# THE EFFECT OF MINDFULNESS-BASED STRESS REDUCTION ON BIOLOGICAL MARKERS OF STRESS, IMMUNE FUNCTION AND CELLULAR AGING AMONG BREAST CANCER SURVIVORS WITH CHRONIC NEUROPATHIC PAIN

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# Abstract

**Background:** Chronic neuropathic pain (CNP) is a common sequalae among breast cancer survivors. Nonpharmacological adjuvants are being increasingly recommended as first-line adjunct treatments for the management of CNP conditions which is consistent with a multidisciplinary biopsychological approach to optimize pain management. Mindfulness-based stress reduction (MBSR) is one of the most commonly applied mindfulness interventions in the treatment of CNP and has been shown to have preferential improvements in pain and overall health-related quality of life. Although mindfulness interventions have shown promise in the treatment of chronic illness and disease, it has yet to be studied in breast cancer survivors living with CNP after medical optimization. Thus, the effect of MBSR on CNP in this highly heterogenous and complex clinical population is unknown. Biological markers are objective measures of biological systems that can be used to gain insight into the mechanisms through which psychological interventions exert their effects. The aim of the first study was to use an interdisciplinary treatment approach to CNP in breast cancer survivors by exploring the effects of MBSR on pain, and biological markers of stress, immune function and cellular aging among breast cancer survivors with CNP after guideline-based medical optimization. A second study was conducted to explore the potential mediating role of mindfulness, and the individual facets, in this change process. **Methods:** A double-blind randomized waitlist control trial was conducted using a sample of 98 breast cancer survivors diagnosed with CNP. Women were randomized to receive an 8-week MBSR intervention or waitlist control condition after undergoing medical optimization. Biological samples and self-report measures of pain, physical function and emotional function were collected at baseline, two-weeks post-intervention and at 3-month follow-up. Separate analyses were performed using intention-to-treat and per-protocol principles. **Results:** MBSR was

delivered with fidelity and women randomized to MBSR demonstrated a significant increase in mindfulness relative to control. The MBSR intervention did not produce the anticipated stress reducing effects typically associated with mindfulness-based interventions. No differential changes in biomarker expression were observed between groups during the trial. Significant improvements in pain severity (intention-to-treat analysis) and pain-related interference (per-protocol analysis) were observed among women randomized to MBSR relative to control. Change in pain-related interference, but not pain severity, was found to be partially mediated by concomitant change in total mindfulness scores among women randomized to MBSR. **Conclusions:** Mindfulness interventions have gained significant traction in the treatment of chronic pain conditions. Despite this increase in popularity, our understanding of the association between mindfulness and pain is still evolving. Null findings can be used to help inform our understanding of adjuvant interventions in complex clinical patient populations, and identify what works for who, when and why. Mindfulness-based interventions are not homogenous, nor are they a panacea for disease and illness.

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# Dedication

This thesis is dedicated to my grandfather, Wilfred Giles,

who would have read every word with pride.

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# List of Abbreviations

| | |
|---|---|
| ACTH | Adrenocorticotropic Hormone |
| ANCOVA | Analysis of Covariance |
| ANOVA | Analysis of Variance |
| BPI-SF | The Brief Pain Inventory – Short Form |
| CNP | Chronic Neuropathic Pain |
| CRF | Corticotrophin Releasing Factor |
| FFMQ | Five Facet Mindfulness Questionnaire |
| HPA-axis | Hypothalamic Pituitary Adrenal Corticoid Axis |
| IL | Interleukin |
| IMMPACT | Initiative on Methods, Measurement and Pain Assessment in Clinical Trials |
| MAAS | Mindful Attention Awareness Scale |
| MBSR | Mindfulness-Based Stress Reduction |
| MCAR | Missing Completely at Random |
| MEMORE | Mediation and Moderation for Repeated Measures |
| NCCN | The National Comprehensive Cancer Network |
| NPSI | The Neuropathic Pain Symptom Inventory |
| PCS | The Pain Catastrophizing Scale |
| PGIC | Patient Global Impression of Change |
| PHQ-9 | The Patient Health Questionnaire –9 |
| POMS2 | Profile of Mood States-Adult |
| PSS | The Perceived Stress Scale |

# Chapter 1. Introduction

## 1.1 Overview

Breast cancer is the most frequently diagnosed cancer among Canadian women, with a lifetime risk of approximately 11% (Canadian Cancer Society, 2018). Although the incidence rate of breast cancer has increased over the past decade, from an estimated 22,000 new cases in 2007 to over 26,000 in 2017, mortality rates have significantly decreased (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2017). Advancements in medical science have led to improvements in detection, treatment and long-term prognosis among women with breast cancer, increasing the 5-year survival rate from 73% in the 1980's to 87% in 2006-2008 (Canadian Cancer Society, 2018). Survivorship refers to living with, through and beyond cancer (Denlinger et al., 2014). As survival rates improve, new challenges begin to emerge. Efforts directed at identifying and addressing the needs of breast cancer survivors has developed as an area of focus for research that seeks to optimize the duration and quality of life for breast cancer survivors.

A cancer diagnosis is followed by an array of interventions designed to target and cure the cancer and will vary based on stage of illness. Breast cancer treatment primarily consists of surgery, chemotherapy, radiation therapy, hormone therapy, and/or targeted therapy. Although the primary goal of treatment is to eliminate the cancer, and recent advancements have led to a favorable prognosis for women with breast cancer, treatment itself is often associated with symptoms that can be long-lasting and debilitating for the patient. A review of long-term symptoms in cancer survivors in the United States reported that more than 50% of breast cancer

survivors experience lasting treatment-related side effects (Valdivieso, Kujawa, Jones, & Baker, 2012), with the most common being depression (approximately 30% following treatment), pain (26-47% in the first 6-months post-treatment), and fatigue (59% within first two years post-treatment; Harrington, Hansen, Moskowitz, Todd, & Feuerstein, 2010). Chronic neuropathic pain (CNP) is a common sequela among breast cancer survivors affecting 25% to 60% of individuals (e.g., post-surgical CNP, acute chemotherapy-induced peripheral neuropathy; Wang et al., 2016).

## 1.2 Neuropathic Pain

Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020). Pain is a multidimensional phenomenon, consisting of sensory-discriminative, affective-motivational, and cognitive-evaluative dimensions. Chronic pain is defined as pain that persists beyond the typical duration of healing, typically defined as 3-months in duration (*Canadian Pain Task Force Report*, 2019). The mechanisms through which chronic pain develops are complex, multifaceted, and poorly understood.

CNP is broadly defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" (Bogduk & Merskey, 1994). It is often described as one of the most common and feared aspects of cancer, and has an adverse impact on quality of life among cancer survivors (Jensen et al., 2010). Neuropathic pain arises as a result of abnormal activation of pain pathways in response to damage within the nervous system (Fear, 2010). Nerve damage produces changes in nerve function both at the site of the injury and in surrounding areas. Neuropathic pain can arise from a variety of etiologies including toxicity (chemotherapy/radiation), metabolic disease (diabetic neuropathy), trauma, compression,

autoimmune disorder, infection or congenital disease (Lema, Foley, & Hausheer, 2010). As a result, nerve fibers may be damaged, dysfunctional or injured. Neuropathic pain is commonly described as burning, shooting or shock-like pain (Gilron, Watson, Cahill, & Moulin, 2006), that is often severe and refractory to treatment (Taylor, 2006).

The Canadian Pain Society consensus statement for pharmacologic management of CNP recommends gabapentinoids, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors as first-line agents for neuropathic pain (Mu, Weinberg, Moulin, & Clarke, 2017). Even with optimal medical management, many individuals with CNP continue to report disabling pain (50% of Canadians with CNP have lived with chronic pain for 10 years or more; Harden & Cohen, 2003; Schopflocher, Taenzer, & Jovey, 2011) and heightened levels of psychological distress (Schou Bredal, Smeby, Ottesen, Warncke, & Schlichting, 2014). Gaining an improved understanding of potential therapeutic interventions targeting both neuropathic pain and commonly comorbid stress-related symptoms hold great significance for breast cancer survivors, as gaining a better understanding of effective treatment options may serve to improve quality of life in survivorship.

Chronic pain is currently classified as Chronic Primary Pain (pain that persists beyond 3 months in duration) and Chronic Secondary Pain (pain initially the results as a symptom of other disease where the disease is viewed as the underlying cause; Treede et al., 2019). Chronic Secondary Pain syndromes include chronic cancer-related pain; chronic postsurgical or posttraumatic pain; chronic neuropathic pain; chronic secondary headache or orofacial pain; and chronic secondary musculoskeletal pain (Treede et al., 2019). The term chronic neuropathic pain have been used in our study to comprise neuropathic pain stemming from breast cancer treatment. Neuropathic pain disorders are typically based on location of a nervous system lesion

(central or peripheral; Colloca et al., 2017). Peripheral neuropathies include unprompted firing of damaged nerves, increased sensitivity of the afferent pathways because of denervation, and sympathetically sustained pain. Central neuropathies include sensitization at the synapse or restructuring of higher-order processes (Swenson, Cohen, Fadul, Jenkyn, & Ward, 2008). Regardless of the origin, when damage occurs, an increase in firing of nerve impulses can produce ectopic impulse generation in pain pathways where transmission and modulatory pain responses do not follow the usual ordered sequence (Fear, 2010). As a result, there can be ongoing transmission of pain signals despite the absence of noxious or peripheral nervous system activation. This has been identified in individuals with phantom limb pain and diabetic neuropathy (Colloca et al., 2017). Individuals who experience CNP often experience paradoxical symptoms such as hypersensitivity at the site of injury and hyposensitivity in the surrounding area (Baron, Binder, & Wasner, 2010).

## 1.3 Cancer-related CNP

Identifying neuropathic pain is a challenge in cancer populations, as factors related to the cancer itself can alter the neurobiological response to pain (Fallon, 2013). Cancer-related neuropathic pain is associated with a variety of mechanisms and often coexists with other pain conditions. It is typically subdivided into tumor-related and treatment-related pain, where over 60% of neuropathic pain in cancer is tumor-related and 20% treatment-related, with 10-15% from comorbid disease (Edwards, Mulvey, & Bennett, 2019).

Chemotherapy, radiation and surgical interventions are among the most commonly used methods in cancer treatment. Chemotherapy can cause peripheral neuropathy (chemotherapy-induced peripheral neuropathy), and is the most common neuropathy to occur as a result of

cancer treatment, affecting roughly 60% of individuals three months after chemotherapy, and 30% of individuals 6 months or greater post-chemotherapy (Seretny et al., 2014). Peripheral neuropathy most commonly results from direct neurotoxic effects on dorsal root ganglion neurons and their axons, resulting in a "stocking-and-glove" distribution of pain, sensory loss, and ataxia (Staff, Grisold, Grisold, & Windebank, 2017). Radiation-induced neuropathy is a chronic pain condition that arises from damage to the nervous system that occurs in the field of radiation treatment (Brown, Ramirez, & Farquhar-Smith, 2014). Lastly, surgical interventions can also lead to the development of post-surgical pain syndromes (i.e., mastectomy; Brown et al., 2014).

CNP in cancer survivors can impede the recovery process and negatively impact quality of life (Esin & Yalcin, 2014). In cancer, and in survivorship, the burden of disease is exacerbated by the added burden of managing CNP, which is associated with fear, anxiety, depression, lack of control, and lack of certainty. Moreover, these are often accompanied by disease specific symptoms including pain, difficulties with sleep, discomfort, weakness, loss of functional abilities and lowered quality of life (Institute of Medicine (US) Committee on Psychosocial Services to Cancer Patients/Families in a Community Setting, 2008). These physical symptoms drive psychological concerns, which further exacerbate physical symptoms in a vicious cycle. Co-occurrence of biopsychosocial factors in cancer pain suggest that interventions targeting one component (i.e., psychological distress and stress) may have carryover effects on other symptoms (i.e., pain; Novy & Aigner, 2014). These include the biological contributions of the pain experience, psychological distress and suffering, and social components including support and its impact on everyday functioning. According to the revised definition of pain proposed by the International Association for the Study of Pain (IASP) task force six additional notes have

been included in the definition of pain to help highlight the key concepts of pain in order to improve understanding of the contribution of biopsychosocial factors in the experience of pain which include: recognition that pain is a subjective experience influence by biological, psychological and social factors; pain cannot be inferred solely from sensory pathways; the concept of pain is learned through life experiences; a person's report of their pain experience should be respected; while pain plays an adaptive role, it may have adverse effects of function and social and psychological well-being; and verbal descriptions of pain are only one of several behaviors that can be used to express pain and the inability to communicate does not negate the possibility of pain (Raja et al., 2020).

Assessment and detection of cancer-related pain relies extensively on standardized screening tools designed to classify pain on the basis of self-reported verbal descriptions of pain characteristics. Screening tools typically ask questions about burning pain, paraesthesias, pain attacks, mechanical and thermal pain, hypersensitivity and numbness (Baron et al., 2010). The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Adult Cancer Pain outline pain assessment as involving (a) quantification of the intensity and characterization of the quality of pain, (b) patient-based pain intensity rating, a description of timing, quality and impact of pain, and (c) patient description of pain characteristics (National Comprehensive Cancer Network, 2014). Assessment of chronic pain seeks not only to identify information about the individual's pain experience itself, but also provides important information informing the management of chronic pain, including guiding the selection of pharmacological, physical, and psychosocial interventions.

The primary goals of CNP treatment include restoration of function, pain management, and treatment of secondary consequences of pain (Wellford, Iii, Lawson, & Backonja, 2016).

According the World Health Organization, a combination of adjuvants and opioids comprise the pharmacological treatment interventions recommended for cancer-related neuropathic pain (Esin & Yalcin, 2014). Unfortunately, pharmacological agents are often unsuccessful in garnering effective pain relief and can cause adverse side effects. Nonpharmacological treatments are being increasingly recommended as first-line treatments for the management of chronic pain, suggesting that pain management should comprise a multidisciplinary biopsychosocial approach with the aim of addressing all aspects of pain.

## 1.4 Biology of Cancer-Related CNP

Pain and stress share common conceptual and physiological processes as both represent maladaptive responses to environmental challenges that compromise an individual's well-being (Abdallah & Geha, 2017). Sustained stress triggers a series of changes in the brain and body through activation of the body's primary stress response systems [i.e., the hypothalamic pituitary adrenal corticoid axis (HPA-axis) and sympathetic nervous system]. At the onset of a stressful event, upregulation of glucocorticoids (i.e., cortisol) and catecholamines (e.g., adrenaline) inhibit secretion of pro-inflammatory cytokines while promoting secretion of anti-inflammatory cytokines. Adversely, when stress is prolonged, sustained activation of the HPA-axis can lead to cortisol resistance, triggering a negative feedback loop leading to upregulation of pro-inflammatory cytokines and downregulation of anti-inflammatory cytokines. This negative feedback is maintained by transcription factors such as nuclear-factor kappa-B (NF-κB; Tian, Hou, Li, & Yuan, 2014). Overexpression of pro-inflammatory cytokines have been associated with premature cellular aging as indexed by an inhibition of telomerase activity and shortening of telomere length (Epel et al., 2004).

### *1.4.1 HPA activity and Cortisol*

Persistent and prolonged chronic stress is associated with both physical and mental illness (Lupien, Juster, Raymond, & Marin, 2018). It is well known that stress is strongly associated with anxiety and depression and is associated with the progression of chronic diseases, such as heart and lung disease and cancer (Salleh, 2008). Several prominent theories have been postulated that explain the pathophysiology of chronic stress. The theory of allostasis proposes that the body seeks to maintain a stable equilibrium or homeostasis. Within this context, stressors result in a disruption in homeostasis and trigger a response (i.e., an acute or adaptive response to stress) to restore homeostasis through physiological, behavioural or psychological changes (i.e., allostasis). Overuse of this system, typically due to prolonged stress, leads to persistent release of stress hormones and dysregulation of biological systems (i.e., allostatic overload). Consistent with this, amygdala activity is increased during stress and stimulates the HPA axis and sympathetic nervous system (Reive, 2019). As a result, the hypothalamus releases corticotrophin releasing factor (CRF), a peptide hormone, that causes the anterior pituitary to release adrenocorticotropic hormone (ACTH) and subsequently cortisol (Peters, McEwen, & Friston, 2017). In the presence of a physical or psychological threat, cortisol levels increase and function to release unbound glucose into the bloodstream, providing energy necessary to cope with stress-inducing stimuli. This is an adaptive response in the short-term; however, excessive or prolonged cortisol release may have significant negative impacts both physically and psychologically (Hannibal & Bishop, 2014).

Chronic pain can be conceived as a stressor that can lead to prolonged cortisol release. This can be further exacerbated by maladaptive pain perception exaggerating the stress response which can perpetuate the experience of chronic pain. Under normal conditions, cortisol acts as an

anti-inflammatory hormone and is regulated via a negative feedback cycle. When cortisol fails to function appropriately (i.e., cortisol dysfunction), unmodulated inflammatory responses can occur in response to stressors (Hannibal & Bishop, 2014). Additionally, symptoms associated with stress-induced cortisol dysfunction include fatigue, depression and pain. Furthermore, exaggerated or prolonged stress response may exacerbate pain and disability (Hall et al., 2011). It has also been shown that cortisol release in response to pain may intensify the pain experience, and has been linked to pain somatization disorders including fibromyalgia and chronic fatigue syndrome (Tak & Rosmalen, 2010). This relationship between the mind and body is thus important to consider when devising treatment options for conditions (both physical and psychological) influenced by stress.

### *1.4.2 Inflammatory Markers of Physiological Distress*

The HPA axis and sympathetic nervous system respond to stress by releasing glucocorticoids (i.e., cortisol) and catecholamines (i.e., noradrenaline and adrenaline), both of which can act on immune cells and induce an immune response. During immune system activity (e.g., stress), immune cells produce inflammatory proteins that circulate throughout the body, acting as extracellular communicators (Zhang & An, 2007). Pro-inflammatory [i.e., interleukin-4 (IL-4); c-reactive protein (CRP)] and anti-inflammatory cytokines (i.e., interleukin-6, -8, -10 cytokines) work synergistically to maintain systemic preservation. When dysregulated, increases in pro-inflammatory cytokines increase risk for disease and poor healing. Pro-inflammatory cytokines promote systemic inflammation resulting in fever, inflammation, tissue degradation, and in severe instances, shock and death (see review - Turner, Nedjai, Hurst, & Pennington, 2014). Chronically elevated pro-inflammatory cytokines is reflective of an immune response to chronic pain where chronically elevated levels of cytokines induce a positive cycle of

inflammation, sensitizing nociceptors, and inducing allodynia (Walker, Kavelaars, Heijnen, & Dantzer, 2014).

