the model for the data and the significant direct and indirect pathways. Furthermore, the model was specified in the same way as was Model T1 and Model T2. This model is referred to as Model T1-T2 Change. Model T1-T2 Change is illustrated in Figure 3. Table 6 contains the covariance matrix for the data at this time point, and Table 7 displays the means and standard deviations for these variables.

#### Results of Hypothesis 4

The final T1-T2 Change Model was estimated to include a path regressing change in FRDI on condition (CBSM or control) to determine whether the change in PA accounted for additional variability above and beyond what was accounted for by group assignment. First, the T1-T2 Change Model was estimated with FRDI change regressed on condition (CBSM, control) only, in place of PA. This model was a good fit for the data,  $\chi^2(3) = 1.23$ ,  $p = .75$ , CFI = 1.0, RMSEA <.000, SRMR = .01. Examination of the direct effects revealed a significant association between condition and FRDI change, such that women assigned to CBSM experienced reduced FRDI from pre- to post-intervention ( $\beta = -.54$ ,  $z = -2.01$ ,  $p = .04$ ). Next, PA was added back into the model, with FRDI change regressed on both PA change and condition, and was adjusted for covariates. Results showed it was a good fit for the data,  $\chi^2(3) = 4.19$ ,  $p = .24$ , CFI = .99, RMSEA = .05, SRMR = .02. Examination of the direct effects revealed a borderline significant association between condition and FRDI change, such that women assigned to the CBSM group showed a reduction in FRDI from T1-T2 ( $\beta = -.50$ ,  $z = -1.84$ ,  $p = .065$ ). Furthermore, the path from PA to FRDI change was significant, such that women who showed an increase in PA reported a decrease in FRDI from pre- to post- intervention,

above and beyond the effects of condition,  $\beta = -.04$ ,  $z = -2.30$ ,  $p = .02$ . Finally, tests of moderation were conducted by adding the interaction between hours of PA at the post-intervention time point and condition as a predictor in the model. In addition, these analyses controlled for the hours engaged in PA at the pre-intervention assessment by including this variable as an additional predictor. Results showed that the interaction term did not account for significant variability in FRDI above and beyond that accounted for by PA and condition ( $p > .05$ ), indicating that moderation does not exist.

## CHAPTER 5: Discussion

The current study provides evidence for relationships among physical activity, fatigue-related daily interference, functional quality of life, rated depression, and depressed mood in women who had undergone surgery for non-metastatic breast cancer and had not yet begun adjuvant treatment. Results suggest that these relationships were the same after the onset of adjuvant treatment. Findings also demonstrate that the relationship between PA and FRDI, functional QoL, rated depression, and depressed mood remains influential, when accounting for the effect of the intervention (CBSM) on these outcomes. This suggests that PA before and during breast cancer treatment may have better mental health outcomes, that PA may protect women from side effects of cancer treatment, and provides further support for the integration of PA as a complementary modality into a comprehensive cancer treatment regimen. This furthermore suggests that women may benefit from stress management in conjunction with an exercise intervention, detailing the need for more research into the combination of these individually efficacious therapies.

### **Relationships amongst PA, FRDI, Functional QoL, Rated Depression, and Depressed Mood**

Data at the baseline time point (post-surgery and pre-adjuvant treatment) were used to determine whether PA was directly associated with FRDI, indirectly associated with functional QoL, rated depression, and depressed mood, and whether FRDI was a pathway by which PA related to functional QoL, rated depression, and depressed mood. Results supported this hypothesis, suggesting that women who were physically active post-surgery and prior to adjuvant treatment reported less daily interference as a result of

fatigue, better functional QoL, fewer depressive symptoms, and lower depressed mood. Furthermore, results of indirect tests showed that less daily interference of fatigue was a pathway by which PA was related to functional QoL, rated depression, and depressed mood. This implies that women who are physically active may have less fatigue interference, and therefore better mental health outcomes. This effect is consistent with mediation, although this was a cross-sectional analysis, and therefore mediation was not tested. The model was adjusted for demographic and medical-related covariates to control for the possible confounding effects on each of the dependent variables in the model. The finding was robust, eliminating the possibility that the observed relationships among PA, FRDI, functional QoL, rated depression, and depressed mood were due to the effects of confounding factors. In addition, a multi-group analysis revealed that the model did not differ as a function of ethnicity.

These findings are unique in that most research has examined these outcomes during or following adjuvant treatment (Courneya & Friedenreich, 1997; 2007), while the current study evaluates relationships prior to the onset of adjuvant treatment. For instance, the benefits of PA have been demonstrated in other cross-sectional studies during cancer treatment. A cross-sectional study by Pinto and colleagues (1998) found that women with breast cancer who exercised at levels recommended by the American College of Sports Medicine (ACSM) showed more vigor and use of adaptive coping strategies. With regard to the outcomes measured in the current study, findings are supported by randomized controlled trials demonstrating that moderate exercise reduces fatigue (Mock et al., 2005) and improves QoL (Courneya & Friedenreich, 1998) in breast

cancer patients undergoing treatment. Findings are also consistent with those of a meta-analysis, which concluded that exercise is an effective intervention to reduce fatigue and improve QoL in breast cancer patients and survivors (McNeely et al., 2006). Furthermore, the results of the current study are consistent with those of an observational study, which found that obese breast cancer survivors who were physically active reported fewer depressive symptoms (Yeter et al., 2006).

Finally, alternative models were tested, including a reversal of the position of the variables, and findings suggested that the originally hypothesized direction of these associations was the most accurate representation of the relationships. The flow of the variables in the current study was such that PA preceded reduced FRDI and predated improvement in other psychological outcomes. However, those who are fatigued are consequently less physically active (Garber & Friedman, 2003), illustrating that fatigue may affect frequency of PA. However, it has been well-established in the literature that when examining this relationship in the context of psychosocial outcomes and the benefits of PA, the directionality is such that PA precedes fatigue changes (Mock et al., 2005). The idea that PA reduces fatigue is evidenced, in part, by studies which show that a lack of PA perpetuates exhaustive fatigue in people with chronic fatigue (Vercoulen et al., 1994). This is supported by theoretical explanations, which describe the directionality of the relationship between fatigue and PA and is put forth by the ACSM (2005). The ACSM suggests that the maintenance of functional capacity via exercise or PA regimen promotes less energy expenditure in activities of daily living. Another proposed mechanism by which PA improves fatigue is via enhanced coping ability and self-

efficacy. Increased self-efficacy and ability to cope with daily stressors may lead to greater participation in daily activities and a lower subjective fatigue appraisal (Courneya et al., 2003). Further explanations are given by Pinto and colleagues (2003) to describe how PA enhances QoL and mood outcomes via decreased fatigue. This theory suggests that while PA leads to a reduction in fatigue, women who are less fatigued are able to participate in daily activities that make life meaningful, and, in turn, these women have better QoL and ultimately fewer depressive symptoms. The current study is unique in that it uses SEM to test these theories at two time points along the cancer spectrum.