### *1.4.3 Cellular Aging and Telomere Shortening*

Telomeres are repetitive DNA sequences that act as protective caps at the ends of chromosomes that serve to protect chromosomal stability (Greider, 1996). A small proportion of DNA is lost from the end of the DNA chain during the process of transcription in cell division. Telomeres absorb this loss by ensuring that meaningful sequencing is not impacted during replication. Regulation of telomere length is modulated by telomerase, an enzyme that is responsible for maintaining telomere length and cell survival (Zvereva, Shcherbakova, & Dontsova, 2010). Disruption of telomerase activity, notably, telomere shortening, has been associated with increased health risks and disease, including increased risk of developing several human cancers (Barrett, Iles, Dunning, & Pooley, 2015; Zhu et al., 2016). Shorter telomere length has been shown to be associated with significant increase in risk of breast cancer, and telomere shortening has been associated with the pathological features of tumor progression (Kammori et al., 2015; Shen et al., 2009). Multiple factors can influence the process of telomere shortening, including environmental stressors and genetic predispositions (Monaghan, 2010).

A growing body of research suggests that there is an association between psychosocial stress and telomere shortening (Mathur et al., 2016). Studies evaluating stress and telomere length report that individuals with chronic mental illness, such as anxiety, depression or schizophrenia, are prone to greater telomere shortening relative to individuals not suffering from these disorders (Vakonaki et al., 2018). Associations between perceived stress and the chronicity of stress reflect physiological responses that may act as a mechanism through which stress affects telomere shortening. Additionally, significant correlations between increased salivary

cortisol reactivity, psychosocial stressors and shortened telomere length support a relationship between cortisol reactivity and telomere shortening (Jiang et al., 2019). Furthermore, short leukocyte telomere lengths have been associated with higher levels of pain and pain sensitivity in women with fibromyalgia (Hassett et al., 2012). This study reported that individuals with shorter telomere lengths also had a lower pain threshold and less grey matter in brain regions involved in pain processing. Higher levels of pain were evidenced among individuals with comorbid depression (Hassett et al., 2012).

## 1.5 Mindfulness-based Interventions

Psychological therapies, such as mindfulness interventions, are emerging as integral components of a comprehensive approach to pain management with the potential to improve pain, physical function, and emotional function among cancer survivors with neuropathic pain.

One of the most well documented mindfulness interventions is Mindfulness-Based Stress Reduction (MBSR). MBSR is the most commonly applied mindfulness-based intervention for individuals suffering from a chronic disease (Carlson, 2012). Standardized by Kabat-Zinn in 1979 for treatment-resistant chronic pain (Kabat-Zinn, Lipworth, & Burney, 1985), MBSR is a group-based intervention focusing on awareness and acceptance of one's inner and outer moment-to-moment experiences. It typically involves 8 to 10 weekly 2- to 2.5-hour sessions as well as a 1-day "retreat" that consists of intensive practice. Emphasis is placed on developing healthy adaptive responses to stress through mindfulness exercises.

Numerous studies on the effects of mindfulness interventions have been published over the past few years, including more than 100 randomized control trials (RCTs). A systematic

review assessing efficacy of these RCTs reported that MBSR resulted in medium effect sizes across mental health outcomes (e.g., Hedge's g= 0.56 for Anxiety; Hedge's g= 0.59 for Depression; g=0.53 for Stress/Distress; g= 0.54 for Overall Mental Health; De Vibe et al., 2017). MBSR has been shown to contribute to improvements in pain, psychological distress (depression, anxiety) and quality of life (Gardner-Nix, Backman, Barbati, & Grummitt, 2008; Kabat-Zinn et al., 1985; Kaplan, Goldenberg, & Galvin-Nadeau, 1993; Veehof, Oskam, Schreurs, & Bohlmeijer, 2011). In Kabat-Zinn's original study, significant improvements were noted in reduction of pain, negative body image, inhibition of activity caused by pain, reduction in symptoms of anxiety and depression, and reduction of pain-related drug use (Kabat-Zinn et al., 1985). According to a theory proposed by Zeidan and Vago, mindfulness training alters sensory and affective pain-related responses by affecting the "evaluation and experience of pain as a function of self-referential processing" (Zeidan & Vago, 2016).

The first study of MBSR with cancer patients was conducted in 2000, and demonstrated improvements in mood and stress symptoms compared to standard care in a randomized wait-list controlled clinical trial (Speca, Carlson, Goodey, & Angen, 2000). Since then, several studies have reported beneficial effects of MBSR, including improvements in psychological distress (Carlson, Ursuliak, Goodey, Angen, & Speca, 2001; Shapiro & Carlson, 2009), fatigue (Carlson & Garland, 2005; Lengacher et al., 2012; van der Lee & Garssen, 2012), fear of cancer progression/recurrence (Lengacher, Shelton, et al., 2014), sleep (Lengacher et al., 2012; Shapiro, Bootzin, Figueredo, Lopez, & Schwartz, 2003; Shapiro & Carlson, 2009), sexual functioning (Brotto & Heiman, 2007), activity levels (Shapiro et al., 2003; Speca et al., 2000), and health-related quality of life (Altschuler, Rosenbaum, Gordon, Canales, & Avins, 2012; Shapiro et al., 2003; Witek-Janusek et al., 2008). Significant results have been echoed across studies assessing

MBSRs effectiveness as a pain management treatment in individuals with cancer. A cross sectional survey of 76 cancer survivors with neuropathic pain reported inverse associations between mindfulness and pain, physical function, pain catastrophizing and emotional function (Poulin et al., 2016). The adaptability of mindfulness interventions complies with a flexible approach to treatment that can be tailored to each individual's experience, focusing on allowing the individual to gain perspective over their illness experience while controlling the influence of fear that can exacerbate their pain experience. Improvements have also been seen in emotion regulation, anxiety and ruminative behaviors and a decrease is experiential avoidance (Labelle, 2012).

A recent review by Reive (2019) provides a list of the biological markers that have been studied in MBSR in healthy and ill populations. These biomarkers included neurological and autonomic measures, and markers of immune, inflammatory, and endocrine systems. Of the 67 articles reviewed, they describe preliminary evidence to support an allostatic top-down/bottom-up processing framework as a potential theory for MBSR's beneficial regulation of biomarkers (Reive, 2019). According to this theory, MBSR effects biological changes in the body through downstream targets of neuronal activation. These downstream targets are the focus of biomarker studies as potential markers of biological changes stemming from psychological interventions. Notably, the effects of MBSR on biomarkers of stress and immune function are the focus of this dissertation.

### *1.5.1 Biomarkers*

The pathophysiological mechanisms through which MBSR improves pain and function are not yet clear but could involve changes in immune function and reactivity of the HPA axis. MBSR has been shown to improve biological markers of stress and inflammation. This is

particularly relevant for the treatment of neuropathic pain which is characterized by an increase in cortisol, shortening of telomeres (reflective of cellular aging), and change in immune responses towards a pro-inflammatory state (Fang et al., 2010; Hassett et al., 2012; Matousek, Dobkin, & Pruessner, 2010; Witek-Janusek et al., 2008a).

#### 1.5.1.1 Cortisol

There is accumulating evidence demonstrating that cortisol levels decrease following MBSR intervention (Matousek et al., 2010); however, findings are varied. A meta-analytic review conducted in 2016 assessed the effect of mindfulness-based interventions on cortisol in healthy individuals (Sanada et al., 2016). Included in this review were five studies looking at the effects of mindfulness-based interventions on salivary cortisol. They concluded that, despite the limited number of studies assessed, mindfulness-based interventions had a significant, near medium, effect size ($g = 0.41$; $p = 0.025$) for improvement in cortisol following intervention, with more pronounced effects with increasing number of sessions and hours of mindfulness-based training (Sanada et al., 2016). Another study assessing cortisol as a marker of stress reduction in cancer patients in response to MBSR yielded non-significant effects but reported a potential moderation effect where the effect of MBSR on awakening cortisol was moderated by baseline cortisol levels, such that low baseline levels of cortisol were associated with an increase in cortisol from baseline to 3-month follow-up, and a decrease in cortisol between baseline and 3-month follow-up was found in individuals with initially high levels of cortisol (Bränström, Kvillemo, & Åkerstedt, 2013). A more recent study reported significant effects of MBSR on reducing cortisol levels from pre- to post-intervention, demonstrating an immediate short-term effect of MBSR on salivary cortisol. However, these findings were not maintained for long-term

effects (6 weeks) on cortisol, nor were they associated with reductions in psychological and physical symptoms, or quality of life (Lengacher et al., 2019).

Cortisol is most commonly measured through saliva or serum, which provide a measure of acute stress at the time of collections. Such measurement captures short-term fluctuations in cortisol, and allows for the measurement of circadian variation through repeated administration over multiple days (Wright, Hickman, & Laudenslager, 2015). This is an expensive and laborious process with significant participant burden. Hair cortisol has emerged as a measure of cumulative HPA axis activity over longer periods of time. Hair samples have been used to assay longer term (weeks to months) levels of cortisol, with one cm of hair reflecting cortisol exposure over a period of about one month. HPA axis activity in response to chronic stress can be reliably measured up to 3-4 months prior to when the sample was taken, and can be compared to new hair growth 3 months later as a measure of change over time (Wright et al., 2015). As a result, scalp hair cortisol is considered a biomarker of chronic stress (O'Brien, Tronick, & Moore, 2012; Russell, Koren, Rieder, & Van Uum, 2012; Stalder & Kirschbaum, 2012). Recently, Van Uum et al. (Van Uum et al., 2008) compared cortisol in hair samples and stress levels in 39 healthy subjects and 14 patients with chronic pain. They reported a significant relationship between hair cortisol samples and stress, where significant increase in hair cortisol was associated with individuals with chronic stress due to a chronic pain syndrome (Van Uum et al., 2008).

To date, only one study has looked at the effects of mindfulness-based interventions and hair cortisol (Goldberg et al., 2014). Hair cortisol was used as a biomarker of stress in mindfulness training for smokers. Cortisol was found to significantly decrease after a 7-week mindfulness training intervention for smokers compared to usual care therapy controls, where decreases in cortisol were also correlated with reduced negative affect (Goldberg et al., 2014).

#### 1.5.1.2 Telomere and Telomerase Activity

Evidence is beginning to emerge that stress-reducing interventions, such as MBSR, may help regulate telomerase activity and improve telomere shortening. Ornish and colleagues (2008) were the first to study the link between mindfulness-based interventions and telomerase activity in a study of 30 males with low-risk prostate cancer. They observed a significant increase in telomerase activity following a 3-month meditation-based intervention where individuals participated in a 3-month comprehensive lifestyle modification program that included modifications to diet (low-fat, plant-based) and exercise (30min/day 6 days/week walking), and included stress management interventions (yoga-based stretching and progressive muscle relaxation), 1-h of group support per week, 4-hours of weekly telephone contact with a study nurse, and participation in a 3-day intensive residential retreat. Individuals had access to a registered dietitian, exercise psychologist, clinical psychologist, nurse and stress management instructor to provide counselling and education, and adherence was assessed with self-report measures. Moreover, increased telomerase activity was correlated with decreased psychological stress.

Additional studies have substantiated the association between meditation and telomerase activity following 3-, and 12- week mindfulness-based interventions in healthy populations (Ornish et al., 2008; Rao et al., 2015; Tolahunase, Sagar, & Dada, 2017). Significant findings have also been reported in clinical populations, including decreased distress and increased telomerase activity in individuals with prostate cancer following 6- 50-min weekly sessions of telephone counselling delivered over 4-months compared to individuals receiving care as usual (Biegler, Anderson, Wenzel, Osann, & Nelson, 2012), and in women with breast cancer

following 6 weekly, 2-hour sessions of MBSR over 3-months compared to usual care (Lengacher, Reich, et al., 2014).

#### 1.5.1.3 Cytokines

Mindfulness-based interventions have been observed to enhance parasympathetic cardiac control (i.e., vagal tone), which acts to suppress pro-inflammatory cytokines through a cholinergic anti-inflammatory pathway (Matousek et al., 2010). Mindfulness interventions are thought to help reduce HPA activity in response to stressful situations leading to reductions in basal cortisol and subsequently mediating other downstream stress-related processes (Rosenkranz et al., 2013, 2016). In healthy individuals, mind-body training is associated with increased production of anti-inflammatory cytokine IL-10, and reduced pro-inflammatory cytokine IL-6 and tumor necrosis factor-alpha (TNF-alpha; Jang, Park, Lee, Lee, & Kang, 2017).

MBSR training was observed to effect cytokine levels among women who experienced breast cancer. Witek-Janusek et al. (2008) measured cytokine levels in 75 women with early-stage breast cancer prior to MBSR intervention (8-weekly 2.5h group session and one full day group session) and observed an increase in IL-4, IL-6, and IL-10 production compared to the cytokine levels of healthy patients. Patients who did not receive MBSR training experienced a continuous increase in IL-4, IL- 6, IL-10 and TNF-α production (Rosenkranz et al., 2013; Witek-Janusek et al., 2008b; Zeichner, Kibler, & Zeichner, 2013). Carlson et al. (2003) conducted an MBSR intervention study for early stage breast and prostate cancer patients who were at least 3 months post-surgery and reported significant improvements in quality of life, stress, sleep quality and increased T cell production of anti-inflammatory cytokine IL-4 (Carlson, Speca, Patel, & Goodey, 2003). Additionally, a single cohort design pilot study involving 24 healthy individuals

found that patients who reported improvement in anxiety and overall distress also showed decreased inflammation as indexed by CRP from baseline to post-MBSR (Fang et al., 2010).

### *1.5.2 Five Facets of Mindfulness*

Mindfulness is a multifaceted construct, and has been operationalized into five facets using an exploratory factor analysis where mindfulness is defined as the capacity to 1) observe; 2) describe; 3) act with awareness; 4) adopt a nonjudgmental attitude; and 5) embrace a nonreactive stance (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006). Despite emerging evidence for a role of MBSR in reductions of biological markers of stress, few studies have assessed which facets of mindfulness are attributable to physiological changes observed following intervention.

One study assessing cortisol changes in response to a social evaluative stress challenge reported that cortisol levels were moderated by trait mindfulness, measured using the Mindful Attention Awareness Scale (MAAS), where participants higher in trait mindfulness showed reduced cortisol levels relative to controls who were not exposed to social evaluation (Brown, Weinstein, & Creswell, 2012). Similarly, changes in cortisol levels were associated with three subscales of the Five Facet Mindfulness Questionnaire (FFMQ) over the course of a 3-month meditation retreat: acting with awareness, observing their experience, and non-reactivity. Higher levels of mindfulness, as defined by the three correlated subscales, were associated with decreased bedtime cortisol compared to wait-list controls (Jacobs et al., 2013). Tomfohr et al., (2015) assessed the relation between trait mindfulness, blood pressure and the inflammatory cytokine IL-6 in a university population. Using the FFMQ, they reported that higher trait mindfulness was associated with lower blood pressure and lower levels of IL-6. Exploratory analyses revealed an interaction between the awareness facet of mindfulness and nonjudgment in

predicting blood pressure, where higher scores on awareness and nonjudgment facets were associated with significantly lower blood pressure. Additionally, the authors reported that the observing and nonreactivity facets of mindfulness interacted to predict IL-6 levels, where higher scores on observing predicted lower IL-6 levels when participants also demonstrated higher levels of nonreactivity (Tomfohr et al., 2015).

Further research is required to better understand the relationship between the individual subscales that comprise the five facets of mindfulness. The present study will perform an exploratory analysis in an effort to gain a better understanding of how the facets of mindfulness contribute to physiological changes in MBSR interventions.

## 1.6 Research Objectives and Hypotheses

The aim of this dissertation was to evaluate the effect of an 8-week MBSR program relative to a waitlist control group on biological markers of stress and cellular aging among breast cancer survivors who developed CNP following treatment of cancer. This dissertation stems from secondary data that was collected as part of a larger scale study. This research represents the secondary outcomes (primary outcomes were self-reported pain and disability) of a randomized controlled trial registered on ClinicalTrials.gov (NCT02758197). A manuscript reporting on the primary outcomes of pain and function is being considered for publication. In addition, the fMRI results from this dataset have been published (Hatchard et al., 2021). This dissertation focuses on the impact of MBSR on biomarkers, as well as mediators and moderators of change. Outcomes of interest for this trial include: 1) cortisol as an indicator of HPA-axis activity; 2) telomere length as an indicator of cellular aging; and 3) change in C- reactive protein, pro-inflammatory cytokines IL-6 and TNF-α, and anti-inflammatory cytokine IL-4 as indicators

of immune function. Exploratory analyses were conducted to evaluate the association between change in biomarkers, and self-report measures of pain and disability (pain-related severity and pain-related interference). Analyses conducted in this study were independent of the primary outcomes manuscript which focused on the co-primary outcomes of change in pain severity and pain-related interference. It was hypothesized that participation in MBSR will result in:

1) Reduced HPA activity as indicated by a reduction in hair cortisol levels between pre- and post-test compared to WLC condition.
2) Reduction in cellular aging as indicated by a reduction in rate of telomere decay between pre- and post-intervention compared to WLC condition.
3) Improvement in immunological function as indicated by a decrease in the pro-inflammatory cytokine IL-6, and C-reactive protein production compared to WLC condition.
4) Increased mindfulness as indicated by changed in FFMQ total scores from pre- to post-intervention, which will be associated changes in biomarker expression compared to WLC condition.
5) Reductions in perceived stress, pain, and disability compared to WLC condition.

# Chapter 2: Mindfulness-based stress reduction and biological markers of stress, immune function and cellular aging in cancer survivors.

# Abstract

**Background:** Mindfulness-based stress reduction (MBSR) is one of the most commonly applied mindfulness interventions in the treatment of chronic neuropathic pain (CNP) and has been shown to have preferential improvements in pain and overall health-related quality of life. Breast cancer survivors are at an increased risk for developing CNP, reducing quality of life in survivorship. The effectiveness of mindfulness interventions in breast cancer survivors living with CNP after guideline-based medical optimization is unknown. Biological markers are becoming increasingly popular as they provide an objective measure of biological systems that can be used to gain insight into the mechanisms through which psychological interventions exert their effects. The aim of the first study was to use an interdisciplinary treatment approach to CNP in breast cancer survivors by exploring the effects of MBSR on pain, and biological markers of stress, immune function and cellular aging among breast cancer survivors with CNP after guideline-based medical optimization. **Methods:** A double-blind (care provider and outcome assessors) randomized waitlist control trial was conducted using a sample of 98 breast cancer survivors diagnosed with CNP. Women were randomized to receive an 8-week MBSR intervention or waitlist control condition after undergoing medical optimization. Biological samples and self-report measures of pain, physical function and emotional function were collected at baseline, two-weeks post-intervention and at 3-month follow-up. Separate analyses were performed using intention-to-treat and per-protocol principles. **Results:** MBSR was delivered with fidelity and women randomized to MBSR demonstrated a significant increase in mindfulness relative to control. The MBSR intervention did not produce the anticipated stress reducing effects typically associated with mindfulness-based interventions. No differential changes in biomarker expression were observed between groups during the trial. Significant improvements in pain severity (intention-to-treat analyses) and pain-related interference (per-protocol analyses) were observed

among women randomized to MBSR relative to control. **Conclusions:** Despite this increase in popularity, our understanding of the association between mindfulness and pain is still evolving. Null findings can be used to help inform our understanding of adjuvant interventions in complex clinical patient populations, and identify what works for who, when and why.

## 2.1 Introduction

Medical advancements leading to better detection, treatment and long-term prognosis for women with breast cancer have resulted in a significant decline in breast cancer related mortality and, subsequently, a larger cohort of breast cancer survivors (Canadian Cancer Society, 2018). It is essential to better understand and characterize unique survivorship needs given that in cancer, and in survivorship, the burden of the disease is often exacerbated by the added burden of managing long-term residual symptoms.

Chronic pain is often described as one of the most commonly feared aspects of cancer, and has a significant adverse impact on quality of life among cancer survivors (Jensen et al., 2010). Defined as pain emanating from the nervous system that persisted beyond the typical duration of healing (> 3 months), CNP is often severe and refractory to treatment (Brook & Kessler, 2017). Pharmacological treatment recommendations set by the World Health Organization comprise a combination of adjuvants and opioids for the treatment and management of cancer-related CNP (Esin & Yalcin, 2014). Unfortunately, pharmacological agents are often unsuccessful in garnering effective pain relief and can cause adverse side effects. Despite optimal medical management, many individuals with CNP continue to report disabling pain (50% of Canadians with CNP have lived with chronic pain for 10 years or more; Harden & Cohen, 2003; Schopflocher, Taenzer, & Jovey, 2011) and have heightened levels of psychological distress (Schou Bredal et al., 2014).

Psychological interventions have become recognized as potential adjunctive therapies that can serve to enhance treatment success through improved functional recovery and quality of life. Pain is often disproportional to tissue damage. This is because the experience of pain is the brain's interpretation of cognitive-evaluative, sensory-discriminative, and motivational-affective

signals traveling along ascending and descending neural pathways (Gatchel, Peng, Peters, Fuchs, & Turk, 2007). Focusing on disease (biological) and illness (experience), the biopsychosocial (BPS) model of chronic pain considers the complex interaction between biological (physiological), psychological and social factors that comprise the pain experience (Novy & Aigner, 2014). This co-occurrence of biopsychosocial factors suggests that treatment interventions targeting one aspect of the pain experience (i.e., stress), may, in turn, have carryover effects that influence other aspects of the pain experience, (i.e., pain; Novy & Aigner, 2014).

Mindfulness interventions are emerging as integral components of a comprehensive approach to pain management with the potential to improve pain, physical function, and emotional well-being among cancer survivors with neuropathic pain. Mindfulness-based stress reduction (MBSR) is the most commonly applied mindfulness-based intervention for individuals suffering from a chronic disease (Carlson, 2012). Standardized by Kabat-Zinn in 1979 for treatment resistant chronic pain (Kabat-Zinn et al., 1985), MBSR is a group-based intervention focusing on awareness and acceptance of one's inner and outer moment-to-moment experiences. MBSR has been shown to contribute to improvements in pain, psychological distress (depression, anxiety), and quality of life (Gardner-Nix et al., 2008; Kabat-Zinn et al., 1985; Kaplan et al., 1993; Veehof et al., 2011). The first study of MBSR with cancer patients was conducted in 2000, and demonstrated improvements in mood and symptoms of stress when compared to treatment as usual in a randomized wait-list controlled clinical trial (Speca et al., 2000). Since this seminal trial, there have been several studies that have reported beneficial effects of MBSR across a variety of heal-related domains (Carlson, Ursuliak, Goodey, Angen, & Speca, 2001; Shapiro & Carlson, 2009; Carlson & Garland, 2005; Lengacher et al., 2012; van der

Lee & Garssen, 2012; Lengacher, Shelton, et al., 2014; Lengacher et al., 2012; Shapiro et al., 2003; Shapiro & Carlson, 2009; Brotto & Heiman, 2007; Shapiro et al., 2003; Speca et al., 2000; Altschuler, Rosenbaum, Gordon, Canales, & Avins, 2012; Shapiro et al., 2003; Witek-Janusek et al., 2008).

There is emerging evidence that mindfulness-based interventions effect change by impacting the neuroendocrine responses to stress (Reive, 2019). MBSR has been shown to improve biological markers of stress (i.e., cortisol; Lengacher et al., 2019; O'Brien, Tronick, & Moore, 2012; Russell, Koren, Rieder, & Van Uum, 2012; Sanada et al., 2016; Stalder & Kirschbaum, 2012; Van Uum et al., 2008), inflammation (i.e., c-reactive protein[CRP], IL-4, IL-6, IL-10; Carlson, Speca, Patel, & Goodey, 2003; Jang, Park, Lee, Lee, & Kang, 2017; Rosenkranz et al., 2016; Witek-Janusek et al., 2008) and cellular aging (Ornish et al., 2008; Rao et al., 2015; Tolahunase et al., 2017). This is particularly relevant for the treatment of neuropathic pain which is characterized by an increase in cortisol, shortening of telomeres (reflective of cellular aging), and change in immune responses towards a pro-inflammatory state (Fang et al., 2010; Hassett et al., 2012; Matousek et al., 2010; Witek-Janusek et al., 2008a).

The primary objective of this study was to evaluate the effect of an 8-week MBSR program on biological markers of stress, immune function and cellular aging among breast cancer survivors who developed CNP following treatment of cancer. The secondary objective was to evaluate the effects of MBSR intervention on self-report measures of mindfulness, stress, pain and disability. We hypothesized that MBSR would result in: reduced HPA activity, as indicated by a reduction in hair cortisol; reduction in the rate of cellular aging as indicated by a reduced rate of telomere decay; and improvement in immunological function as indicated by a decreased in pro-inflammatory cytokines IL-6 and CRP. We also hypothesized that MBSR

would yield preferential changes in self-report measures of pain, physical function and emotional function relative to WLC condition.

## 2.2 Methods

### *2.2.1 Experimental design*

A double-blind (care providers and outcome assessors) randomized, waitlist-controlled trial evaluating the effect of an 8-week online MBSR program on pain, function, and biological markers of stress, inflammation, and cellular aging among breast cancer survivors with CNP was conducted. After medical optimization to coincide with clinical practice guidelines for the pharmacological management of CNP, women were randomly assigned to MBSR or waitlist control. Outcome data (self-report measures and biomarker samples) for both groups were collected at 4 time points: (T1) pre-medical optimization; (T2) after medical optimization (pre-MBSR); (T3) 2-weeks post-MBSR; and (T4) 3 months post-MBSR (Appendix E). Women in the waitlist control arm were offered MBSR after 3-month follow-up (delayed MBSR group) and outcome data for this group was collected at 3 additional timepoints: (T5) prior to initiating MBSR; (T6) 2-weeks following completion of MBSR; and (T7) 3-months following completion of MBSR. Conduct of this trial was approved by The Ottawa Hospital Research Ethics Boards. The trial was pre-registered on ClinicalTrials.gov (NCT02758197).

### *2.2.2 Population*

Breast cancer survivors with CNP were eligible to participate if they met the following conditions: 1) ≥ 1-year post-cancer treatment; 2) experienced neuropathic pain for ≥ 6 months; and 3) a baseline pain severity score ≥4 (i.e., moderate to severe). Diagnosis of CNP was confirmed by a pain physician prior to entry into the study. Women who were prescribed

medications were required to be on a stable medical management for a minimum of 2 weeks prior to being randomized to a group.

## 2.3 Procedures

### *2.3.1 Participant recruitment*

Breast cancer survivors with CNP were recruited through poster advertisements displayed at local centres (e.g., Maplesoft Cancer Centre), referrals from health care teams at the Ottawa Hospital (Cancer Centre, Psychosocial Oncology Program, and Pain Clinic) and the Ottawa Regional Cancer Foundation, and self-referral. Patients who expressed interest in the study were contacted by the Research Coordinator to undergo telephone screening of eligibility criteria. Eligible patients completed informed consent and study questionnaires during their first study visit. Hair and blood samples were also collected at this time.

### *2.3.2 Pharmacologic Treatment of Neuropathic Pain*

After the baseline assessment, patients were treated by a physician with expertise in chronic pain to ensure optimal pharmacologic management using two recent evidenced-based consensus statements. The adjustment or substitution of the patient's current medications required individual consideration. Patients were required to be on a stable drug regimen for at least 2 weeks before randomization and efforts were made to ensure they were tolerating their new medication regimen to reduce the likelihood that changes would be required during the remainder of the study.

### *2.3.3 MBSR Program*

MBSR was offered in groups of approximately 8-12 participants. It consisted of eight weekly 2-hour sessions and one 6-hour retreat held midway through the course. Sessions comprised of psychoeducation and mindfulness practices, and were conducted by registered healthcare providers with experience in chronic pain, formal MBSR training, and a minimum of 5 year's experience leading MBSR groups.

Sessions were recorded and a random selection of 12% were rated for fidelity by an MBSR trainer with certification from the University of Massachusetts Centre for Mindfulness in Medicine, Health Care and Society. The Bangor, Exeter and Oxford Mindfulness-Based Interventions: Teaching Assessment Criteria Scale (Crane et al., 2012) and adherence component of the Mindfulness-Based Relapse Prevention Adherence and Competence Scale (MBI:TAC; Chawla et al., 2010) were used by the reviewer to rate the extent to which the facilitator adhered to the following domains: 1) organization of session curriculum; 2) relational skills; 3) embodiment of mindfulness; 4) guiding mindfulness practices; 5) conveying course themes through interactive inquiry and didactic teaching; and 6) holding of group learning environment.

## 2.4 Measures

*Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) recommended measures* (Dworkin et al., 2009, 2008): IMMPACT guidelines consist of recommendations for measures that should be harmonized across chronic pain trials. Recommended core outcome measures for clinical trials of chronic pain treatment include pain, physical functioning, emotional functioning, participant ratings of improvement and satisfaction with treatment, symptoms and adverse events, and participant dispositions. In line with this, BPI-

SF pain severity and pain-related interference, Profile of Mood States, Patient Global Impression of Change, and adverse events were recorded.

*The Perceived Stress Scale (PSS).* The PSS (Cohen, Kamarck, & Mermelstein, 1983) is a well-validated 10-item self-report instrument which evaluates an individual's global measure of perceived stress. Items are rated using a 4-point Likert scale (0= never, 4= very often) with total scores ranging from 0-40, with cut-off points indicating low, moderate and high perceived stress.

*The Brief Pain Inventory – Short Form (BPI-SF).* The BPI-SF (Cleeland, 1989) measures pain intensity (i.e., pain severity index is calculated as the mean rating of present, average, least, and worst pain experienced over 24-hour period), the impact of pain on seven daily activities (e.g., activity, mood, work, relations with other people), and analgesic use. The BPI is more sensitive to neuropathic pain than generic measures of health-related quality of life. A one-point change represents a minimally clinically important change (Dworkin et al., 2009). Therefore, a responder was defined as a participant who showed a decrease of ≥ 1.0 on pain intensity or pain-related interference.

*The Neuropathic Pain Symptom Inventory (NPSI). The NPSI (*Bouhassira et al., 2004) is a self-report questionnaire that consists of 10 pain descriptors and two temporal items. Responses are rated on a numerical scale (0-10) and a total intensity score is calculated. Five subscores are also derived: spontaneous burning pain, spontaneous pressing pain, paroxysmal pain, evoked pain and paresthesia/dysesthesia. The NPSI has been shown to be reliable, valid, and sensitive to the effects of treatment.

*The Patient Health Questionnaire –9 (PHQ-9).* The PHQ-9 (Kroenke, Spitzer, & Williams, 2001) is a 9-item scale assessing the severity of symptoms of depression over the past two weeks based on DSM-IV diagnostic criteria. It has been widely used in medical and

hospital-based populations (Rentsch et al., 2007; Rosemann et al., 2007). Total scores range from 0 to 27, and clinical cut-points correspond to mild, moderate, moderately severe, and severe depression. The PHQ-9 takes only a few minutes to complete and has a high level of concordance with diagnoses made by mental health professionals using structured interviews (Spitzer, 1999). Its brevity, demonstrated sensitivity to change (Löwe, Kroenke, Herzog, & Gräfe, 2004), and apparent psychometric superiority to other common depression measures (P. W. Lee, Schulberg, Raue, & Kroenke, 2007; Löwe, Spitzer, et al., 2004) suggest that this measure is appropriate for the present purpose. A 5-point decrease on the PHQ-9 is considered to be the minimum clinically significant change (Löwe, Unützer, Callahan, Perkins, & Kroenke, 2004).

*The Pain Catastrophizing Scale* (PCS). The PCS (Michael Sullivan, Bishop, & Pivik, 1995) is a well-validated 13-item instrument which evaluates the degree to which patients have negative self-statements and catastrophizing thoughts and ideations when in pain. The PCS consists of three subscales (rumination, magnification, helplessness). Each individual item is rated using a Likert scale (0=not at all, 4=all the time). The psychometric values of the PCS are well-documented and suggest good reliability (total score = $\alpha = 0.86$), test-retest stability, and concurrent, criterion-related and discriminant validity (Sullivan, Martel, Tripp, Savard, & Crombez, 2006; Michael J.L. Sullivan, Lynch, & Clark, 2005). The PCS has been found to be factorially valid and appropriate for use with both men and women (D'Eon, Harris, & Ellis, 2004).

*Five Facet Mindfulness Questionnaire* (FFMQ). The FFMQ (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006). The FFMQ is a 39-item instrument measuring five aspects of mindfulness: non-reactivity to inner experience; observing, describing, acting with awareness,

and non-judging of experience. Participants are asked to use a 5-point Likert-type scale to rate how true of them they believe each statement to be. The FFMQ has been found to have adequate to good reliability, with alpha coefficients ranging from .75 to .91 for all subscales. The combined mindfulness facets have been found to account for a significant proportion of the variance in pain catastrophizing, pain-related fear, pain hypervigilance and disability (Schütze, Rees, Preece, & Schütze, 2010).

*Profile of Mood States-Adult* (POMS2). The POMS2 (Heuchert & McNair, 2012): The POMS2 is a 65-item questionnaire, rated on a five-point scale ranging from "not at all" to "extremely", that assesses the mood states of individuals. The POMS2 measures six different scale scores and total mood disturbance score. The six scale scores comprise: anger-hostility, confusion-bewilderment, depression-dejection, fatigue-inertia, tension-anxiety, and vigour-activity.

*Patient Global Impression of Change* (PGIC). The PGIC (Ferguson & Scheman, 2009) is a 7-point scale that depicts an individual's rating of overall improvement in response to treatment.

*Mindfulness-Based Interventions Teaching Assessment Criteria (MBI:TAC).* The MBI:TAC (Crane et al., 2013) is a tool developed to assess teacher adherence and competence when delivering mindfulness-based interventions. It is comprised of six domains of competence: Coverage, pacing and organization of session curriculum; Relational skills; Embodiment of mindfulness; Guiding mindfulness practices; Conveying course themes through interactive inquiry and didactic teaching; and Holding the group learning environment. Each domain is rated on a 6-point continuous scale (Incompetent, Beginner, Advanced Beginner, Competent, Proficient, Advanced).

## 2.5 Biomarkers

*Hair Cortisol*: Hair samples were collected prior to initiating MBSR and 3-months following MBSR (i.e., T2 and T4 among the entire sample, and T5 and T7 among women allocated to waitlist control). Three cm of hair adjacent to the scalp was collected for each patient. Samples were stored until study completion and then sent to an independent laboratory for analysis.

*IL-6 and CRP production*: Whole blood was obtained from participants and centrifuged at 1,000-2,000 x g for 10 minutes in a refrigerated centrifuge. The resulting supernatant plasma was immediately transferred into a clean polypropylene tube using a Pasteur pipette. The samples were maintained at 2-8°C while handling (Thavasu, Longhurst, Joel, Slevin, & Balkwill, 1992). The concentrations of IL-6 were quantified by ELISA using a customized Milliplex MAP Human Cytokine/Chemokine Panel (Cat# HCYTOMAG-60K-4, Millipore, Schwalbach, Germany). CRP production was measured by CRP ELISA Kit obtained from antibodies, Cat#: ABIN649450. The measurement of cytokine secretion was performed according to the manufacturer's instructions. All samples and standards were analyzed in duplicate on a Luminex 200 device (BioRad, München, Germany) using the BioPlex Manager Software (Version 5, BioRad; Möller et al., 2012) performed at the Ottawa Hospital Research Institute (OHRI).

*Measurement of Telomere Length*: Total genomic DNA was extracted from 0.1 mL of whole blood using QIAampH DNA Mini Kit (Qiagen). The relative average telomere length was determined by qPCR as described by Cawthon (2002). The primer sequences used for the telomeres (T) are Tel F 5'-CGGTTTGTTTGGGTTGGGTTTGGGTTTGGGTTTGGGTT-

3'and Tel R, 5'-GGCTTTGCCTTACCCTTACCCTTACCCTTACCCTTACCCT-3', and for the single copy gene 36B4 (encodes acidic ribosomal phosphoprotein) (S) are 36B4 F, 5'-CAGCAAGTGGGAAGGTGTAATCC-3'and 36B4 R, 5'-CCCATTCTATCATCAACGGGTACAA-3' (Côté et al., 2012). For both telomere (T) and (S) PCRs, 8 µL of LightCyclerH 480 SYBR Green with MgCl2 (Roche) master mix with 2µL of DNA extract were added to each well. Samples were randomized and analyzed in duplicate. The PCR is performed on a LightCycler thermocycler (Roche) with condition of 95 °C for 10 min followed by for (T): 45 cycles of 95°C for 5 s, 56°C for 10 s and 72°C for 60 s and for (S): 45 cycles of 95°C for 5 s, 58 °C for 10 s and 72°C for 40 s.

Standard curves are included in each run and prepared by serial dilutions (1:2) of pooled human blood genomic DNA, ranging from 30,000 to 469 copies of (S) and 90 to 1.4 copies of (T) and DNA concentrations ranging from ~13.8 ng/ml to 0.22 ng/ml. LightCyclerH 480 Software 1.5.0 (Roche) were used to generate the standard curve based on the maximum secondary derivative of each reaction and to determine the T and S copy numbers in each test sample. TL is expressed as the relative T/S ratio. The intra-and inter-assay coefficients of variation were 5% and 10% respectively (Côté et al., 2012).

## 2.6 Data Analysis

### *2.6.1 Data cleaning*

Statistical analyses were performed using SPSS version 26 (IBM Corporation, USA). Data from 98 participants were screened for univariate and multivariate outliers. A total of 15 univariate outliers were identified across variables in the dataset with values in excess of the recommended cutoff z-score of 3.29 (Kim, 2013) and values were winsorized to reduce their

influence on the overall pattern of results. Multivariate outliers were assessed using Mahalanobis distances. There were no multivariate outliers identified that exceeded the cutoff of $\chi^2(70)_{critical}$ 112.31.

### *2.6.2 Statistical Analyses*

Statistical analyses were performed using intention-to-treat principles. Little's test for missing completely at random (MCAR) indicated that data were missing at random $\chi^2 = 1966.376$, $p=1.00$. Missing data were imputed using a single imputation performed with missing values analysis Estimation Maximization procedure in SPSS. The assumption of normality was assessed through an evaluation of skewness and kurtosis. Values of skewness and kurtosis were divided by their respected errors (SE) and values in excess of 3.29 ($p<.001$) were considered to be significantly skewed or kurtotic (Tabachnick & Fidell, 2013). Descriptive statistics were analyzed using independent samples t-tests to compares baseline demographic and clinical characteristics between intervention and waitlist control arms.