As noted, this model was estimated at the 3-month post-intervention time point to determine whether these relationships were comparable, when women were farther along in treatment. This is yet another unique aspect of the study, as an examination of the stability of a proposed model at two time points based on theoretical explanations has not been tested before in breast cancer research. Results supported the hypothesis that these direct and indirect relationships are stable over time, such that women who were physically active while receiving adjuvant treatment reported less daily interference as a result of fatigue, better functional QoL, fewer depressive symptoms, and less depressed mood. The model was again adjusted for treatment-related covariates to control for confounding factors. After tests of alternative models and a multi-group analysis to test for differences based on ethnicity, the best representation of the relationship was consistent with that of Model T1. The relationship between PA and FRDI slightly changed, such that this association, while significant at the baseline assessment, was found to be borderline significant at this post-intervention assessment. It is plausible that



individual differences in the timing of the women's adjuvant therapy regimens may account for differences in FRDI and should therefore be accounted for. However, this was not measured in the current study.

Given that many of the women in this study had received chemotherapy or radiation, it is possible that the fatigue experienced at this time point is even greater as a result of biological changes, and therefore difficult to change. For instance, adults receiving chemotherapy and radiation experience a decline in lymphocyte populations, such as CD4 T cells. Furthermore, these immune components are slow to recover following cancer treatment (Hakim et al., 1997). Lower CD4 T cell natural killer cell counts have been associated with cancer-related fatigue (Bower, Ganz, Aziz, & Fahey, 2002). Inflammatory processes at the time of treatment are also responsible for increased fatigue (Bower, Ganz, Irwin, Arevalo, & Cole, 2011). Therefore, one possibility is that PA and FRDI are not as highly related as they were at baseline because fatigue at this time point may be compounded by inflammatory and immune-related factors tied to dosage and regimens of adjuvant therapies. On the other hand, it is possible that the observed association between PA and FRDI at this time point is in fact due to a decrease in inflammation. As a result of evidence of reduced inflammatory processes via PA, investigators have suggested it is a worthwhile behavioral therapy for reducing cancer patients' inflammation-related fatigue (Bower et al., 2011).

Overall, the findings at this time point during adjuvant treatment are consistent with prior studies of PA in the context of active cancer treatment. Physical exercise interventions, both home-based (Mock et al., 1997; Schwartz, Mori, Gao, Nail, & King,

2001) and hospital-based (Dimeo et al., 1999), have been shown to successfully reduce fatigue levels in women undergoing active treatment for breast cancer (both radiation and chemotherapy). In addition, while most studies relating QoL and PA have been conducted in the survivorship phase of breast cancer, some studies have evaluated this relationship during active treatment and found that PA improves QoL (Mock et al., 2005; Holmes et al., 2005; McNeely et al., 2006). With regard to outcomes of depressed mood and rated depression, most studies have also focused on breast cancer survivors, and the information is lacking about the potential benefits for PA on depression during active treatment (Markes et al., 2006). However, studies have found that aerobic exercise for breast cancer survivors decreased depression over time (Segar et al., 1998). The potential mechanisms of the beneficial effects of PA on fatigue, QoL, rated depression, and depressed mood are the same as those described above in relation to the T1 model. However, precautionary measures should be taken, when engaging in PA while undergoing active treatment. Cancer patients who have co-morbid conditions, especially those related to cardiovascular health, should consult their physician prior to engaging in a strenuous exercise routine. Furthermore, patients who experience side effects of adjuvant treatment such as chemotherapy-induced anemia, thrombocytopenia, and neutropenia, should be carefully monitored while engaging in exercise. A study by Courneya and colleagues (2008) tested the effects of exercise for anemic cancer patients and found it to be feasible for these patients. Although these are usually temporary states, it would be important for the patients to have medical supervision if they are at risk for these conditions (Courneya & Friedenreich, 1999). Furthermore, most research has been

conducted in non-metastatic disease, including the current study. Therefore, it would be advisable for patients with metastatic disease to consult an exercise specialist and their physician before engaging in exercise. For breast cancer patients in particular, the risk of developing lymphedema in the affected arm following removal of positive lymph nodes has been of concern. While women often do limit movement to avoid risk of injury to this arm, a recent randomized controlled trial demonstrated that women in a weight lifting group were no more likely to develop lymphedema than women who were not in the exercise group (Schmitz et al., 2010). A study testing the safety and feasibility of a group exercise training program for women with breast cancer reported no adverse events, further highlighting the safety of aerobic exercise for women at risk of developing lymphedema (Kolden et al., 2002). Despite the safety and feasibility of aerobic exercise, factors such as variability in stage of disease, type of adjuvant treatment, pre-existing health conditions, and individual exercise tolerance, reinforce the importance of consulting a medical expert prior to engaging in exercise. Given that PA is mostly safe and feasible for women with breast cancer, the following sections elaborate on the most prevalent treatment-related symptoms and the specific relationships among PA, fatigue, depression, and functional QoL.

Stability of the model computed with difference scores for each variable provided further evidence for the consistency of the relationships and their causal flow in the model. This study is unique in the evaluation of the relationships in a complex model with respect to change over time during the cancer spectrum. The model estimated with change scores demonstrated that change in PA was directly associated with change in

FRDI and change in functional QoL and depressed mood via FRDI. The model was adjusted for covariates and alternative tests were performed, again revealing that the original estimation was the superior fit. However, while the indirect path from PA to depressed mood was significant using the change scores, the indirect path from PA to rated depression was no longer significant. It is possible that once the CBSM intervention is administered, other intervention-related factors may account for the effect on rated depression above and beyond the benefits of PA. For instance, previously published findings of the effects of the 10-week CBSM intervention by this group demonstrated that women in the CBSM group showed improved depression (Antoni et al., 2006a) as well as social well-being, positive states of mind, benefit finding, and positive affect (Antoni et al., 2006b). Furthermore, findings suggested that the improved psychosocial outcomes were mediated by an increase in confidence about the ability to relax. This provides evidence for the possibility that the stress management skills contribute more significantly to outcomes of depression than do PA once the intervention is administered.

While some research has demonstrated beneficial effects of PA on depression in breast cancer survivors, more studies are needed to determine whether PA may have this effect prior to onset of adjuvant treatment (Segar et al., 1998). The indirect effect finding of PA and rated depression and depressed mood in the T1 and T2 models adds to this evidence base by showing that PA is beneficial in reducing depressive symptoms following surgery and during active treatment. Furthermore, while investigators are beginning to explore potential mechanisms by which exercise reduces depression, these mechanisms are largely unknown (Ströhle, 2009). The current finding that less daily

fatigue interference is a pathway by which PA and rated depressed mood are associated suggests that FRDI is a potential mediator, thereby contributing to the understanding of these previously unknown mechanisms. The findings of the post-intervention model, which are pertinent to women who are receiving or completed radiation, chemotherapy, or endocrine treatment, are consistent with studies showing that breast cancer survivors who report to be engaged in a regular exercise routine are less depressed, less fatigued, and report a higher QoL (Daley et al., 2007; Pinto & Trunzo, 2004).