### *2.6.3 Manipulation check*

Manipulation checks were performed to evaluate the effectiveness of our MBSR intervention in eliciting the intended improvements in self-reported total mindfulness and the anticipated stress-reducing effects characteristic of MBSR intervention programs. Manipulations checks were performed using a series of 2 (Time: Pre-MBSR, Post-MBSR,) x 2 (Group: MBSR, Waitlist control) mixed model ANCOVAs to examine whether MBSR intervention affected FFMQ total mindfulness and perceived stress scores in predicted ways.

### *2.6.4 Primary Analyses*

This study sought to evaluate the effect of an 8-week MBSR intervention on biological markers of stress, immune function and cellular aging relative to waitlist control among breast cancer survivors with CNP. Intention-to-treat analysis was conducted using a series of 2 (Time: Pre-MBSR, Post-MBSR) X 2 (Group: MBSR, Waitlist control) mixed model analysis of covariance (ANCOVA) for change in CRP and IL-6 after adjusting for change in respective biomarkers that occurred between medical optimization and Pre-MBSR. For each outcome measure, data collected pre- and post-medical optimization was used as a covariate (change in response to medical optimization). Follow-up analyses were performed using a 2 (Time: Post-MBSR, 3-month post MBSR) X 2 (Group: MBSR, Waitlist control) analysis of variance (ANOVA) when significant differences were detected to determine if these differences were maintained 3-months following MBSR intervention. Hair cortisol was only obtained at Pre-MBSR and 3-month post MBSR and was evaluated using a 2 (Time: Pre-MBSR, 3-month post MBSR) X 2 (Group: MBSR, Waitlist control) mixed model ANOVA. An independent samples t-test was used to assess fold-change in telomere length between study groups. Due to budgetary constraints, data for change in IL-6 and hair cortisol, but not CRP and telomere length, was available from the waitlist control condition who completed MBSR intervention (delayed MBSR) and included in the analysis.

### *2.6.5 Secondary Analyses*

Secondary analyses were conducted to evaluate the effect of MBSR intervention on self-report measures of pain, physical function, emotional function, mindfulness and stress. A series of 2 (Time: Pre-MBSR, Post-MBSR) X 2 (Group: MBSR, Waitlist control) mixed model ANCOVAs were run analogous to those described for CRP and IL-6. Follow-up analyses were performed using a 2 (Time: Post-MBSR, 3-month post MBSR) X 2 (Group: MBSR, Waitlist

control) analysis of variance (ANOVA) when significant differences were detected to determine if these differences were maintained 3-months following MBSR intervention.

### *2.6.6 Sensitivity Analyses*

Sensitivity analyses were performed by repeating analyses among the sample of patients who completed 8 out of a possible 9 contacts (8 sessions and a one-day retreat) and completed the trial. Results were comparable whether participants attended 6 or greater sessions, and thus per-protocol attendance was defined as 8+ MBSR sessions. Given similarity between intention-to-treat and per-protocol analyses, per-protocol analyses are only presented in circumstances where differences were observed. Refer to *Appendix A-C* for complete per-protocol analysis results.

## 2.7 Results

A total of 118 women were enrolled, 20 of whom withdrew consent to use data prior to randomization (Figure 1). An additional 34 women discontinued participation after randomization (18 from the intervention and 16 from control). Women who withdrew did not differ from those who completed the trial on demographic characteristics or variables of interest collected at T2 (Appendix D). Analyses were performed in accordance with intention-to-treat principles resulting in a final sample of 98 women. Waitlist control participants were provided the opportunity to complete MBSR intervention after 3-month follow-up. A total of 29 women completed the MBSR intervention following waitlist (delayed MBSR group). Where available, data from these participants were included in statistical analyses (intervention sample of 78 women). Of the 49 participants that were randomly assigned to the intervention group, a total of 23 women attended a minimum of 8+ sessions of MBSR and a total of 10 women from the delayed MBSR group (8+ MBSR session sample of 33 women).

### *2.7.1 Sample Characteristics*

Participant demographic and clinical characteristics appear in Table 1. Participants (n= 98) were female between 33 and 81 years of age (*M* =53.27, *SE*= 1.02), who were experiencing neuropathic pain for a minimum of 6 months (average years living with pain= 3.1, SE= 0.2) and who were at least 1-year post-breast cancer treatment (average time since diagnosis= 3.4 years, SE= 0.2; average time post-cancer treatment= 2.6 years, SE= 0.2). Participants were primarily Caucasian (80.6%) and had some post-secondary education (74.0%), and forty-five percent were employed either full-time or part-time. No between-group differences were observed.

### *2.7.2 Medication Change Throughout the Trial*

Pharmacy records at baseline and 3-months follow up were available for 64 participants. More than half of participants (n= 52, 81.2%) had no change in their medication during the study. Despite recommendation to stay on a stable medical regimen, 8 (12.5%) had their medication increased, and 4 had their medications reduced (6.25%). There was a greater proportion of participants in the control group that increased their reliance on medication during the study period (z = 2.2136, $p$ = .03).

### *2.7.3 Medication Management*

Change in indicators from pre- to post guideline-based optimal medication management were used as covariates for respective outcome measures. With the exception of depression, measured by PHQ9 total scores (t[125]= -2.786, $p$= .006), statistical tests indicated that no reliable change was observed in outcomes of interest from pre- to post-medical optimization.

### *2.7.4 Treatment Fidelity to MBSR*

The mean MBI:TAC score (average across 8 recordings) was within the "proficient" range with a mean of 5.49 (SD = 0.27, range 5.0-5.75). The means and standard deviations for the individual domains were: 5.75 ± 0.43 (coverage/organization), 5.75 ± 0.43 (relational skills), 5.6 ± 0.48 (embodiment), 5.6 ± 0.48 (guiding practices), 5.25 ± 0.82 (inquiry and teaching), and 5 ± 0.7 (group facilitation).

### *2.7.5 Manipulation Check*

Figure 2. Manipulation checkA depicts change in mindfulness across the trial. There was a significant group by time interaction of MBSR on mindfulness ($F$[1,123]= 7.087, $p$= .009, $\eta_p^2$= .054), after statistically adjusting for change in mindfulness following medical optimization. Women who completed MBSR evidenced greater improvement in FFMQ total scores ($M_{diff}$= 6.013, $SE$= .102) compared to waitlist controls ($M_{diff}$= -1.35, $SE$= .018) This suggests that MBSR intervention had a significant positive effect of increasing self-reported levels of total mindfulness compared to waitlist controls[1]. This pattern held for per-protocol analyses (Figure 2. Manipulation check*B*).

Figure 2. Manipulation checkC depicts change in perceived stress across the trial. There was no significant group by time interaction of MBSR on level of perceived stress ($F$[1,123]= .548, $p$= .461, $\eta_p^2$=.004)[1], after statistically adjusting for change in perceived stress that occurred following medical optimization. There was also no main effect of group ($F$[1,123]= .762, $p$= .385, $\eta_p^2$= .006). There was, however, a statistically significant main effect of time ($F$[1,123]= 35.036, $p$= .000, $\eta_p^2$= .222), where level of perceived stress decreased significantly from pre-

[1] Data includes waitlist control participants that completed MBSR intervention after 3-month follow-up.

intervention (*M=18.123, SE*= .675) to post-intervention (*M*= 14.928, *SE*= .601) when averaged across groups. This pattern held for per-protocol analyses (Figure 2. Manipulation check*D*).

### *2.7.6 Primary Analyses: The Effect of MBSR on Biomarkers*

#### 2.7.6.1 C-Reactive Protein

There was no statistically significant group by time interaction (*F*[1,95]= .001, *p*= .969, $\eta_p^2$=.000) on CRP concentration after statistically adjusting for change in CRP-concentration from medical optimization to pre-intervention (Figure 3*A*). There were no significant main effects of group (*F*[1,95]= 1.400, *p*= .240, $\eta_p^2$= .015) or time (*F*[1,95]= 1.823, *p*= .180, $\eta_p^2$= .019) on CRP-concentration (Figure 3*A*). This pattern held for per-protocol analyses; Figure 3*B*).

#### 2.7.6.2 Interleukin 6 (IL-6)

There was no statistically significant group by time interaction (*F*[1,123]= .867, *p*= .354, $\eta_p^2$= .007) on IL-6 concentration while controlling for change in IL-6 concentration from medical optimization to pre- intervention (Figure 4*A*)[1]. There was no main effect of group (*F*[1,123]= .583, *p*= .447, $\eta_p^2$= .005). There was a main effect of time on mean IL-6 concentration (*F*[1,123]= 12.545, *p*= .001, $\eta_p^2$= .093) that revealed a significant linear contrast (*F*[1,123]= 12.545, *p*= .001, $\eta_p^2$= .093) with IL-6 concentration decreasing significantly from pre-intervention (M= 3.555, *SE*= .204), to post-intervention (*M*= 2.675*, SE*= .165) when averaged across group. This pattern held for per-protocol analyses *(*Figure 4*B*).

#### 2.7.6.3 Hair Cortisol

There was no statistically significant group by time interaction (*F*[1,124]]= .790, *p*= .376, $\eta_p^2$= .006) on cortisol (Figure 5*A*)[1]. There was no main effect of group (*F*[1,124]= .224, *p*= .637,

[1] Data includes waitlist control participants that completed MBSR intervention after 3-month follow-up.

$\eta_p^2$= .002). There was a statistically significant main effect of time ($F$[1,124]= 17.250, $p$= <.0001, $\eta_p^2$= .122), with a significant linear contrast ($F$[1,124]= 17.250, $p$= <.0001, $\eta_p^2$= .122), indicating an increase in cortisol concentration from pre-intervention ($M$= 31.361, $SE$= 1.021) to post-intervention ($M$= 37.069, $SE$= .653) when averaged across groups. This pattern held for per-protocol analyses (Figure 5*B*).

#### 2.7.6.4 Telomere Length

Two independent-samples t-tests were performed to determine if there were differences in fold-change relative to pre-intervention telomere length between groups and across time points. There were no significant differences in fold-change across timepoints: pre-medical optimization relative to pre-MBSR (t[96]= .573, $p$= .568) between MBSR ($M$= 1.944, $SE$= .715) and waitlist controls ($M$= 2.456, $SE$= .545); and post-MBSR relative to pre-MBSR (t[96]= .036, $p$= .972) between MBSR ($M$= .6900, $SE$= .031) and waitlist controls ($M$= .6916, $SE$= .031; Figure 6*A*); per-protocol analyses yielded consistent results (Figure 6*B*).

### *2.7.7 Secondary Analyses: The Effect of MBSR on Pain, Physical Function and Emotional Function*

#### 2.7.7.1 Pain Severity

There was a statistically significant group by time interaction ($F$[1,123]= 4.694, $p$= .032, $\eta_p^2$= .037) after statistically adjusting for change in pain severity that occurred during medical optimization (Figure 7*A)*[1]. BPI pain severity decreased significantly among MBSR participants from pre-intervention ($M$= 4.336, $SE$= .191) to post-intervention ($M$= 3.798, $SE$= .230) when

[1] Data includes waitlist control participants that completed MBSR intervention after 3-month follow-up.

compared to waitlist controls (pre-intervention *M*= 4.320, *SE*= .234; post-interventions *M*= 4.302, *SE*= .281). This pattern held for per-protocol analyses (Figure 7*B)*. Significant group by time interactions were not maintained post-MBSR to 3-month follow-up for both intention-to-treat ($F$[1,123]= 4.336, $p$= .143, $\eta_p^2$= .017) and per-protocol analyses ($F$[1,78]= 1.086, $p$= .476, $\eta_p^2$= .007).

#### 2.7.7.2 Pain Interference

There was no statistically significant group by time interaction on pain interference ($F$[1,123]= 1. 2.176, $p$= .144, $\eta_p^2$= .017)[1] after statistically adjusting for change in pain interference that occurred during medical optimization (Figure 8*A)*. There was no significant main effect of group ($F$[1,123]= .010, $p$= .920, $\eta_p^2$= .000). There was a statistically significant main effect of time ($F$[1,123]= 7.758, $p$= .006, $\eta_p^2$= .059) with a linear contrast where BPI interference scores decreased significantly from pre-intervention (*M*= 4.092, *SE*= .202) to post-intervention (*M*= 3.682, *SE*= .214) when averaged across groups. Per-protocol analyses showed there was a significant group by time interaction ($F$[1, 78]= 4.009, $p$= .049, $\eta_p^2$= .049), where participants that attended a minimum of 8 MBSR sessions reported a significant reduction in pain interference scores from pre-intervention (*M*= 4.480, *SE*= .419) to post-intervention (*M*= 3.191, *SE*= .455) compared to waitlist controls (pre-intervention *M*= 4.035, *SE*= .316; post-intervention *M*= 3.895, *SE*= .343; Figure 8*B*). Reductions in pain interference were not maintained at 3-month follow-up ($F$[1, 124]= 1.303, $p$= .256, $\eta_p^2$= .010). Significant group by time interaction was not maintained post-MBSR to 3-month follow-up for per-protocol analyses ($F$[1,78]= 2.560, $p$= .301, $\eta_p^2$= .014).

#### 2.7.7.3 Neuropathic Pain

There was no significant group by time interaction ($F$[1,123]= .001, $p$= .971, $\eta_p^2$=.000) after statistically adjusting for change in NPSI from medical optimization to pre-intervention (Figure 9*A)*. There was no main effect of group ($F$[1,123]= .586, $p$= .446, $\eta_p^2$= .009). There was a significant main effect of time ($F$[1,123]= 7.198, $p$= .008, $\eta_p^2$= .055) on NPSI scores where NPSI scores decreased significantly from pre-intervention ($M$= .351 $SE$= .013) to 3-month follow-up ($M$= .313, $SE$= .017) when averaged across group. This pattern held for per-protocol analyses (Figure 9*B)*.

#### 2.7.7.4 Pain Catastrophizing

There was no significant group by time interaction on the PCS ($F$[1,123]= 2.414, $p$= .123, $\eta_p^2$=.019) after statistically adjusting for change in PCS from medical optimization to pre-intervention (Figure 10*A)*. There was no main effect of group ($F$[1,123]= .011, $p$= .918, $\eta_p^2$= .000). There was a significant main effect of time ($F$[1,123]= 10.539, $p$= .002, $\eta_p^2$= .079) on PCS scores where PCS scores decreased significantly from pre-intervention ($M$= 18.242 $SE$= .987) to post-intervention ($M$= 15.387, $SE$= 1.036; *Figure 4D*) when averaged across group. This pattern held for the per-protocol analyses (Figure 10*B)*.

#### 2.7.7.5 Depression

There was no significant group by time interaction on PHQ-9 (F[1,123]= .000, p= .987, ηp2=.000) after statistically adjusting for change in PHQ-9 from medical optimization to pre-intervention (Figure 11A). There was no main effect of group (F[1,123]= .094, p= .759, $\eta p^2$= .001) and no significant main effect of time (F[1,123]= 2.457, p= .120, $\eta p^2$= .020). Per-protocol analyses reported a significant main effect of time ($F$[1, 78]= 4.926, $p$= .029, $\eta_p^2$= .059) where PHQ-9 scores decreased significantly from pre-intervention ($M$= 9.180, $SE$= .714) to post-intervention ($M$= 8.005, $SE$= .682) when averaged across groups (Figure 11*B*).

#### 2.7.7.6 Mood Disturbance

There was a near, but non-significant group by time interaction on POMS2 total mood disturbance scores ($F$[1,123]= 3.672, $p$= .058, $\eta_p^2$=.029)[1] after statistically adjusting for change from medical optimization to pre-intervention (Figure 12*A)*. Analysis of simple main effects showed no significant main effect of group ($F$[1,123]= .027, $p$= .871, $\eta_p^2$= .000). However, there was a significant main effect of time ($F$[1,123]= 6.584, $p$= .001, $\eta_p^2$= .051), where POMS2 total mood disturbance scores decreased significantly from pre-intervention ($M$=62.943, $SE$= 1.173) to post-intervention ($M$= 60.259, $SE$= 1.393) when averaged across groups. This pattern held for the per-protocol analyses (Figure 12*B*).

#### 2.7.7.7 Global Impression of Change

PGIC reflects perceptions about the efficacy of treatment and therefore no PGIC scores were collected at T1 (pre-medical optimization). There was no significant group by time interaction ($F$[1,124]= 3.228, $p$= .075, $\eta_p^2$=.025; Figure 13*A*). There was no significant main effect of group on PGIC scores ($F$[1,124]= 10.336, $p$= .063, $\eta_p^2$= .028). There was a significant main effect of time ($F$[1,124]= 15.711, $p$= .000, $\eta_p^2$= .112) where PGIC scores increased significantly from pre-intervention ($M$= 4.217, $SE$= .125) to post-intervention ($M$= 4.844, $SE$= .095) when averaged across group. Per-protocol analyses showed a significant group by time interaction ($F$[1, 78]= 5.791, $p$= .018, $\eta_p^2$= .068) where participants who attended a minimum of 8 MBSR sessions reported significantly greater improvement in PGIC scores at post-intervention ($M$= 5.355, $SE$= .192) relative to pre-intervention ($M$= 4.300, $SE$= .260) compared to waitlist controls (pre-intervention $M$= 3.898, $SE$= .196; post-intervention $M$= 4.201, $SE$= .145; Figure

[1] Data includes waitlist control participants that completed MBSR intervention after 3-month follow-up.

13*B*). These results were not maintained at 3-month follow-up ($F$[1,79]= 2.153, $p$= .146, $\eta_p^2$= .027)

### *2.7.8 Discussion*

This study is among the first to investigate the effects of MBSR offered as an adjuvant intervention on biological markers of stress, immune function and cellular aging among breast cancer survivors with CNP who received medication optimization. Ninety-eight women were enrolled and allocated to an MBSR (N=49) or waitlist control (N=49) group after having their medication optimized to coincide with clinical practice guidelines for the pharmacological management of CNP. Thirty-four women discontinued participation (18 from MBSR) with 29 women originally assigned to the waitlist control proceeding to complete MBSR. Analyses were performed using intention-to-treat principles with per-protocol analyses conducted among women who attended 8 or more MBSR sessions.

#### 2.7.8.1 Manipulation check

Women who completed the MBSR program reported improvements in mindfulness from pre- to post-intervention relative to controls. This suggests that MBSR was having the intended effect of increasing mindfulness. In contrast, women who completed the MBSR program did not report decreases in stress, suggesting that participants exposed to the MBSR intervention successfully learned the principles of mindfulness, but were unable to realize the stress-reducing effects.

Golden-Kreutz and Browne (2009) assessed stress in women diagnosed with breast cancer using the PSS at the onset of cancer treatment and 12- and 24-month follow-up. They reported that level of perceived stress declined over time, where initial PSS scores may have reflected the stress that accompanies diagnosis, treatment, and uncertainty. It was suggested that

declines in perceived stress may reflect resolution of stress in response to end of cancer treatment (Golden-Kreutz, Browne, Frierson, & Andersen, 2004). In the present study, cancer survivorship is accompanied by the added stressor of living with CNP. It is possible that the PSS, a measure of perceived stress, is not sensitive enough to accurately capture recurring stress after treatment of breast cancer subsequent to the development of CNP (into survivorship). Significant declines in level of perceived stress across time irrespective of group assignment may also suggest the possibility that optimal medication management may have provided some degree of resolution to stress associated with CNP, similar to results reported by Golem-Kreutz and Browne (2009). Global reductions in perceived stress regardless of group allocation may also highlight the possibility that MBSR may offer little benefit above and beyond optimal pharmacological management within the first 3 months. It is possible that women were unable to implement mindfulness practice in a manner that helped them better manage stress. Mindfulness is a skill that requires dedicated practice to master. It is possible that participants were in the process of learning a newly acquired skill and thus changes in overall reported level of stress may be unable to be detected.

#### 2.7.8.2 Primary analyses

Our hypotheses that the MBSR intervention would yield associated reductions in biomarkers of stress, inflammation and cellular aging were not supported. After adjusting for medical optimization, no between group effects were observed for cortisol, Il-6, CRP or telomere decay over time.

A lack of associated changes in biomarker expression is not surprising given that no significant self-reported reductions in stress were observed. Additionally, breast cancer survivors represent a unique and complex population where pre-existing comorbidities and the residual

effects of cancer treatment(s) are further complicated by the development of CNP which is often refractory to treatment (Mendlik & Uritsky, 2015). Biobehavioural studies in cancer and survivorship populations frequently report the difficulty of accurately detecting biological changes following psychosocial interventions due, in part, to the variability across psychological, social and physical factors that influence them (Andersen, Godiwala Goyal, Westbrook, Bishop, & Carson III, 2017; Reich et al., 2017; Robins et al., 2013). Notably, our study is unique in that we sought to identify the additive effects of MBSR intervention in the treatment and management of CNP in breast cancer survivors following guideline-based medical optimization. The complex nature of our sample, while externally valid, may itself render the ability to capture any changes in biomarker expression imparted by the MBSR intervention challenging.

Characterizing biological correlates of psychological interventions is also challenged by the numerous biological processes that are implicated in the body's stress response, each with differing natural trajectories that can be influenced by the lingering effects of cancer, treatment and pre-existing comorbidities. For example, the natural trajectories of cancer-related stress, depressive symptoms and immunity in women with breast cancer from diagnosis to five years following diagnosis have shown that there is a high degree of variability among markers of immunity while cancer related stress and depressive symptoms follow a more gradual and stable course of improvements (Andersen, Godiwala Goyal, et al., 2017). Biological markers are further influenced by long-term effects of cancer treatment. Chemotherapy and/or radiation are successful in cancer treatment as a result of their ability to damage cancer cells. However, the cytotoxic effects of these treatments also result in damage to healthy cells and normal tissue. For example, Scuric et al., (2017) reported significantly greater DNA damage and lower telomerase activity among a cohort of women 3-6 years post-breast cancer diagnosis who received radiation

and/or chemotherapy as part of their cancer treatment compared with women whose treatment regimen did not include radiation and/or chemotherapy. Furthermore, cytokine activity has also been shown to vary in response to type of cancer treatment. Reich et al., (2017) reported small, but consistent correlations between IL-6 and type of cancer treatment, with mastectomy and chemotherapy being associated with lower levels of IL-6 and radiation being associated with higher levels of IL-6. Although type of cancer treatment was not significantly different between groups in our study, the variability in biomarker expression in response to type of cancer treatment may further challenge the ability to determine the presence of any MBSR related changes in biological markers of stress, immunity and cellular aging.

It is also important to consider the patterns of biomarker expression and the timing of data sampling. One study reported that changes in cytokine expression (IL-6 and TNFα) among breast cancer survivors who attended a 6-week MBSR intervention occurred during the 6-12 week follow-up period rather than during the training period itself (Reich et al., 2017). It is possible that our sampling period of 2-weeks post-MBSR, with follow-up at 3-months, may not have been specific enough to capture change in cytokine expression in response to the MBSR intervention that may have occurred outside of that window. Most studies assessing change in cortisol in response to mindfulness interventions have used salivary cortisol. Salivary cortisol has been shown to respond favorably in response to mindfulness interventions (near medium effect sizes), with larger effect sizes reported as the number of hours and sessions of mindfulness training increase (Sanada et al., 2016). Salivary, urine and serum cortisol samples reflect measures of acute stress at the time of collection (Wright et al., 2015). Hair cortisol has emerged as a measure of cumulative HPA axis activity over longer periods of time, with one cm of hair reflecting cortisol exposure over a period of about one month. Only one study has evaluated the

effect of mindfulness-based interventions on hair cortisol, in a relatively healthy sample of smokers (Goldberg et al., 2014). Whether MBSR dampens HPA-axis activity and produces subsequent change in cortisol that can be detected in hair samples among women breast cancer survivors with CNP requires further study. Notably, hair cortisol samples were collected pre-MBSR (post-medical optimization) and at 3-month follow-up. It is possible that the sample of hair collected is insufficient in capturing MBSR effects on hair cortisol that occur during or immediately after treatment.

#### 2.7.8.3 Secondary Analyses

Secondary analyses assessed the impact of the MBSR intervention after medical optimization on self-report measures of pain, physical function and emotional function. Women who attended 8 or more MBSR sessions reported significantly greater improvement in pain severity and pain interference post-MBSR compared to controls. Moreover, women who attended 8 or more sessions of MBSR reported experiencing a more meaningful change to their life on the patient global impression of change scale relative to waitlist control. This suggests that MBSR intervention as a therapeutic treatment option among breast cancer survivors with CNP may be more beneficial when attendance and participation is high. These effects were no longer present at follow-up, which may indicate that both greater attendance and participation in mindfulness interventions may require prolonged (maintained) engagement in order to maintain preferential views for treatment. Unfortunately, no other MBSR-related functional improvements were detected across other self-report measures.

All participants underwent medical optimization prior to randomization of group assignment. Surprisingly, medical optimization resulted in little improvement in primary and secondary outcomes pre-MBSR. It is unclear how long medical optimization takes to reach the

correct therapeutic window and the main effect of time, regardless of group allocation, may be partly attributable to long-term benefits of medical optimization. Medical optimization offers external validity but may have obscured between group differences over time (in part due to the effect of expectation, and in part due to the effect of pharmacological management).

Mindfulness and mindfulness-based interventions have become increasingly studied in the past decade and have shown beneficial effects among a broad range of outcomes and across a variety of populations (*Refer to Review by* Creswell, 2017). Despite sharing similar conceptual features, mindfulness-based interventions are not homogenous, nor are they a panacea for disease and illness. A common criticism of mindfulness interventions is the lack of a universally accepted definition from which they can be operationalized (Van Dam, van Vugt, Vago, Schmalzl, Saron, Olendzki, Meissner, Lazar, Kerr, Gorchov, R Fox, et al., 2018). The implications of this has led to differences in delivery methods, including duration and frequency of mindfulness practice, as well as how mindfulness is measured among participants. This can present challenges in interpreting the efficacy of mindfulness programs, as differences in delivery afford challenges in making comparisons across studies. For example, Reich et al. (2017) explored the effect of MBSR on inflammatory biomarkers among breast cancer survivors. Similar to our study, their MBSR program was adapted from Jon Kabat-Zinn's original MBSR program, however, their participants received 2-hr weekly sessions for 6-weeks, as well as take-home training material for guided in-home practice. Participants were also asked to record their practice times and were contacted weekly for the duration of the study (12-weeks total) to address participant concerns and act as reminders for continued daily practice of a recommended 15-45 min per day (Reich et al., 2017). Additionally, the potential for a dose-response relationship in mindfulness interventions, with greater mindfulness practice producing larger

scalable effects, has been suggested (Creswell, 2017), and is consistent with the per-protocol analyses identified in this study where women who attended 8 or greater mindfulness sessions demonstrated some improvement. While these differences represent caveats when interpreting mindfulness literature, they may also shed light on the aspects of mindfulness interventions and various facets of mindfulness that are importance in the change process.

Mindfulness-based interventions have gained significant traction in their use in the treatment of chronic pain conditions. Despite this increase in popularity, our understanding of the association between mindfulness and pain is still evolving. A systematic review, including 38 RCTs on mindfulness interventions for the treatment of chronic pain in adults, details the beneficial effects of mindfulness in improving pain, symptoms of depression, and quality of life (Hilton et al., 2017). It is important to note that the effects are small and the quality of evidence poor, due largely to small sample sizes, inadequate control groups and short duration of follow-up. Our results suggest that mindfulness may provide some benefit in reducing the degree of pain severity and pain interference when session attendance is high.

It may be beneficial to look more carefully at the various aspects that comprise how we have operationalized mindfulness in order to better understand how mindfulness may contribute to the findings reported in this study. The five facet mindfulness questionnaire characterizes total mindfulness through five facets; observing, describing, acting with awareness, nonjudgment and nonreactivity (Baer et al., 2006). There is evidence to suggest that increased in mindfulness may mediate the effect of mindfulness on psychological outcomes (Keng, Smoski, Robins, Ekblad, & Brantley, 2012). It has also been reported that mindfulness may mediate the relationship between the amount of time spent in formal mindfulness practice (Carmody & Baer, 2008). The effect of MBSR intervention on psychological outcomes, and subsequently biomarker expression, in our

population may require a more in-depth look to determine if there are specific aspects of mindfulness that may serve as mediators in the effectiveness of MBSR interventions.

#### 2.7.8.4 Limitations

There are important limitations in this study that warrant consideration. First, neuropathic pain does not respond consistently to pharmacological interventions. Despite efforts to maintain a stable medication regimen throughout the duration of the study, adjustment to medications were made when required. Therefore, medication regimens varied somewhat across participants. It is possible that variability among pharmacological agents and the degree of effectiveness could impact biomarker expression and subsequent self-report indices of functional and psychological factors. Second, we did not collect information about control participants exposure to mindfulness throughout the study, or if participants sought independent mindfulness practice. Cancer survivors have the option of accessing various programming with mindfulness-based options being particularly abundant, and it is possible that some women allocated to control sought out and received mindfulness-based programming independent of the trial. Third, while session attendance was recorded, mindfulness practice outside of MBSR sessions was not recorded making it difficult to determine uptake of MBSR skills. This is particularly relevant for the follow-up period, during which time no data was collected to provide an indication of continued mindfulness practice. Fourth, significant patient heterogeneity is likely further impacted by the small sample size. Although attrition rates were relatively high, there were no discernable differences between participants that did not complete the trial. Further, Little's test for missing completely at random and single imputation analyses were used to address missing data due to participant drop-out. Lastly, the biomarkers assessed in this study are among several biological markers involved in the body's response to stress, immunity and cellular aging. It is

important to recognize that these biomarkers are part of a broad network of biological responses and may not fully capture the mechanism through which MBSR effect change on biological correlates of stress.

#### 2.7.8.5 Strengths

It is important to highlight the strengths of this study. This study was pragmatic in its approach whereby it was designed to assess the effects of MBSR interventions among a pre-existing and complex population of breast cancer survivors with CNP. The trial was conducted in a hospital setting with guideline-based medical optimization. MBSR was delivered by individuals with significant training and experience. MBSR followed a well-established program that has been used widely among the mindfulness literature. Attendance (approximating dose) at MBSR sessions was measured and evaluated, and measurement of biomarkers and self-report data was comprehensive.

#### 2.7.8.6 Conclusions

Our study only partially supported MBSR as an effective adjunctive intervention for CNP in breast cancer survivors after optimal pharmacological medical management. Future studies directed towards identifying mindfulness as a potential mediator in mitigating the body's stress response are warranted. Importantly, mindfulness-based interventions are designed to target the physiological correlates of pain, not necessarily the intensity of an individual's pain, therefore improvement in the degree of pain interference is a significant finding that warrants further investigation into how MBSR effects this change. Lastly, this is the first study to report the effects of MBSR on biomarkers of stress, inflammation and cellular aging among breast cancer survivors with CNP, therefore the null findings reported in this study are important indicators for guiding future studies in determining the mechanisms through which mindfulness-based

interventions can provide a beneficial effect in the treatment of chronic illness and disease. By looking more closely as the aspects that bring about change, we can begin to understand how mindfulness interventions can be used to ameliorate the quality of life and survivorship among breast cancer survivors.

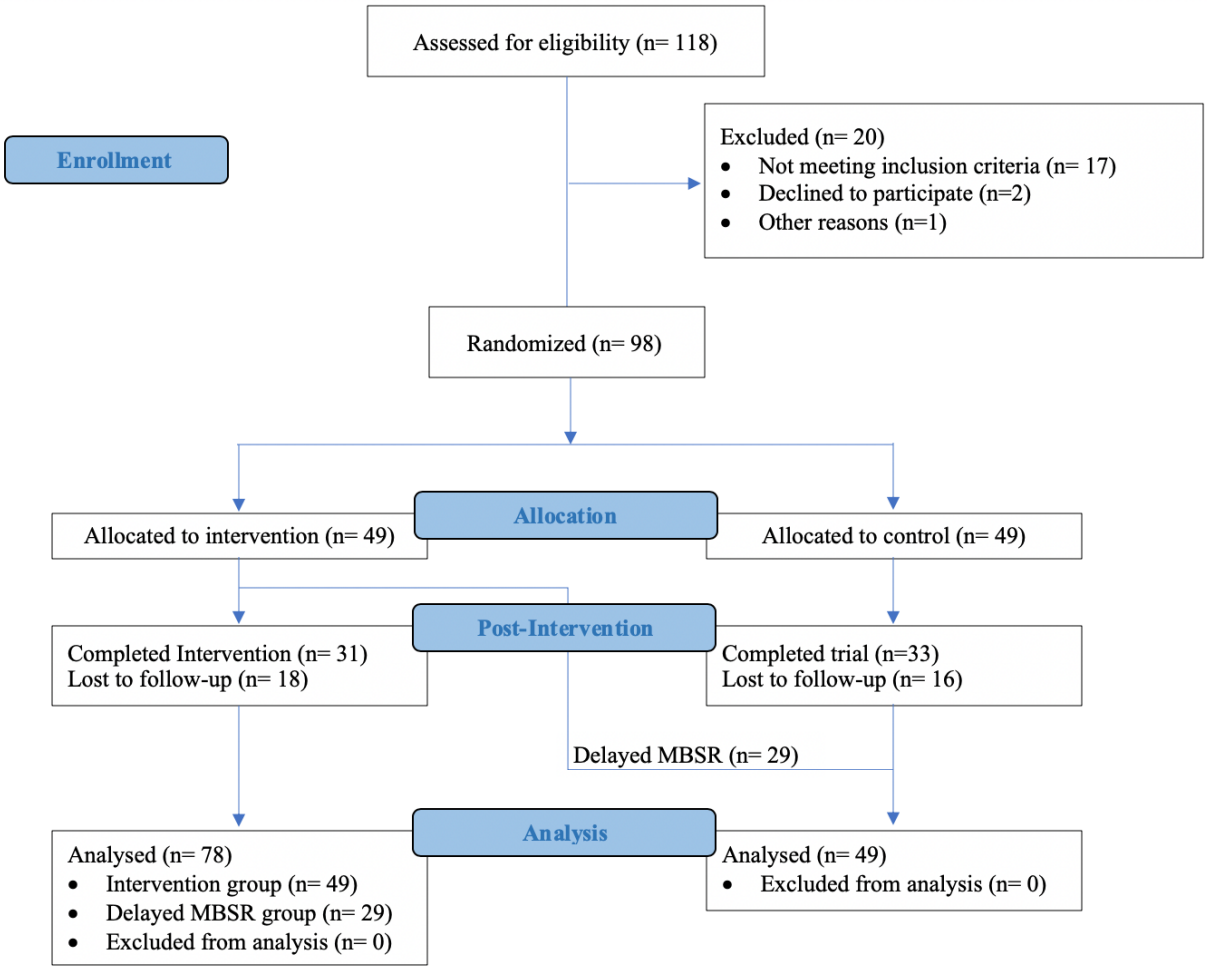


*Figure 1. CONSORT flowchart*

*Table 1. Demographic and clinical characteristics for all respondents (n= 98).*

| | Total Sample (n= 98) | Treatment Group (n= 49) | Waitlist Control Group (n= 49) |
|---|---|---|---|
| **Gender** | | | |
| *n* | 98 | *49* | *49* |
| *% Female* | 100% | *100%* | *100%* |
| *% Male* | 0% | *0%* | *0%* |
| **Age** (*Mean*, *SE*) | 53.1 (1.1) | *51.3 (1.6)* | *55.1 (1.4)* |
| **Ethnicity** | | | |
| *n* | 94 | *48* | *46* |
| *Caucasian n, %* | 79 (80.6%) | *40 (81.6%)* | *39 (84.8%)* |
| *African n, %* | 1 (6.4%) | *1 (2.0%)* | *0 (0.0%)* |
| *Asian n, %* | 6 (6.4%) | *2 (4.1%)* | *4 (8.7%)* |
| *First Nations n, %* | 2 (2.1%) | *1 (2.0%)* | *1 (2.2%)* |
| *Other n, %* | 6 (6.4%) | *4 (8.2%)* | *2 (4.3%)* |
| **Education** | | | |
| *n* | 96 | *49* | *47* |
| *Grade School n, %* | 2 (2.1%) | *1 (2.0%)* | *1 (2.0)* |
| *High School Diploma n, %* | 22 (22.9%) | *10 (20.4%)* | *12 (24.5%)* |
| *Bachelor's Degree n, %* | 34 (35.4%) | *15 (30.6%)* | *19 (38.8%)* |
| *Master's Degree n, %* | 28 (29.2%) | *16 (32.7%)* | *12 (24.5%)* |
| *Doctoral Degree n, %* | 9 (9.4%) | *6 (12.2%)* | *3 (6.1%)* |
| **Employment Status** | | | |
| *n* | 98 | *49* | *49* |
| *Full-Time Employed n, %* | 34 (34.7%) | *16 (32.7%)* | *18 (36.7%)* |
| *Part-Time Employed n, %* | 10 (10.2%) | *3 (6.1%)* | *7 (14.3%)* |
| *Unemployed n, %* | 12 (12.2%) | *8 (16.3%)* | *4 (8.2%)* |
| *Other[a] n, %* | 42 (42.9%) | *22 (44.9%)* | *20 (40.8%)* |
| **Years with Pain** (*Mean, SE*) | 3.1 (0.2) | *2.8 (0.3)* | *3.3 (0.4)* |
| **Years post BC Diagnosis** (*Mean, SE*) | 3.4 (0.2) | *3.4 (0.3)* | *3.4 (0.3)* |
| **Years post BC Treatment** (*Mean, SE*) | 2.6 (0.2) | *2.5 (0.3)* | *2.6 (0.2)* |
| **Type of Cancer treatment** | | | |
| *n* | 98 | *49* | *49* |
| *Chemotherapy (n, %)* | 81 (82.7%) | *42 (85.7%)* | *39 (79.6)* |
| *Radiation (n, %)* | 90 (91.8%) | *47 (95.9%)* | *43 (87.8%)* |
| *Surgery (n, %)* | 97 (99.0%) | *48 (98%)* | *49 (100%)* |
| **Time (days) Post-Medical Optimization and Intervention Start** (*Mean, SE*) | 15.4 (0.9) | 15.2 (1.2) | 15.9 (1.3) |

[a] Leave of absence, retired, disability, home maker

No statistically significant between group differences were found for; Age (t[94]= 1.762, *p*= .081); Ethnicity ($\chi^2$[4]= 2.304, *p*= .680); Education ($\chi^2$[5]= 3.184, *p*= .672); Employment ($\chi^2$[3]= 3.146, *p*= .370); Years with pain (t[95]= 1.005, *p*= .317); Years post-BC diagnosis (t[90]= -.035, *p*= .972); Years post-BC treatment (t[89]= .309, *p*= .758); Type of cancer treatment: Chemotherapy ($\chi^2$[1]= .641, *p*= .424; Radiation ($\chi^2$[1]= 2.178, *p*= .140); Surgery ($\chi^2$[1]= 1.010, *p*= .315); and Time between medical optimization and intervention start (t[96]= .350, *p*= .727).