These findings inform future research questions. Though the model in which Hispanic and non-Hispanic white women were grouped separately was not a better fit for the data, future work may want to explore this question in more detail, especially as it relates to Spanish-speaking Hispanic women and other racial groups, such as African American women. Furthermore, future work could investigate whether this model is stable at a post-treatment, survivorship period, when women are experiencing fewer side effects from treatment, but may be experiencing side effects from long-term endocrine treatment or late-onset effects. While this study included only women with non-metastatic stage 0-III disease, future research could examine the effects of PA on fatigue, QoL, rated depression, and depressed mood in women with metastatic breast cancer. Finally, these findings may or may not generalize to other cancer patients. For example, evidence suggests that a PA intervention for men with prostate cancer may be beneficial in alleviating fatigue and depressive symptoms (Culos-Reed et al., 2010). Investigation into whether these findings exist in different racial and ethnic groups, patients of a more

advanced disease stage, and patients with different types of cancer, including men, is important in order to determine the generalizability of the results.

### **Additive Effects of Physical Activity and CBSM**

The final hypothesis in the current study aimed to determine if PA had an additive effect on FRDI once the known effects of CBSM on FRDI were accounted for. Results showed that the association between PA and FRDI added significantly to the model. This suggests that women who were not randomized to the intervention group may still be able to reduce their fatigue by way of PA. This is important because it further supports evidence for both psychosocial interventions and PA interventions as category 1 non-pharmacological interventions for reducing cancer-related fatigue (Mock et al., 2007). In addition, this may be important information for investigators to keep in mind, when interpreting outcomes of a psychosocial intervention trial. For instance, researchers may want to collect comprehensive information about the patterns of PA of their participants (type, duration, frequency, and intensity) using gold standard measures. Furthermore, researchers may consider controlling for potential confounding effects of PA on the outcome they are measuring by incorporating duration, frequency, and intensity of PA in the analyses. This will minimize the possibility of not finding effects due to confounding effects of PA, by removing variability related to PA from both groups. Furthermore, the significant association between PA and FRDI when accounting for condition may suggest a combined effect, such that women who received CBSM and were correspondingly physically active had even less daily interference due to fatigue.

This evidence is consistent with recent studies evaluating the effects of a combined psychosocial and PA intervention (Courneya et al., 2003). This randomized controlled trial evaluated the effects of a combined group psychotherapy and PA intervention versus group psychotherapy alone on outcomes of fatigue and QoL for survivors of different cancer types. These researchers hypothesized that while the psychotherapy component would lead to improved psychological outcomes, the PA component would result in better physical outcomes, such as physical QoL, and therefore the combined intervention would span both improved psychological and physical outcomes. Findings revealed that participants in the combined group psychotherapy and PA intervention reported less fatigue and greater functional QoL than participants in the group psychotherapy alone (Courneya et al., 2003). The findings of the current study are consistent with these, in that both PA and a psychosocial intervention were significantly associated with fatigue and functional QoL. Other similarities between the current study and one described here, include outcome measures of fatigue and QoL as important determinants of mental health. In addition, the current study uses functional QoL, as the other study did, given evidence that functional QoL, out of all QoL dimensions, maps on the best to overall life satisfaction (Courneya & Friendreich, 1997).

The Courneya study has some limitations. To begin, the study design compared a group psychotherapy plus exercise to group psychotherapy alone. Without a true control group, it is difficult to determine whether the effects are a result of the intervention or a product of social support and group dynamic. The current study compares CBSM to an educational control, and therefore it is accurate to make the interpretation that changes in

the intervention group, which are not seen in the control group, are actually due to techniques and skills learned in the intervention or to extra attention in the CBSM versus the control group. Second, Courneya's study did not include longer-term follow-up assessments. A strength of the current study is the two time points along the cancer spectrum that may be compared and contrasted to determine the stability of the PA-FRDI relationship over time. Third, participants in the study by Courneya and colleagues range from 1 to 5 years post-diagnosis. This is time range may include surgical procedures, adjuvant treatment, reconstruction, and prolonged endocrine therapy. This broad time frame complicates the interpretation of the findings due to the many different factors at play during these years, which could influence mental health outcomes. In contrast, the current study analyzes the effects at each time point separately and also controls for the number of days since diagnosis was made in the model. Furthermore, while the study by Courneya and colleagues incorporates all patients with different types of cancer, potentially increasing generalizability of findings, this can also be misleading as one of the cancer groups may be driving this effect. Therefore, a strength of the current study is the homogenous sample of breast cancer patients. In addition, since Courneya's study contained a mostly non-Hispanic white sample, analyses to determine differences among groups were not conducted. This is a strength of the current study. An additional strength of the current study, as compared to Courneya and colleagues, is the tests of psychosocial mediators to determine the underlying processes between PA-QoL and PA-depression associations. Moreover, the larger sample size is a strength of the current study as compared to the one by Courneya and colleagues. Finally, the use of SEM in the current



study is a strength because it allows for flexibility and unique causal modeling. Specifically, SEM allows for testing of multiple linear regressions in one complex model, rather than separate tests of each association. In addition, it allows for comparison of plausible models through nested chi-square tests to determine the best representation. SEM also provides an efficient approach for handling missing data (Tomarken et al., 2005).

Hypotheses of another randomized controlled trial, which investigated the effects of a brief intervention consisting of stress management psycho-education and PA for breast cancer survivors were supported by a different school of thought, the theory of unifying PA. The theory of unifying PA (Salmon et al., 2001) illustrates that while exercise has disagreeable aspects, PA ultimately reduces depressive and anxiety symptoms and increases stress resistance. Unpleasant aspects of exercise include levels of exercise intensity that are above the normal level for that individual, and which, in turn, may worsen mood. Another unpleasant aspect may be an exercise that is associated with a competitive nature, and therefore, in turn, also likely to lead to a negative, rather than positive mood. The model purports that once tolerance for these dislikeable aspects is in place, tolerance for other stressors also increases. As a result, adherence to an exercise regimen is maintained. Furthermore, the theory takes into account the interaction of biological and psychological mechanisms by demonstrating that biological changes, such as PA-induced increases in serotonin, norepinephrine, and opioids, results in increases in energy and mood. This model shows evidence for psychological effects of PA that are mediated by biological changes and also provides an explanation for how PA may

enhance the ability to adapt to and manage stress (Salmon et al., 2001). Therefore, these researchers hypothesized that stress reduction via both PA and stress-management education would lead to better health outcomes than either modality alone. Results of this study found that breast cancer survivors who received this intervention had less fatigue, more energy, less emotional distress, and better physical QoL as compared to those in the control group (Fillion et al., 2008). Findings of the current study are consistent with those of Fillion and colleagues, although women in their study were in the survivorship period. A strength of the current study is the longer intervention time span of 10-weeks, while the stress management and PA intervention used by Fillion and colleagues was only a brief 4-week period of time. In addition, the study is limited by a smaller sample size ( $n = 87$ ). The generalizability of their findings is limited given their inclusion criteria that women must have received some form of radiotherapy. In contrast, in the current study, women who had all types or combinations of adjuvant treatment were included, and therefore findings are applicable to a more broad range of women.