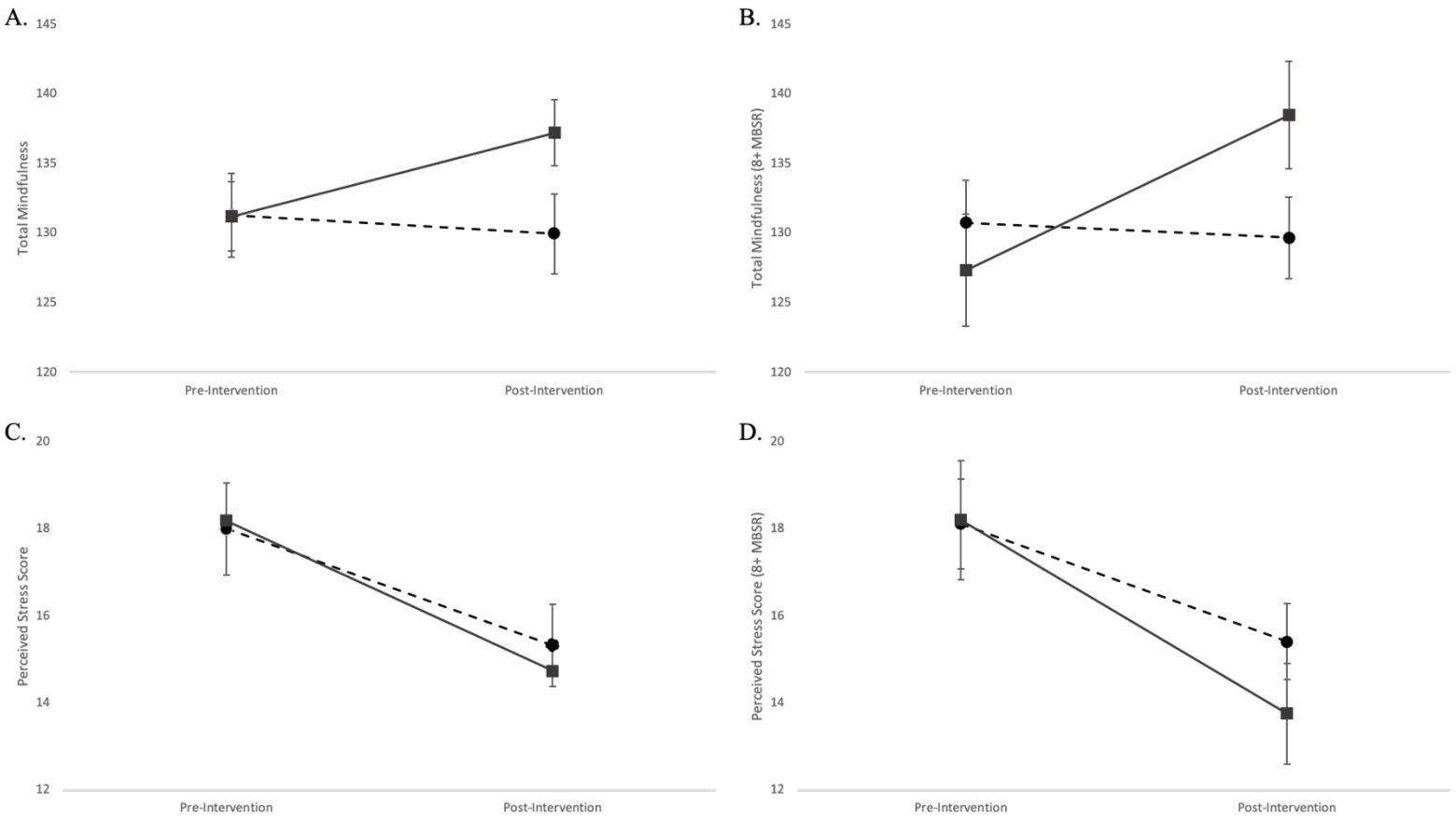


*Figure 2. Manipulation check: Effects of MBSR intervention on self-report levels of perceived stress (PSS) and total mindfulness [FFMQ; Control (---), Intervention (—)] at pre- and post-intervention. (A) Self-report level of total mindfulness (intention-to-treat analyses) with significant group by time interaction (p< .01). (B) Self-report total mindfulness (per-protocol analyses - 8+ MBSR sessions) with significant group by time interactions (p< .001 (C) Self-report perceived stress (intention-to-treat analyses). (D) Self-report perceived stress (per-protocol analyze - 8+ MBSR sessions). Error bars represent one standard error above and below the mean.*

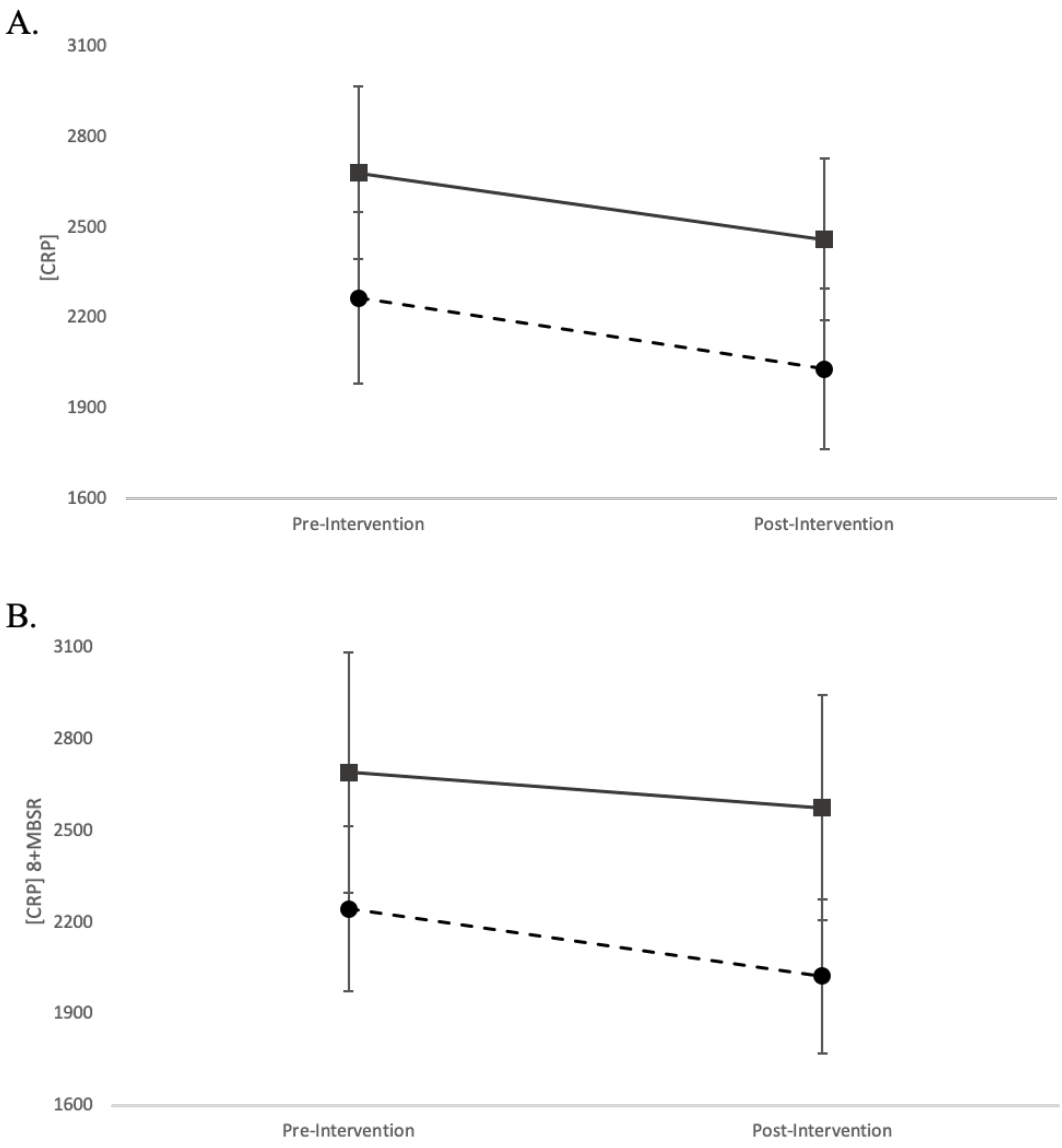


*Figure 3. Effects of MBSR intervention on CRP expression for intention-to-treat (A) and per-protocol (B) analyses [Control (- - ), Intervention (—)] at pre- and post-intervention. Error bars represent 1 standard error above and below the mean.*

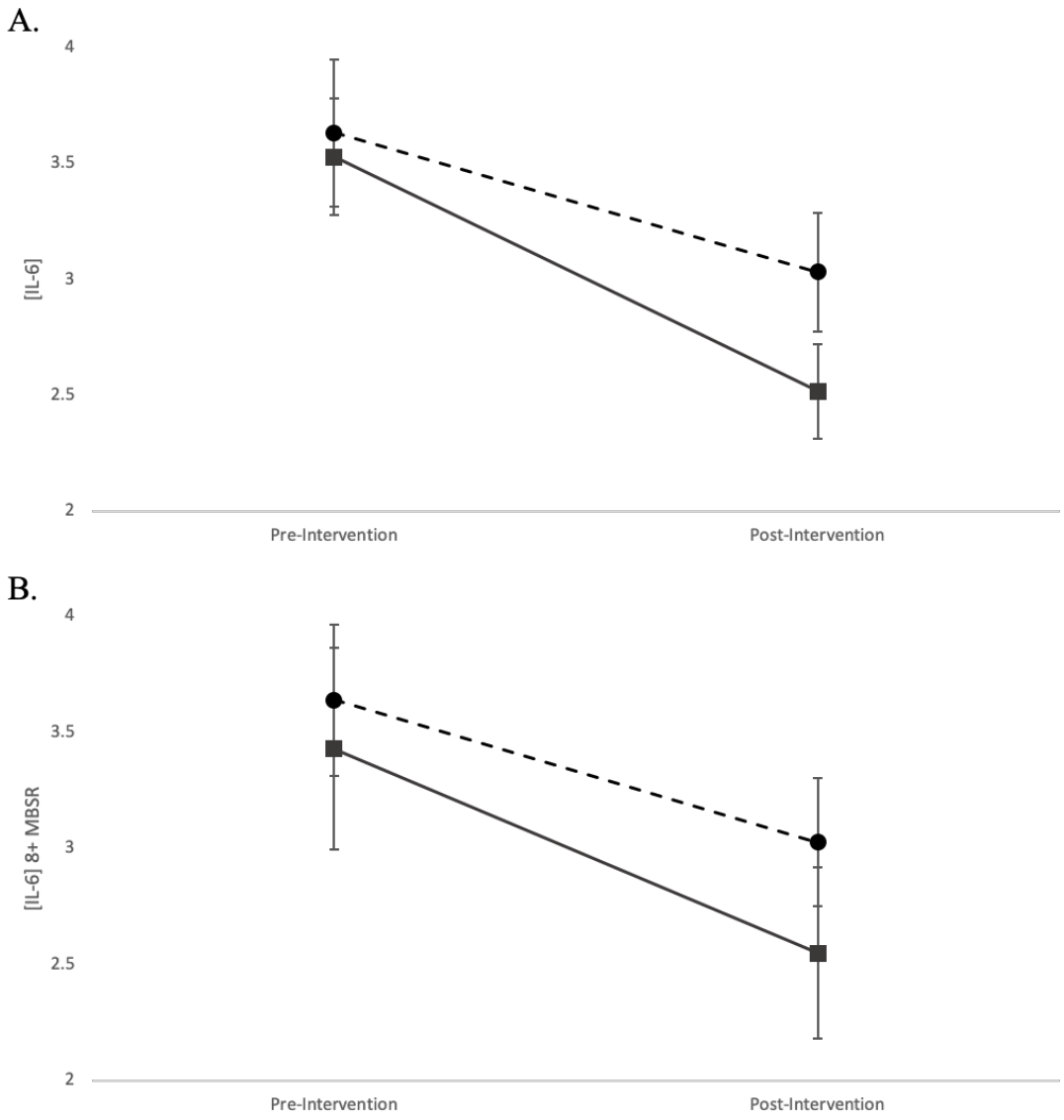


*Figure 4. Effects of MBSR intervention on IL-6 expression for intention-to-treat (A) and per-protocol (B) analyses [Control (- -), Intervention (—)] at pre- and post-intervention. Error bars represent 1 standard error above and below the mean.*

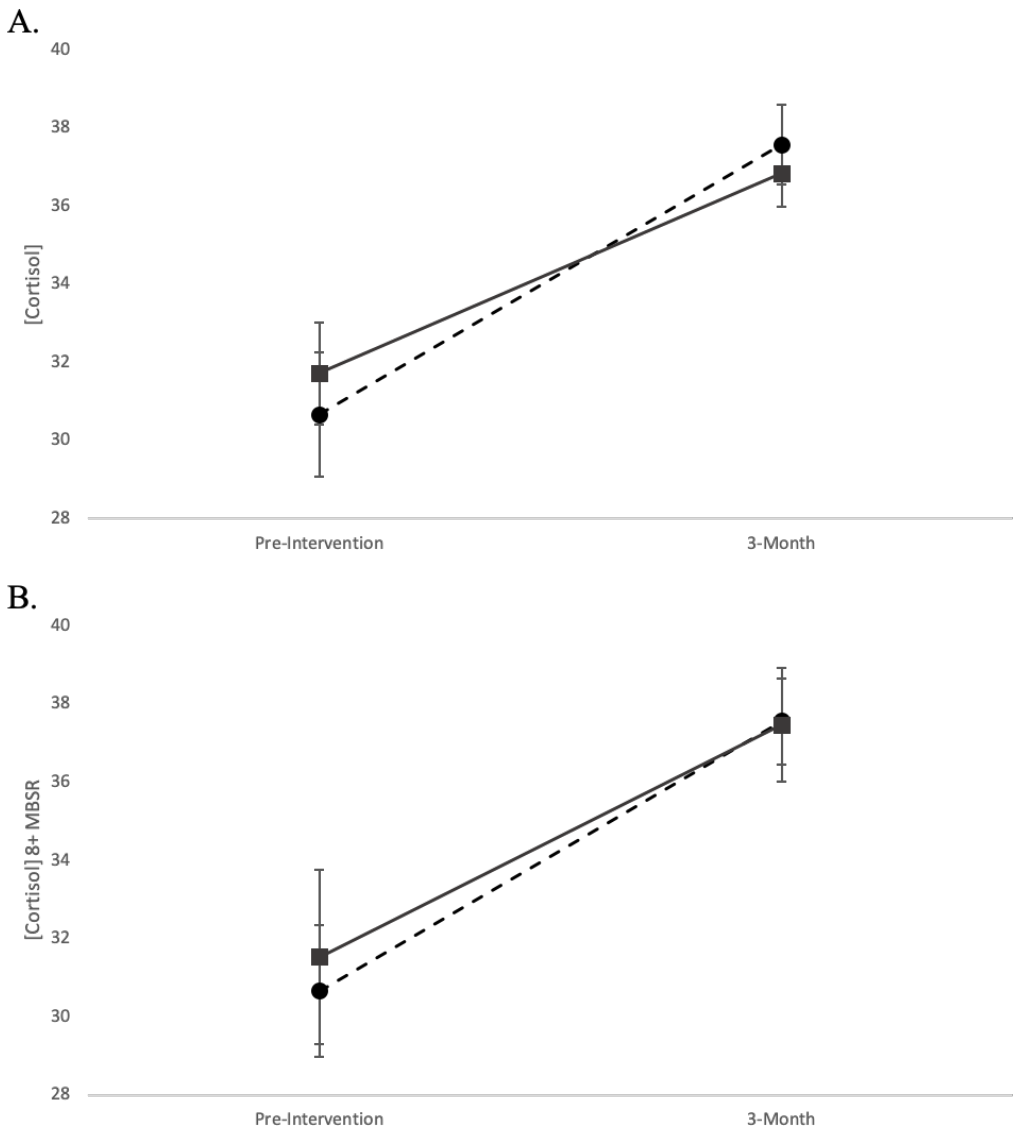


*Figure 5. Effects of MBSR intervention on cortisol expression for intention-to-treat (A) and per-protocol (B) analyses [Control (- - -), Intervention (—)] at pre-intervention and 3-month follow-up. Error bars represent 1 standard error above and below the mean.*