While studies combining a physical exercise intervention and a psychosocial intervention has increased, more research is needed related to breast cancer patients and in chronic illness overall. A recent meta-analysis concluded that studies are needed that combine behavioral interventions, such as physical exercise with psychosocial interventions, suggesting that a combined intervention may have greater effects (Duijts, Faber, Oldenburg, van Beurden, & Aaronson, 2011). In addition, in order to best determine whether these combined effects are superior, study designs should compare a combined PA and psychosocial intervention to PA intervention alone, a psychosocial

intervention alone, and an attention-matched control group (Fillion et al., 2008). A breakdown of the study arms in this way will allow researchers to disentangle the intervention and better understand the processes of each intervention alone versus both combined. Furthermore, a limitation of the study by Courneya and colleagues (2003) is the unsupervised PA component. Future research should use a supervised PA intervention, so that it is standardized across all participants. Furthermore, studies should measure participation in PA outside of the intervention, including work-related PA and leisure and non-leisure PA to control for these effects. Moreover, different types of physical exercise should be evaluated in addition to a cardiovascular training routine. For example, evidence supports the benefits of integrated yoga program for reducing anxiety, depression, perceived stress, and cortisol levels in breast cancer patients undergoing active treatment (Raghavendra et al., 2009). In addition, a combined aerobic and resistance training program has been shown to have beneficial effects on QoL in breast cancer survivors (Herrero et al., 2006), while not increasing risk for lymphedema (Schmitz et al., 2010).

### **Mechanisms: PA and FRDI**

Preliminary analyses by our group have shown that participation in CBSM leads to statistically significant reductions in fatigue-related disruption. The results of this study show that increases in PA are associated with reduced FRDI above and beyond the association between CBSM and PA. Interpretation of these results may be that PA and CBSM have additive effects. It may be that PA and CBSM are beneficial in reducing FRDI via different mechanisms. While the evidence in support of the relationship

between PA and fatigue is strong (Mustian et al., 2007; Mitchell et al., 2007; Conn et al., 2006), the mechanisms by which PA causes a reduction in fatigue-related phenomena is less studied. The effect of PA on fatigue-related disruption may be mediated by an increase in self-efficacy (McAuley, White, Rogers, Motl, & Courneya, 2010; Ströhle, 2009). Literature that supports self-efficacy as a mechanism suggests that women who are more physically active have greater self-confidence in their functional capacity and therefore engage in activities involving energy expenditure and rate their subjective fatigue as less intrusive or disruptive. Furthermore, theories that explain the benefits of PA for reducing fatigue suggest that decreased PA during cancer treatment results in a reduced capacity for physical functioning, which leads to an increased energy expenditure in activities of daily living and therefore increased fatigue (ACSM, 2005). In addition, the unifying theory of PA, as described previously, is another potential mechanism by which PA improves levels of fatigue through an interaction of psychological and biological changes. The results of the current study did not reveal changes in levels of fatigue intensity. A plausible explanation for this is that changes in FRDI are less attributed to physiological changes and are more so attributed to a change in a woman's attitude or cognitions about completing her daily routines (self-efficacy). This would suggest that while PA and CBSM may not alter cancer-related fatigue, these behavioral modalities lead a woman to adjust her perception of fatigue as intrusive, in turn, enhancing her ability to perform activities of daily living as usual.

## Physical Activity and Cancer Progression

Both inflammation and suppressed immune function have been identified as important biological factors in the progression and recurrence of cancer, and along with other biomarkers, are the focus of many epidemiological studies assessing cancer risk (Campbell & McTiernan, 2007). Cancer progression has been shown to be influenced by psychosocial and physiological processes relating to stress, depression, and social isolation (Lutgendorf, Sood, & Antoni, 2010). In patients with hepatobiliary carcinoma, depression and immunity were significant predictors of survival, and preliminary evidence suggests that the relationship between depression and survival may be mediated by natural killer cell counts (Steel, Geller, Gamblin, Olek, & Carr, 2007). Stress-related immunosuppression has been shown to decrease tumor surveillance, leading possibly to cancer progression or metastases (Lutgendorf et al., 2010). These underlying stress processes involved in cancer progression are evidence for the importance of implementing behavioral techniques to help cancer patients adaptively cope with stress, reduce depression, and enhance use of social support.

It has been suggested that PA can affect the biological processes associated with preventing the initiation and progression of carcinogenesis (Rogers, McAuley, Courneya, & Verhulst, 2008). Research suggests that the endogenous opiates, which are elevated during exercise, have effects on immune function (LaPerriere, Ironson, Antoni, & Schneiderman, 1994). Benefits of PA are conceptualized as protective, referring to the increase in activity and quantity of innate immune cells, such as macrophages, cytotoxic T lymphocytes, and natural killer cells, following bouts of exercise (Shepard & Shek,

1995). However, the field of exercise immunology has elaborated on this statement based on the varied dosage effects. The “Inverted J Hypothesis” illustrates that while moderate intensity exercise leads to enhanced immune function, high, vigorous intensity results in immunosuppression (Woods et al., 1994). This theory is well-supported. For instance, while exercise of a moderate intensity is associated with decreased upper respiratory tract infections (URTI’s), high intensity and exhaustive training is actually linked with an increase in URTI’s (Nieman, 1994). Following exercise of moderate intensity, production of pro-inflammatory cytokines, such as interleukin1- $\beta$  (IL-1 $\beta$ ), IL-6, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interferon- $\gamma$  (INF- $\gamma$ ), are shown to increase (Moldovean, Shephard, & Shek, 2001). On the contrary, exhaustive and rigorous training has been found to have an initial pro-inflammatory response, followed by immune suppression, identified by the increase in production of anti-inflammatory cytokine antagonists such as IL-1 receptor antagonist, IL-4, and IL-10, as well as substantial drops in numbers of innate immune cells (Nieman, 1997; Pedersen, Ostrowski, Rhode, & Bruunsgaard, 1998). Based on these observations, investigators call attention to the crucial balance of pro-inflammatory and anti-inflammatory responses to maintain optimal immune function (Allgayer, Nicolaus, & Schreiber, 2004).