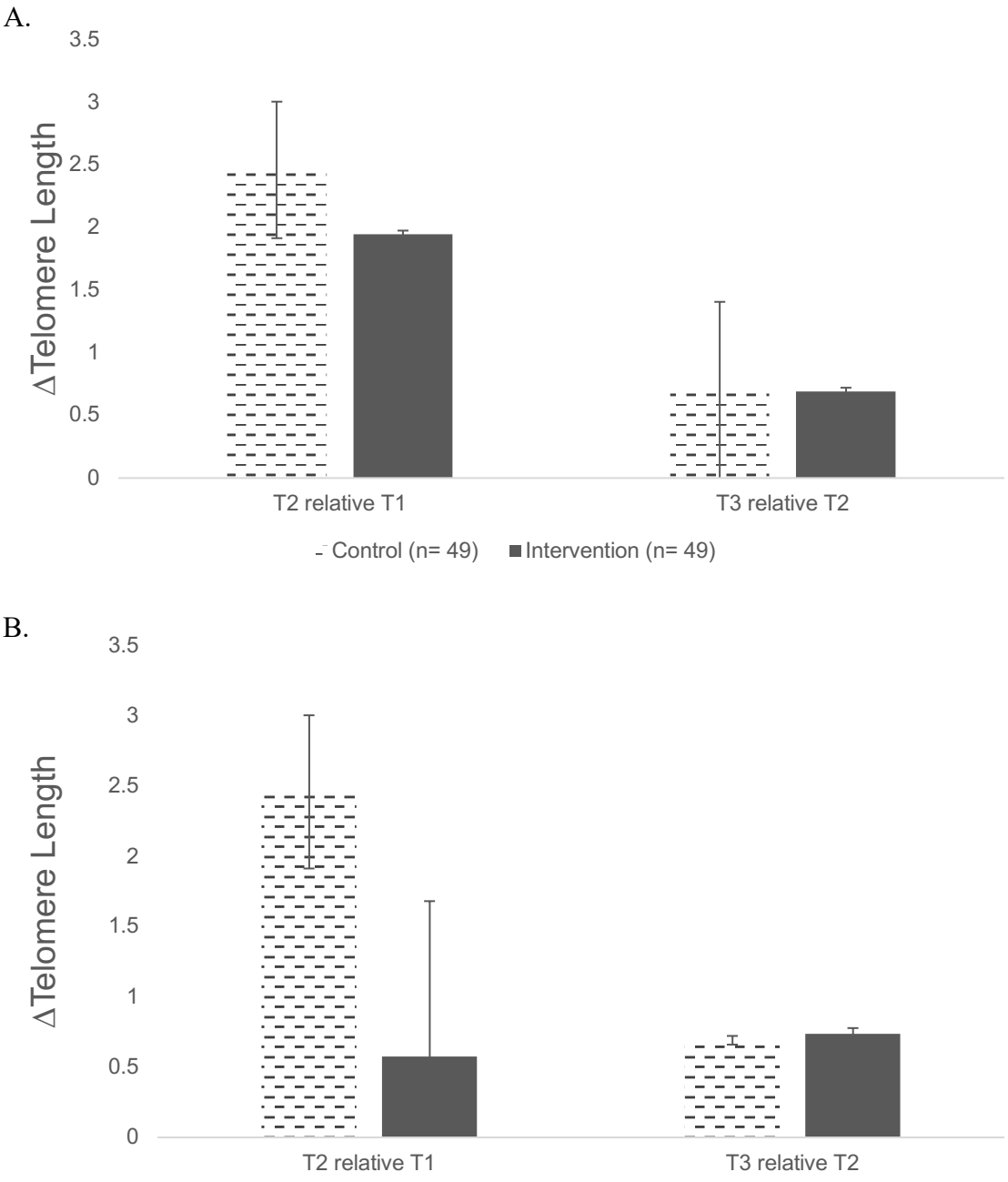


*Figure 6. Effects of MBSR intervention on telomere length (fold change) for (A) intention-to-treat and (B) per-protocol analyses [Control (- - -), Intervention (—) at pre-intervention relative to pre-medical optimization and post-intervention relative to pre-intervention. Error bars represent 1 standard error above and below the mean.*

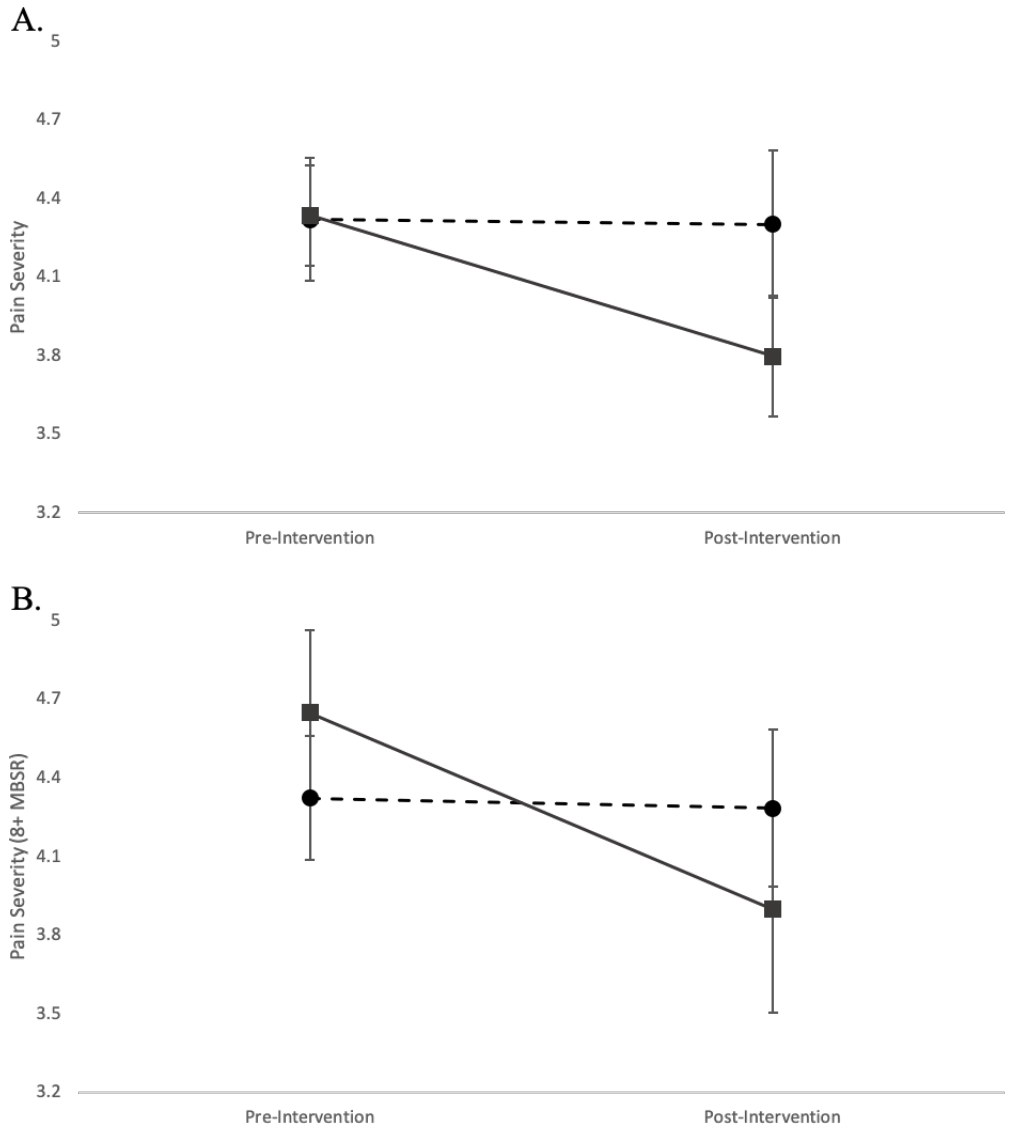


*Figure 7. Effects of MBSR intervention on BPI pain severity for intention-to-treat (A) and per-protocol (B) analyses [Control (- - -), Intervention (—)] at pre- and post-intervention. Error bars represent 1 standard error above and below the mean.*

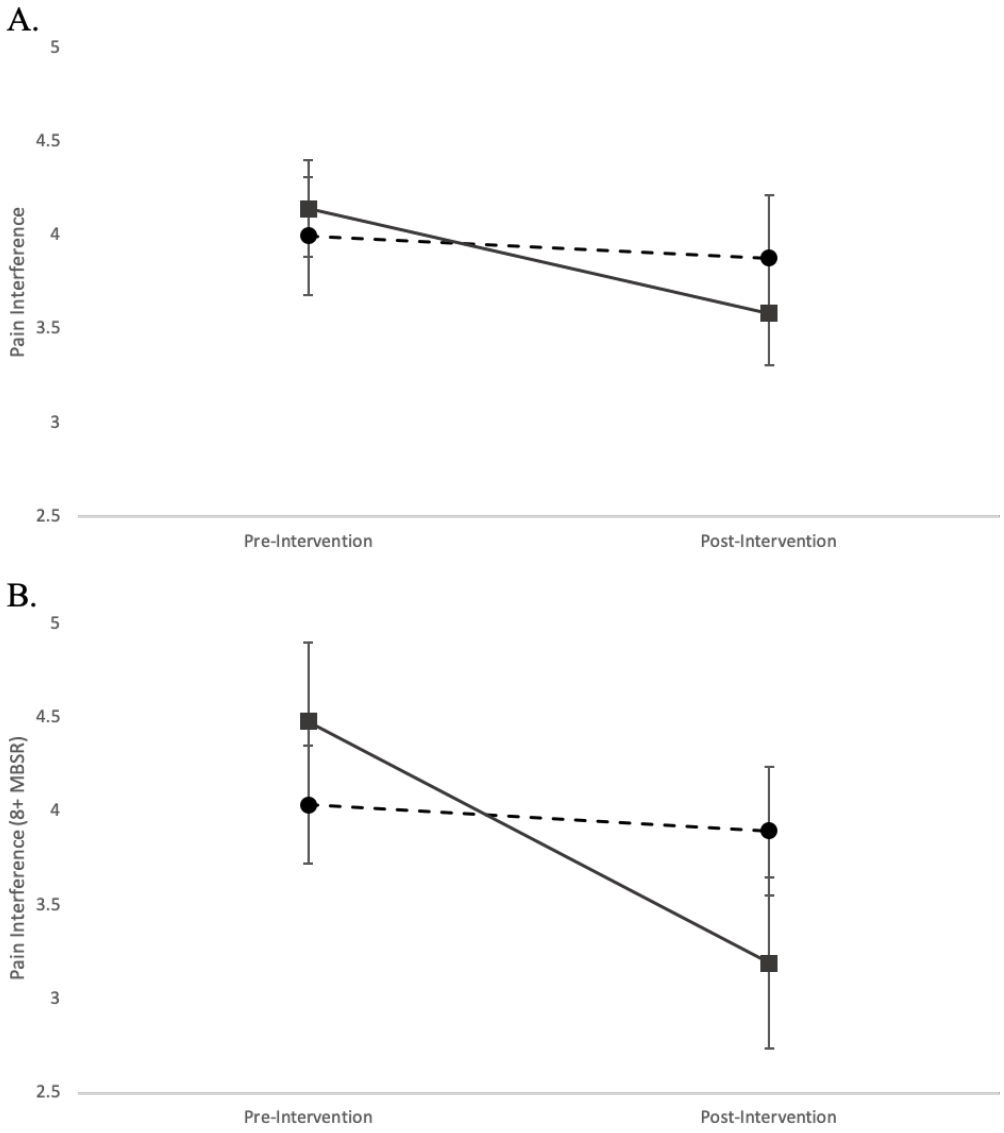


*Figure 8. Effects of MBSR intervention on BPI pain interference for intention-to-treat (A) and per-protocol (B) analyses [Control (- - -), Intervention (—)] at pre- and ~~post~~-intervention. Significant group by time interaction was found for per-protocol analyses ($p < .05$). Error bars represent 1 standard error above and below the mean.*

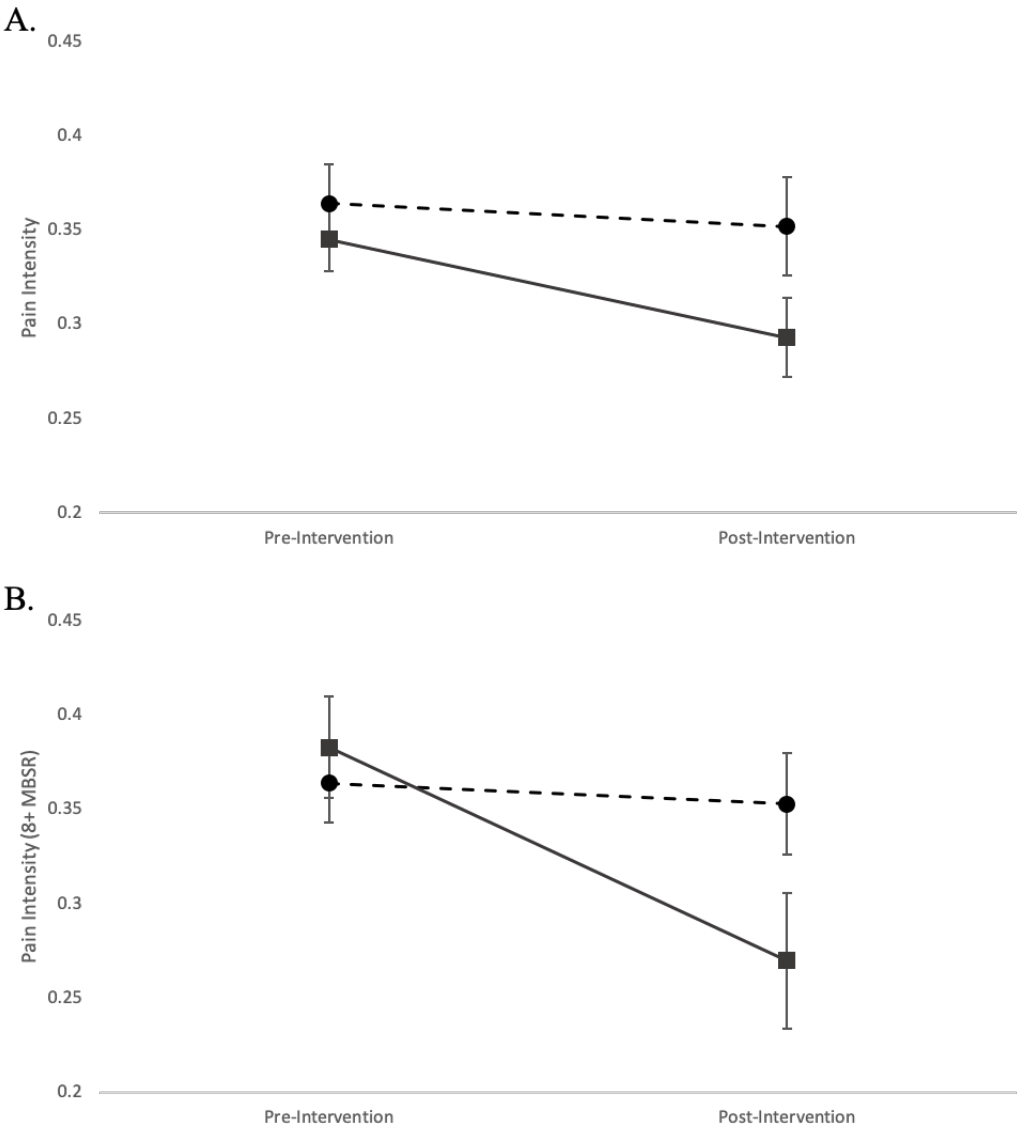


*Figure 9. Effects of MBSR intervention on neuropathic pain intensity (NPSI) for intention-to-treat (A) and per-protocol (B) analyses [Control (- - -), Intervention (—)] at pre- and post-intervention. Error bars represent 1 standard error above and below the mean.*

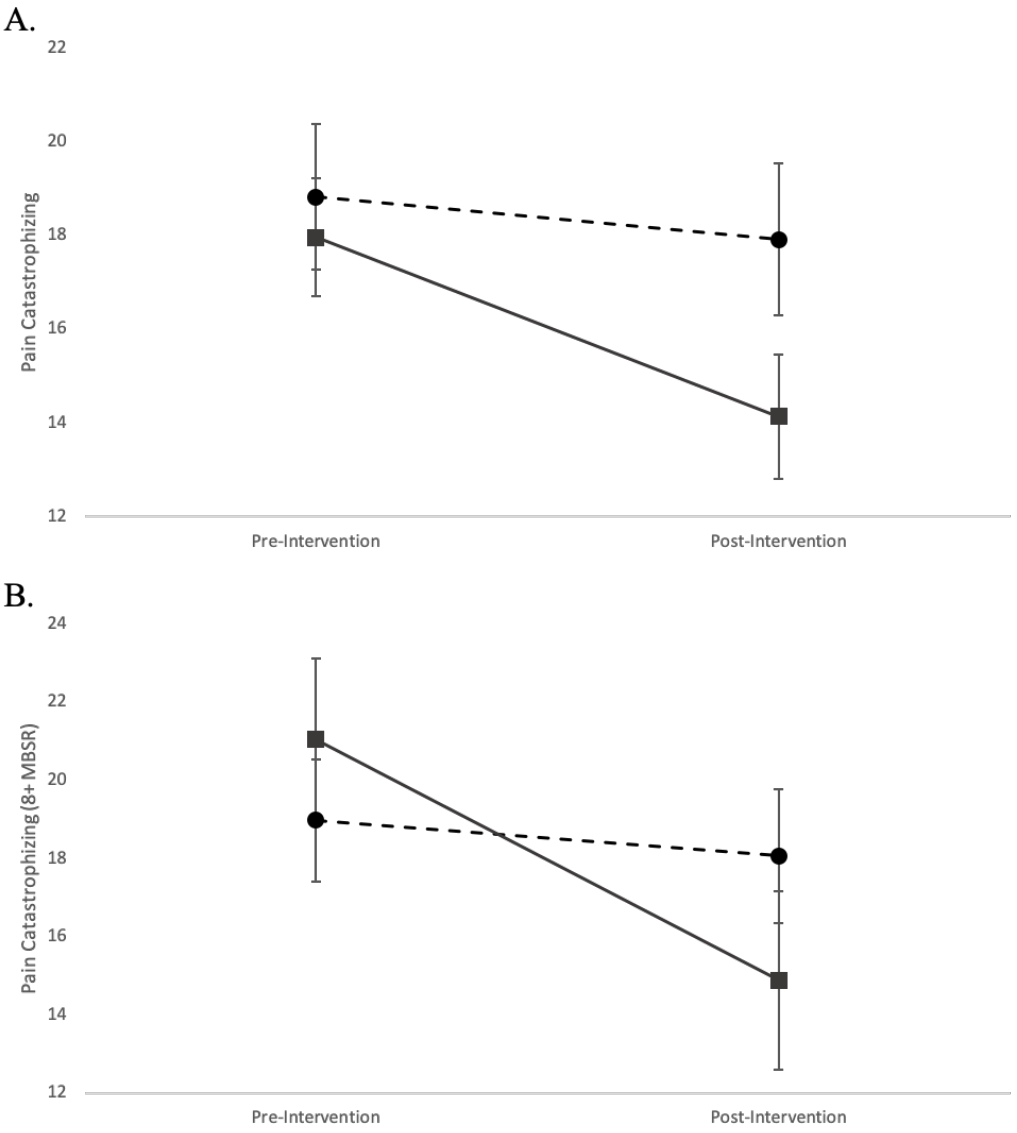


*Figure 10. Effects of MBSR intervention on pain catastrophizing (PCS) for intention-to-treat (A) and per-protocol (B) analyses [Control (- - -), Intervention (—)] at pre- and post-intervention. Error bars represent 1 standard error above and below the mean.*