Research by Marcell and colleagues (2005) supported an inverse relationship between systemic inflammation and PA. In fact, different levels of PA can affect both local and systemic production of cytokines (Marcell, McAuley, Traustadóttir, & Reaven, 2005). For instance, IL-1, one of the initial cytokines to be released in response to exercise-induced stress, is highly dependent on dosage of exercise, including intensity

and duration. Furthermore, the pro-inflammatory cytokine TNF- $\alpha$  may be influenced by improved functional capacity as a result of regular exercise and increased endurance (Moldoveanu et al., 2001). Additional studies are needed to explore the exercise-mediated immune shift to a more pro-inflammatory response and any possible connections with clinical outcomes, disease progression, and tumor recurrence (Allgayer et al., 2004). While preliminary research suggests that biobehavioral pathways underlying tumor progression and recurrence can be altered through psychosocial and/or PA interventions, more research is needed to examine these mechanisms (Lutgendorf et al., 2010).

### **Research Contribution**

The current study adds to the literature base outlining the benefits of PA for women with breast cancer. First, most research examines benefits of PA on depression post-treatment or in the survival phase (Markes et al., 2006). Exercise intervention trials during treatment have recently increased, yet more studies need to be conducted. Therefore, this research contributes to the evidence base by examining psychological outcomes during the post-surgical period as women are preparing for adjuvant treatment and during active treatment. The current findings are sensitive to the period of time between surgery and adjuvant treatment for non-metastatic breast cancer, when health behaviors such as PA may be instrumental in improving recovery from surgery and adjuvant treatments and possibly longer-term prognosis. In addition, many studies examining the effects of PA on functional and emotional outcomes in women with breast cancer have small sample sizes (<100), thereby minimizing power of statistical analyses.

A strength of this study is the larger sample size. Few studies have applied SEM to identify symptom clusters and predictive relationships due to small sample sizes. The current study has a sufficient sample size to use such statistical modeling to test hypotheses concerning predictive relationships (direct effects) and the intermediary paths explaining these associations (indirect effects). While research has revealed the potential benefits of PA on QoL and FRDI for women with breast cancer, the current study identifies that a reduction in fatigue-related daily interference may mediate the PA-QoL relationship and the association of PA and depression in this population. Furthermore, this study uniquely assesses the additive contribution of a psychosocial intervention (CBSM) and PA, which is less studied in the context of active treatment for breast cancer. The finding that PA produces an added effect to the group-based stress management informs future research in combining psychosocial treatments with PA or evaluating their effects separately.

### **Limitations**

Limitations of the current study should be considered in the interpretation of the results. To begin, all measures used in the current study were self-report (including the interviewer-administered HRSD) and therefore may be subject to participant report bias. For instance, women may over- or under-estimate the amount of PA they engage in per week as well as over-/under-estimate their fatigue-related disruption, depressive symptoms and QoL. Second, it should be of note that this study was not a PA intervention study, nor was the intervention designed to increase duration or frequency of PA behavior. Physical activity was measured as a variable of interest, and therefore



future research may implement objective measures of PA (such as cardiovascular fitness with a  $VO_2$ max assessment or pedometer recordings) to improve accuracy in reporting. Third, since the latent fatigue construct was not a good fit for the data, a specific subscale of the FSI (fatigue-related daily interference) was used instead. Fatigue as a latent construct may lead to more generalizable findings. Fourth, the Hamilton Rating Scale for Depression contains a specific item related to somatic manifestations of depressed mood. This item includes fatigue and therefore may be confounded with the FSI. Thought was given as to whether to re-compute the scale without this item. However, the item was retained, due to the fact that the particular item refers to any musculoskeletal complaints and headaches. Furthermore, although analyses controlled for whether women received adjuvant treatment, it would be helpful to control for the date that adjuvant treatment was completed. These data were not collected systematically in the present study, however it would be beneficial to incorporate adjuvant treatment offset in future research. In addition, future analyses may take into account whether women are taking medications which affect depression, anxiety, and sleep. Finally, due to the cross-sectional nature of the mediational type model, caution must be taken in interpreting the results. Although alternative tests were conducted to provide support for the most plausible flow of the relationships from one to another, mediation cannot be inferred without a longitudinal study design.

### **Clinical Implications**

These findings have clinical implications for the type of information that women receive upon diagnosis in reference to lifestyle changes. Research shows that levels of PA

drop significantly following a breast cancer diagnosis, and that this effect is even larger for women undergoing radiation and chemotherapy treatment (Irwin et al., 2003). It may be important for the medical care team to encourage patients to maintain or increase PA in an effort to minimize depressive symptoms, enhance QoL, and mitigate treatment side effects, such as cancer-related fatigue. Staff may refer women for supervised PA with trainers who specialize in exercise for women with breast cancer. Furthermore, engaging in PA throughout the course of adjuvant treatment may also be beneficial in maintaining these psychological improvements and preventing worsening of fatigue upon completion of adjuvant treatment. Finally, these findings suggest that it would be important for women to receive some type of psychosocial support, psychotherapy, or CBSM in addition to maintaining a physically active lifestyle. With more research into the combined effects of PA and psychosocial intervention, comprehensive cancer centers that offer support for patients may be able to integrate these services and encourage patients to participate in both.

Overall, this study contributes to the evidence base for the benefits of PA for women with breast cancer at time of surgical recovery and during active treatment. These findings provide support for the possible benefits of moderate to vigorous PA on FRDI, functional QoL, rated depression, and depressed mood for women who have recently undergone surgery for non-metastatic breast cancer. Women who are diagnosed with non-metastatic, stage 0-III breast cancer may be able to reduce the amount of fatigue that interferes with their daily activities, attenuate depression and depressive symptoms, and enhance their functional QoL through increased physical exercise. In addition, results

suggest that these beneficial effects are maintained while women are receiving active adjuvant treatment for breast cancer. Finally, findings suggest that CBSM in combination with moderate to vigorous PA is associated with attenuated daily fatigue interference. Future research is needed to delineate mechanisms by which PA and FRDI are related for breast cancer patients, and more randomized controlled trials are needed to assess whether a combined PA and psychosocial intervention is superior to either PA or psychosocial intervention alone.

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Table 1  
Demographic and Medical Variables by Condition at Baseline.

Variable	Control	Intervention	Statistic	p
Age	50.99 (9.06)	49.69 (8.98)	$F(1, 238) = 1.25$	0.27
Years education	15.47 (2.26)	15.69 (2.5)	$F(1, 238) = 0.53$	0.47
Ethnicity	74 (61.7%) White non-Hispanic 31 (25.8%) Hispanic 10 (8.3%) African American 4 (3.3%) Asian	78 (65.0%) White non-Hispanic 30 (25.0%) Hispanic 11 (9.2%) African American 1 (.8%) Asian		
Married/partnered	75 (62.5%)	75 (62.5%)	$\chi^2(3, N=239) = 1.97$	0.58
Employed	92 (76.7%)	86 (71.7%)	$\chi^2(1, N=240) = .000$	1.00
Stage	19 [0]; 51 [I]; 41 [II]; 8 [III]	19 [0]; 39 [I]; 50 [II]; 11 [III]	$\chi^2(1, N=240) = .783$	0.38
Procedure	52 (43.3%) Mastectomy 68 (56.7%) Lumpectomy	66 (55.0%) Mastectomy 54 (45.0%) Lumpectomy	$\chi^2(3, N=238) = 2.96$	0.40
Radiation	51 (42.5%)	48 (40.0%)	$\chi^2(1, N=240) = 3.27$	0.07
Chemotherapy	48 (40.0%)	55 (45.8%)	$\chi^2(1, N=193) = .463$	0.79
Hormonal	50 (41.7%)	56 (46.7%)	$\chi^2(1, N=193) = 2.52$	0.28
Time since surgery (days)	44.7 (25.47)	36.63 (19.99)	$F(1, 229) = 7.21$	.008**

Note: Standard deviations and percentages are in parentheses, \*\*p<.01

Table 2  
Covariance Matrix for Variables in Model II

	1.	2.	3.	4.	5.	6.	7.	8.	9.
1. FRDI	3.877								
2. Functional QoL	-6.572	33.554							
3. Rated Depression	4.472	-13.216	27.811						
4. Depressed Mood	2.924	-9.325	7.381	10.345					
5. Hours of PA	-1.806	5.794	-2.663	-1.421	22.221				
6. Time Since Surgery	-0.118	9.148	4.978	-0.836	11.161	539.196			
7. Age	-2.562	7.096	-8.537	-0.836	0.427	2.482	81.802		
8. Stage	0.316	-1.261	0.419	-5.61	-0.387	0.035	-1.512	0.695	
9. Procedure	0.035	0.027	-0.031	0.022	0.19	1.036	0.019	-0.053	0.475

Table 3  
Means and Standard Deviations for Study Variables at the Baseline (T1) Assessment.

Variable	Mean (SD) or Percentage
FRDI	3.55 (1.97)
Functional QOL	18.37 (5.77)
Rated Depression	7.37 (5.46)
Depressed Mood	9.87 (3.22)
Hours of PA	2.81 (4.76)
Days since Surgery	40.7 (23.19)
Age	50.55 (9.03)
Stage	15.8% [0]; 3.9% [I]; 3.9% [II]; 7.9% [III]
Procedure*	48.2% (1); 49.8% (2)

\* For surgical procedure, 1=mastectomy, 2=lumpectomy



Table 4  
Covariance Matrix for Variables in Model T2

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
1. FRDI	2.975										
2. Functional QoL	-6.426	28.304									
3. Rated Depression	4.647	-15.109	26.476								
4. Depressed Mood	1.79	-6.736	5.622								
5. Hours of PA	-1.217	1.873	-2.651								
6. Time Since Surgery	-0.819	-5.987	-7.706	5.17	31.366	561.204					
7. Age	-2.591	7.091	-7.195	-1.806	-4.743	11.568	76.229				
8. Procedure	-0.014	0.229	-0.256	-0.017	-0.093	0.815	0.429	0.464			
9. Chemotherapy	0.301	-0.784	0.383	-0.007	-0.071	-1.269	-1.286	-0.03	0.249		
10. Radiation	0.00	0.138	-0.288	-0.086	-0.187	0.239	0.681	0.069	0.006	0.291	
11. Tamoxifen	-0.142	0.477	-0.216	-0.268	-0.317	-1.894	0.258	0.022	-0.024	0.024	0.247

Table 5  
Means and Standard Deviations for Study Variables at the Post-Intervention (T2) Assessment

Variable	Mean (SD) or Percentage
FRDI	2.84 (1.77)
Functional QOL	20.83 (5.30)
Rated Depression	6.07 (5.1)
Depressed Mood	8.89 (2.67)
Hours of PA	4.98 (6.96)
Age	51.6 (9.03)
Procedure <sup>1</sup>	48.2% (1); 49.8% (2)
Chemotherapy <sup>2</sup>	37.5% (1); 42.9% (2)
Radiation <sup>2</sup>	39.2% (1); 41.3% (2)
Tamoxifen <sup>2</sup>	36.3% (1); 44.2% (2)

<sup>1</sup>For surgical procedure, 1 = mastectomy, 2 = lumpectomy.

<sup>2</sup>For each adjuvant regimen: 1 = no, 2 = yes.

Table 6  
Covariance Matrix for Variables in T1-T2 Change Model

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.
1. FRDI $\Delta$	3.299										
2. Functional QoL $\Delta$	-4.007	27.2									
3. Rated Depression $\Delta$	1.348	-2.51	26.55								
4. Depressed Mood $\Delta$	1.628	-6.466	2.719	9.732							
5. Hours of PA $\Delta$	-2.231	5.962	-4.206	-3.041	51.138						
6. Time Since Surgery	0.927	-17.146	-11.128	6.368	20.235	561.204					
7. Age	0.479	-0.892	0.76	3.582	-4.524	11.568	76.229				
8. Procedure	-0.032	0.261	-0.079	-0.113	-0.306	0.815	0.429	0.464			
9. Chemotherapy	0.057	-0.002	0.056	-0.285	0.246	-1.269	-1.286	-0.03	0.249		
10. Radiation	0.077	-0.285	-0.324	-0.022	-0.42	0.239	0.681	0.069	0.006	0.291	
11. Tamoxifen	-0.065	0.184	-0.138	-0.205	-0.063	-1.894	0.258	0.022	-0.024	0.024	0.247

Table 7  
*Mean Difference Scores for Predictor, Mediator, and Outcome Variables (T1-T2)*

Variable	Mean (SD)
FRDI $\Delta$	-0.736 (1.84)
Functional QOL $\Delta$	2.403 (5.21)
Rated Depression $\Delta$	-1.313 (5.25)
Depressed Mood $\Delta$	-1.001 (3.13)
Hours of PA $\Delta$	2.178 (7.9)

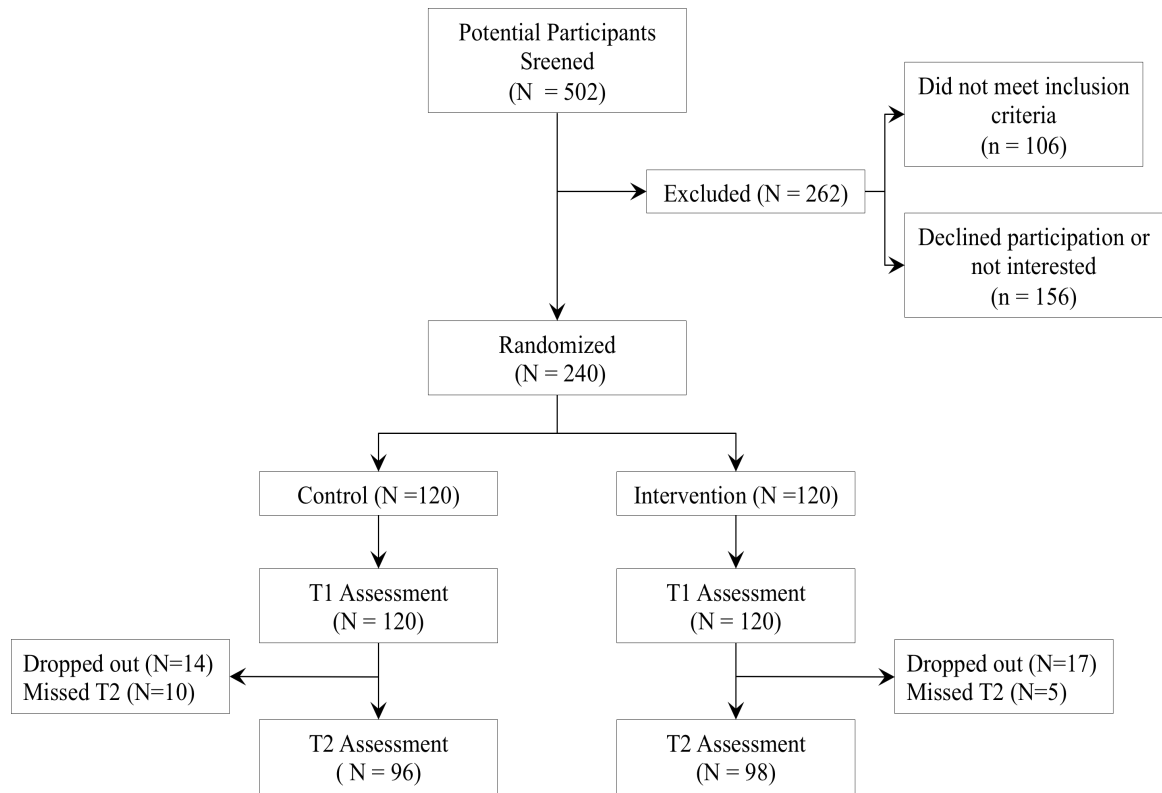


Figure 1 .CONSORT Diagram

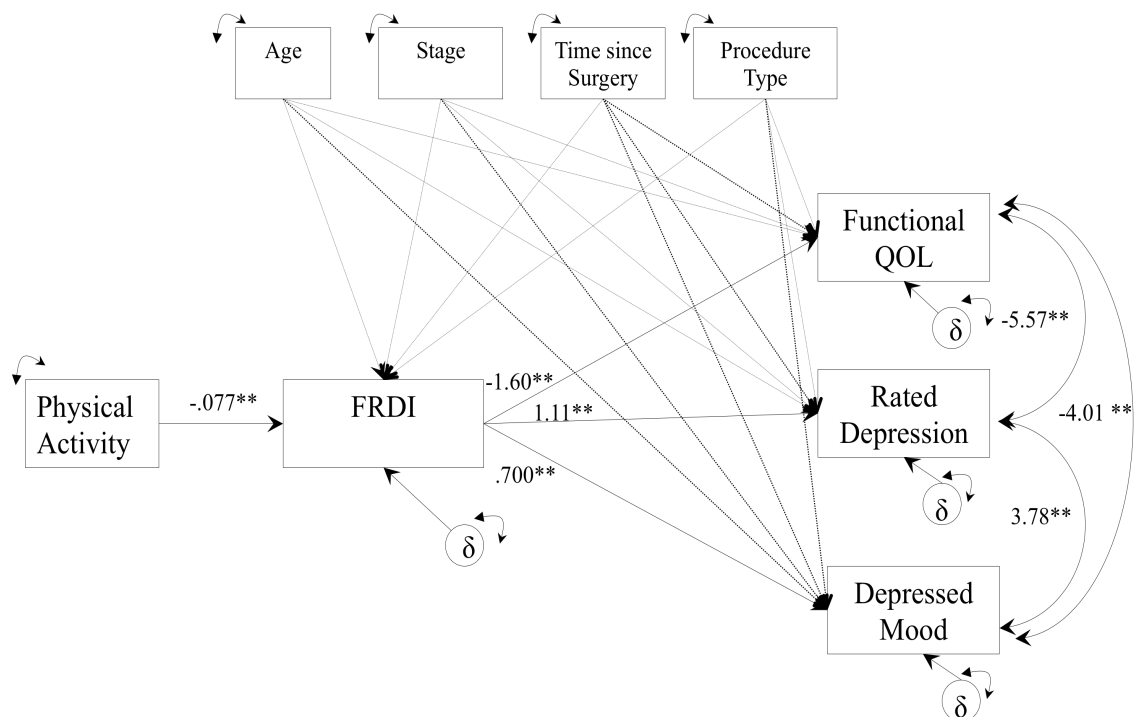
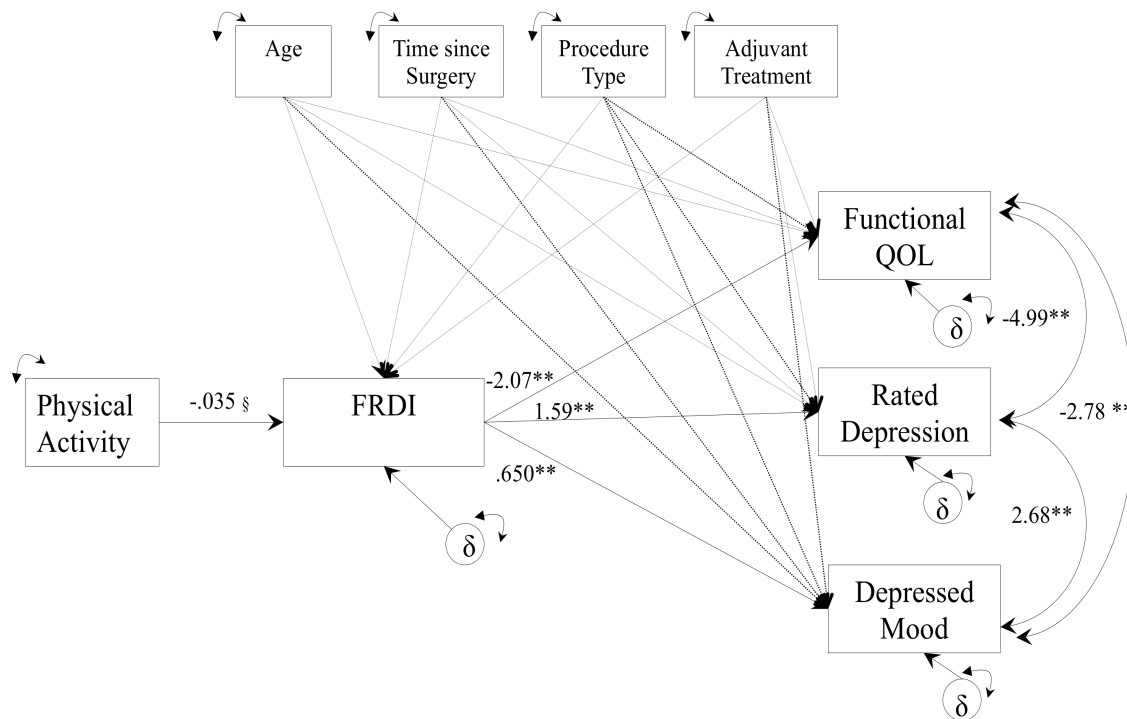
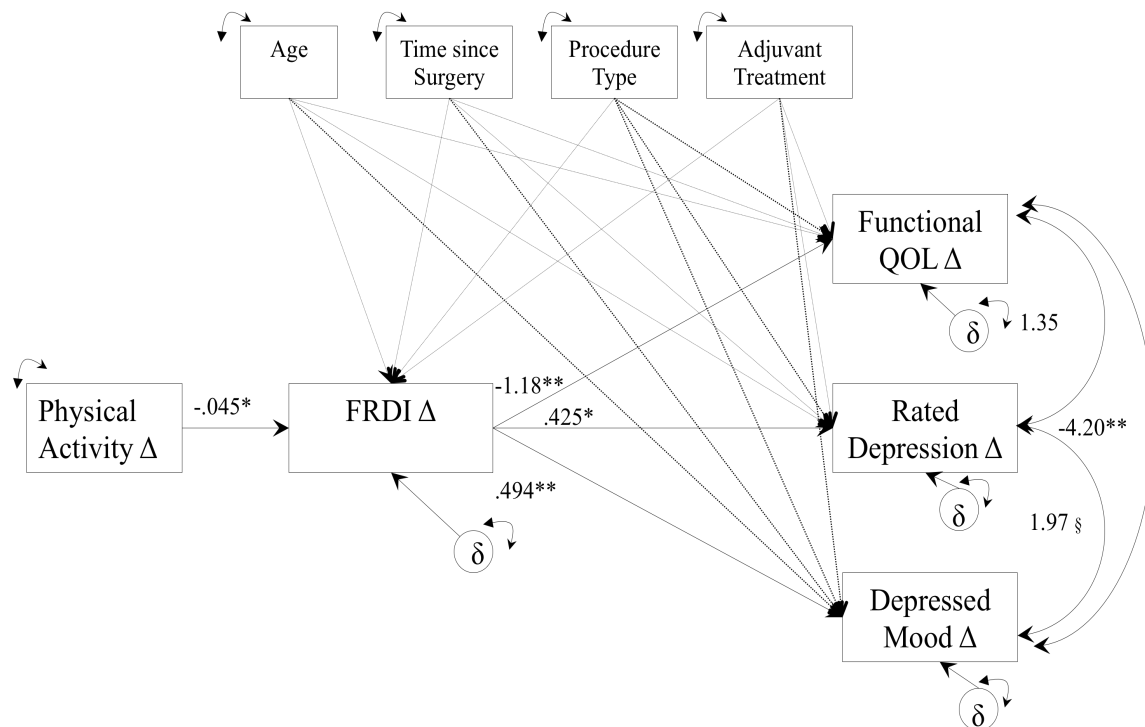


Figure 2. Model T1 (Baseline) Illustrating the Direct Paths between Physical Activity and Fatigue-Related Daily Interference (FRDI), and Indirect Paths between Physical Activity and Functional QoL, Rated Depression, and Depressed Mood, via FRDI (Tests of Aim1).  $**p < .01$ .



*Figure 3.* Model T2 (Post-intervention) Illustrating the Direct Paths between Physical Activity and Fatigue-Related Daily Interference (FRDI), and Indirect Paths between Physical Activity and Functional QoL, Rated Depression, and Depressed Mood, via FRDI (Tests of Aim 2).  $^{**}p < .01$ ; §  $p < .1$ .



*Figure 4.* T1-T2 Change Model (Difference From Pre-to Post-Intervention) Illustrating the Direct Paths between Physical Activity Change and Fatigue-Related Daily Interference (FRDI) Change, and Indirect Paths between Physical Activity Change and Functional QoL Change, Rated Depression Change, and Depressed Mood Change, via FRDI Change (Tests of Aim 3).  $^{**}p < .01$ ;  $^*p < .05$ ;  $§ p < .1$ .



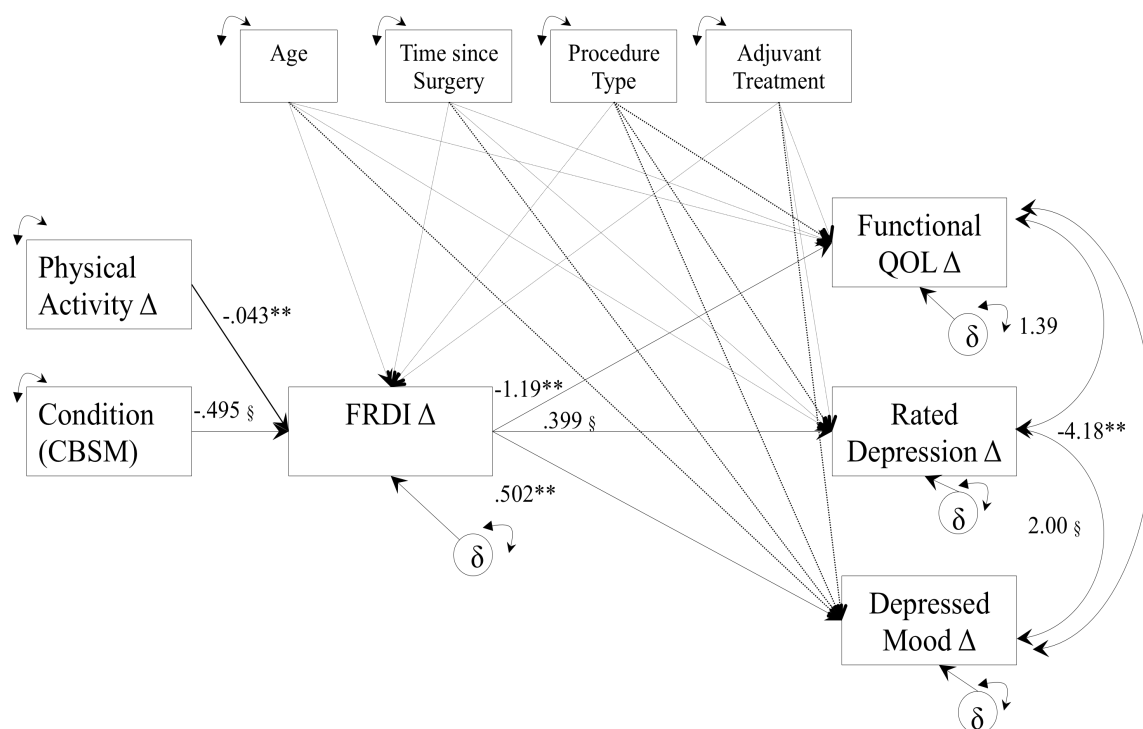


Figure 5. T1-T2 Change Model Illustrating the Additive Effects of Physical Activity Change and Cognitive-Behavioral Stress Management on Fatigue-Related Daily Disruption (FRDI) Change (Tests of Aim 3).  $^{**}p < .01$ ;  $^*p < .05$ ;  $\S p < .1$ .