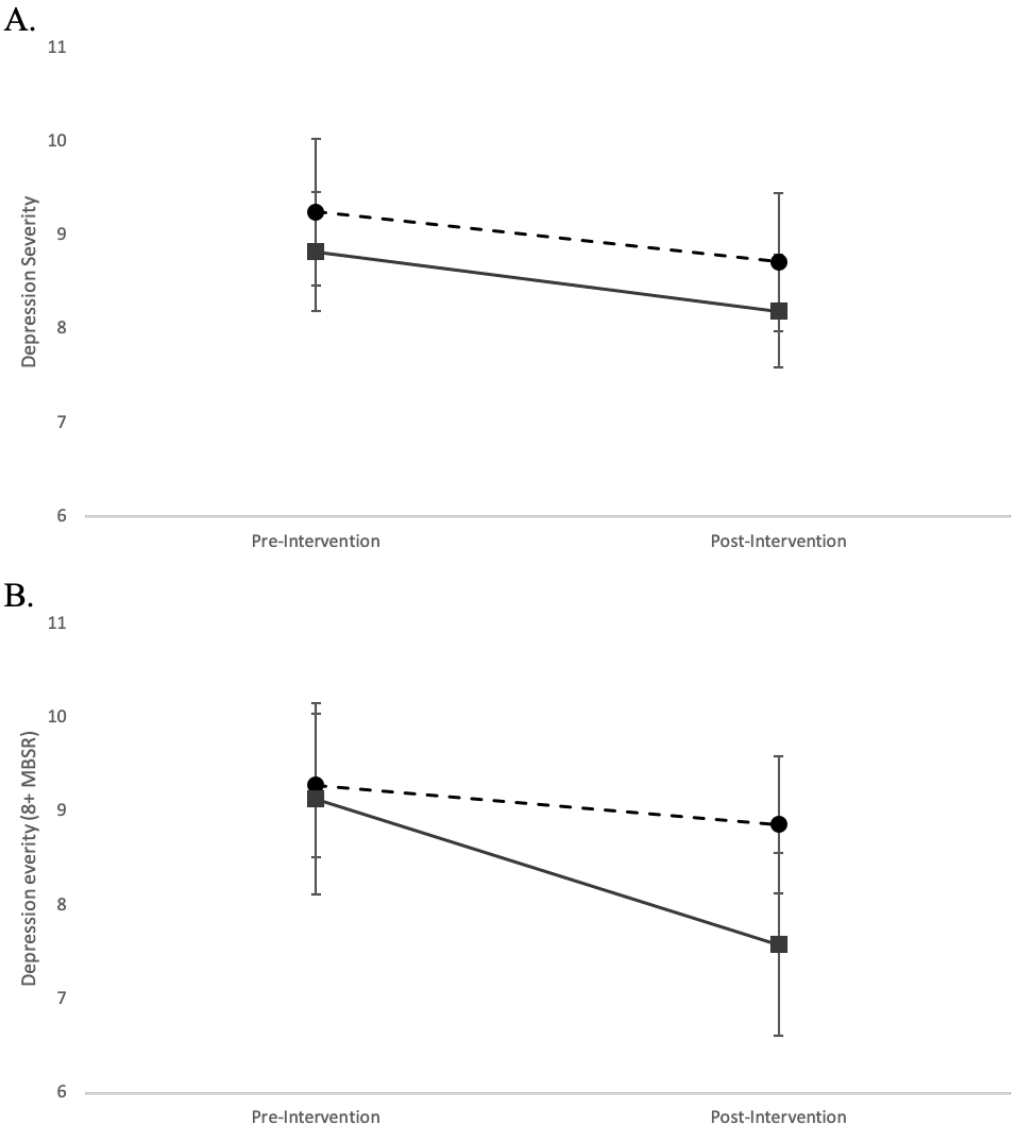


*Figure 11. Effects of MBSR intervention on depression (PHQ-9) for intention-to-treat (A) and per-protocol (B) analyses [Control (- - -), Intervention (—)] at pre- and ~~post~~-intervention. Error bars represent 1 standard error above and below the mean.*

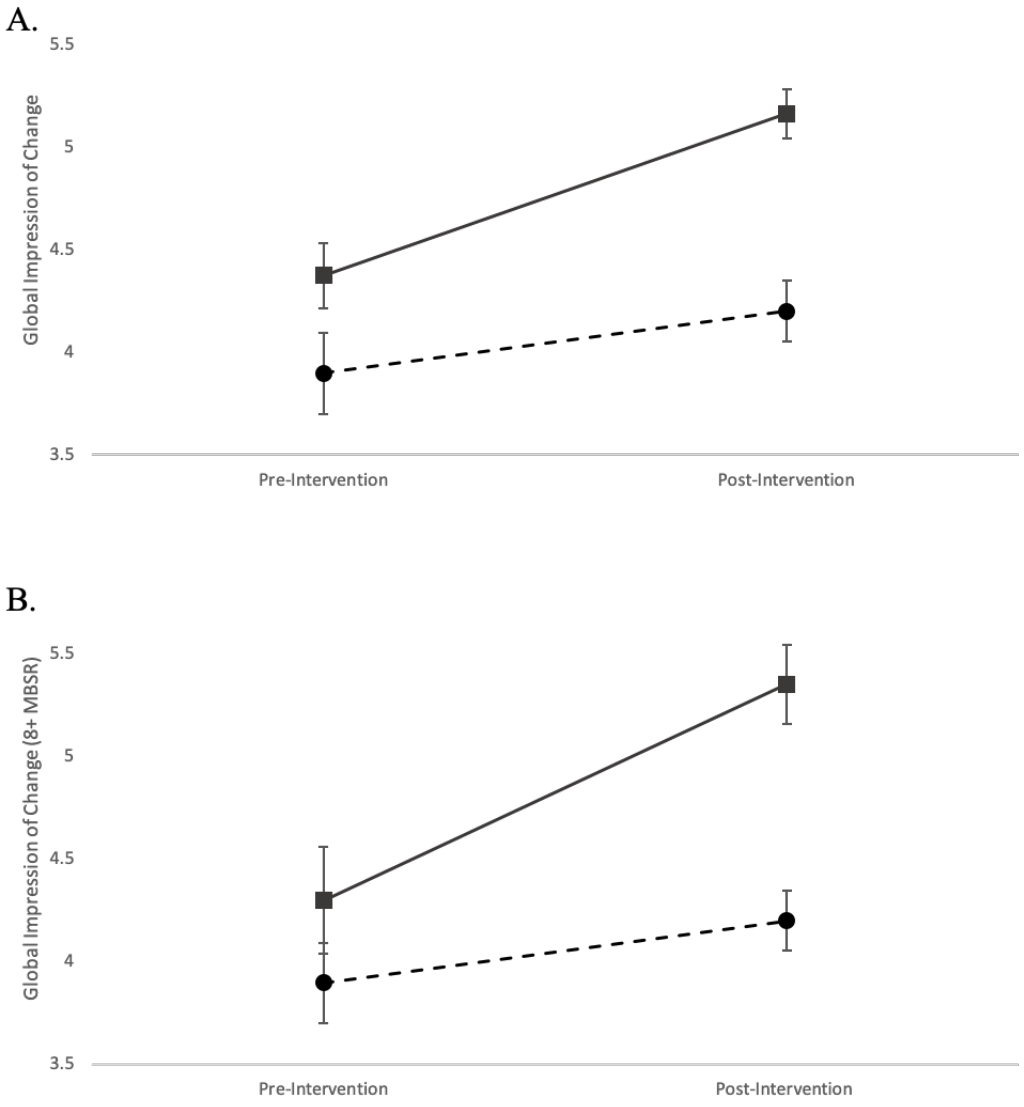


*Figure 12. Effects of MBSR intervention on perceived global impression of change (PGIC) for intention-to-treat (A) and per-protocol (B) analyses [Control (- - -), Intervention (—)] at pre- and post-intervention. A significant group by time interaction was found for per-protocol analyses ($p < .05$). Error bars represent 1 standard error above and below the mean.*

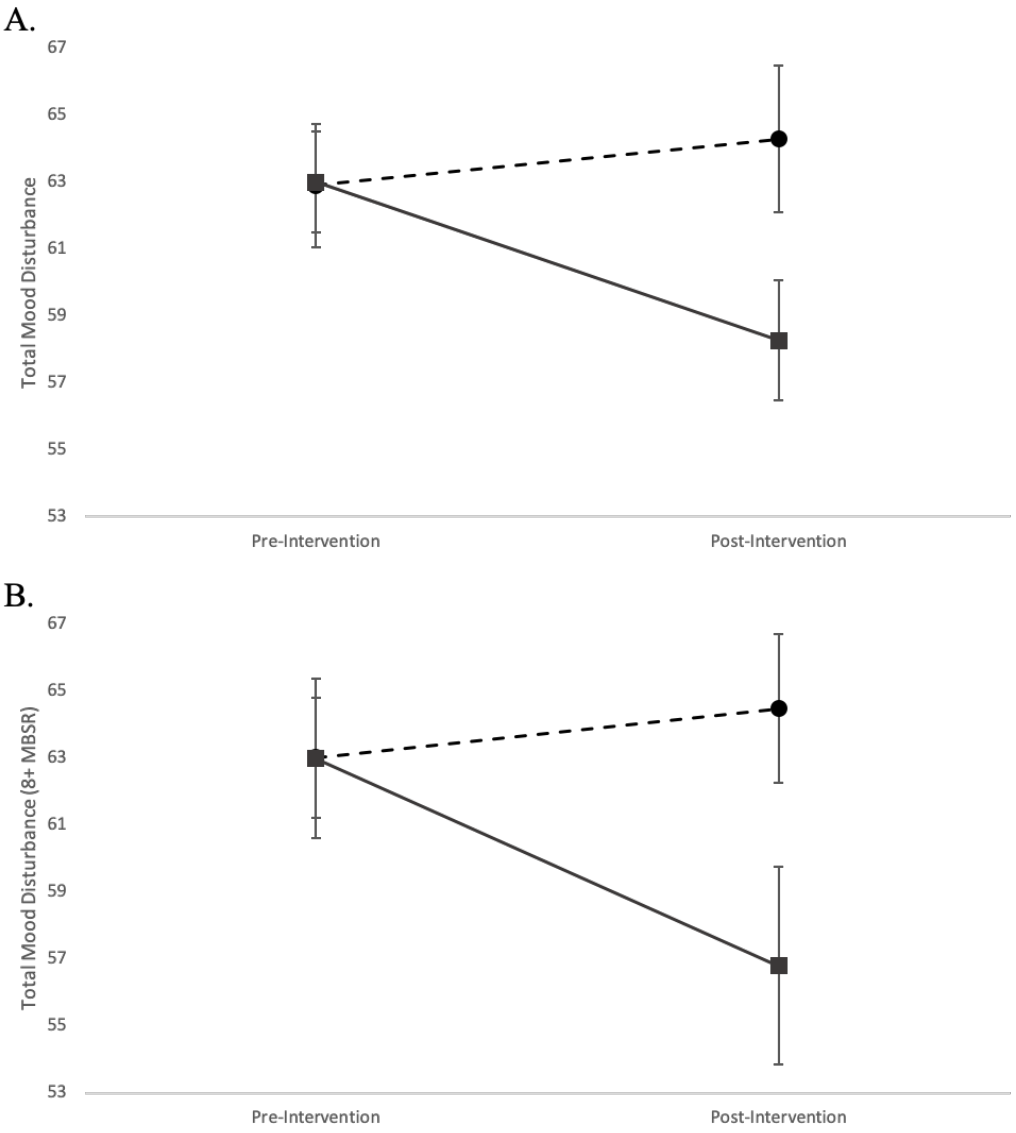


*Figure 13. Effects of MBSR intervention on total mood disturbance (POMS2tmd) for intention-to-treat (A) and per-protocol (B) analyses [Control (- - -), Intervention (—)] at pre- and post-intervention. Error bars represent 1 standard error above and below the mean.*

# Chapter 3: The Role of Mindfulness Facets in Mediating MBSR-Related Changes in Pain Among Cancer Survivors with CNP

# Abstract

**Background:** MBSR has been widely studied among chronic pain patients due to promising outcomes on pain-related symptoms and improvements in mood, physical function, and quality of life; however, the mechanisms through which MBSR exerts its effects are not well understood. We have previously demonstrated that MBSR leads to preferential improvements in pain-severity and pain-related interference in breast cancer survivors with chronic neuropathic pain (CNP) and guideline-based medical optimization. The purpose of the present study was to explore whether change in mindfulness and its facets that occurred following completion of an MBSR intervention mediate concomitant change in pain and pain-related interference. **Methods:** Data obtained from a double-blind randomized waitlist control trial conducted using a sample of 98 breast cancer survivors diagnosed with CNP who were randomized to receive an 8-week MBSR intervention or waitlist control condition after undergoing medical optimization were used in this study. Mediation analyses were conducted and a Sobel test was used to evaluate the significance of a mediation effect. Change in total mindfulness and individual mindfulness facets (observing, acting with awareness, describing, nonjudging and nonreactivity) were used as mediators. Change in pain-related severity (BPI severity scores) and pain-related interference (BPI interference scores) were entered as outcomes of interest. The intention of this study was to explore, a posteriori, the potential role of mindfulness, and its facets, in changes in MBSR associated changes in pain severity and interference **Results:** Exploratory analyses did not reveal significant mediating effects for changes in total mindfulness or individual mindfulness facet scores on previously identified self-reported changes in pain severity or pain-related interference. Changes in pain-related interference were shown to be partially mediated by change in total mindfulness scores. **Conclusions:** These findings suggest that change in total mindfulness would seem to play some role in ameliorating pain-related interference but fails to account for self-reported changes in pain

severity. The complexities of studying clinical populations with complex and comorbid illness and disease suggests that the mechanism through which effective interventions improve clinical outcomes is likely equally complex. Future studies directed towards building this understanding are required for the identification of clinical populations who may best benefit from particular interventions and subsequently in developing individualized and empirically supported treatment plans.

## 3.1 Introduction

Mindfulness practice has origins in Buddhist traditions that are centered around present moment awareness and acceptance of moment-to-moment experiences. Mindfulness-based stress reduction (MBSR), one of the most well-known mindfulness intervention programs (Kabat-Zinn et al., 1985), has sparked a global expansion of mindfulness-based strategies with applications spanning across medical and mental health disciplines.

Standardized in 1993 by Jon-Kabat Zinn for treatment resistance chronic pain, MBSR has been widely studied among chronic pain patients due to promising outcomes on pain-related symptoms and improvements in mood, physical function, and quality of life. In addition, mindfulness-based interventions have demonstrated beneficial effects among cancer survivors (Altschuler et al., 2012; Lengacher et al., 2012; Lengacher, Shelton, et al., 2014; Shapiro et al., 2003; Speca et al., 2000; M. L. van der Lee & Garssen, 2012; Witek-Janusek et al., 2008a), including improvements in health-related quality of life among women who develop chronic pain conditions after treatment (Labelle, 2012; Poulin et al., 2016).

Despite growing support for mindfulness-based interventions among individuals who develop chronic disease, the mechanisms through which mindfulness promotes beneficial effects is not well understood. One common critique of mindfulness-based interventions is the lack of an agreed upon definition of mindfulness, rendering it difficult to determine how such interventions contribute to functional and psychological improvements. Mindfulness is best described as a multifaceted construct (Baer et al., 2006, 2008). According to the five-facet operationalization, mindfulness is comprised of five component skills that include: observing; describing; acting with awareness of present moment experiences; nonjudgment of inner experience; and nonreactivity to one's inner experience (Baer et al., 2006).

One approach that can allow for a better understanding of how mindfulness yields preferential improvements in chronic pain management is through an examination of these individual facets. Baer et al., (2008) explored whether facets of mindfulness mediated the relationship between meditation experience (defined by the number of months of regular practice) and well-being among a sample of experienced meditators (regular ongoing meditation practice) and non-meditating comparison groups (demographically similar, community and student samples). They reported that meditation experience was significantly, and positively, correlated with four mindfulness facets (observing, describing, non-judging and non-reactivity) when controlling for age and education. When they explored the relationship between mindfulness and psychological symptoms and well-being, they identified describing, acting with awareness, nonjudging and non-reactivity facets as significantly correlated with lower self-reported psychological symptoms and increased psychological well-being. These facets were also shown to completely mediate the relationship between meditation experience and well-being (Baer et al., 2008). Similarly, Cash and Whittingham (2010) reported incremental validity of facets of mindfulness in predicting depression, anxiety and stress among a community sample of experienced meditators and non-meditators. Nonjudging predicted lower levels of depression, anxiety and stress, and acting with awareness predicted lower levels of depression. These results led the authors to propose that adopting a nonjudgmental mindset and acting with awareness may be integral in improving psychological symptoms (Cash & Whittingham, 2010).

The relationship between depression, mindfulness and pain-related outcomes was recently evaluated among a sample of 190 adults with chronic pain in order to better understand the mechanism of change underlying mindfulness as an effective therapeutic treatment (Cash & Whittingham, 2010). All five mindfulness facets were significantly negatively correlated with

depression and all but the observing facet were significantly correlated with pain severity and pain interference. Nigol & Di Benedetto (2020) explored the relationship between mindfulness facets, depression and pain (severity and interference) among a sample of 158 Australian women and 32 men. Path models found that mindfulness facets observing and describing had a direct effect on pain interference and the observing facet had a direct effect on pain severity. Indirect effects were reported such that depression mediated direct effects of describing, non-judging and non-reacting facets on pain interference and pain severity (Nigol & Di Benedetto, 2020). This suggests that the describing, non-reactivity and non-judging facets may account for the mechanism of change in mindfulness interventions through their beneficial effects on decreasing depressive symptoms among individuals with chronic pain. These studies highlight the role of the effects of individual mindfulness facets in mediating the relationship between mindfulness practice and pain.

## 3.2 Objectives of the Present Study

The purpose of the present study was to explore whether change in mindfulness and its facets that occurred following completion of an MBSR intervention mediate concomitant change in pain and pain-related interference. Secondary analysis was performed on data from a waitlist-controlled trial evaluating the impact of an MBSR intervention among breast cancer survivors who developed CNP. Results presented in Chapter 2 showed that women who participated in an MBSR intervention program experienced significant reductions in self-reported pain severity relative to controls; however, only those who attended a minimum of 8 sessions of MBSR intervention (per-protocol analysis) reported significant improvement in pain-related interference post-MBSR relative to controls.

## 3.3 Methods

This study utilized secondary analysis of data obtained from a double-blind (care providers and outcome assessors) randomized, waitlist-controlled trial evaluating the effect of an 8-week online MBSR program on pain, function, and biological markers of stress, inflammation, and cellular aging among breast cancer survivors with CNP. Refer to Chapter 2 for a detailed description of trial methodology. Briefly, participants underwent guideline-based medical optimization prior to random assignment to MBSR or waitlist control. Outcome data (self-report measures and biomarker samples) were collected at 4 timepoints: (T1) pre-medical optimization; (T2) after medical optimization (pre-MBSR); (T3) 2-weeks post-MBSR; and (T4) 3 months post-MBSR. Waitlist control participants were offered MBSR after 3-month follow-up (delayed MBSR group) and outcome data for this group were collected at 3 additional timepoints: (T5) prior to initiating MBSR; (T6) 2-weeks following completion of MBSR; and (T7) 3-months following completion of MBSR. MBSR treatment was based on Jon Kabat-Zinn's original program (Kabat-Zinn et al., 1985), was offered in group of approximately 8-12, and consisted of eight weekly 2-hour sessions with one 6-hour retreat.

## 3.4 Data Analysis

Statistical analyses were performed using SPSS version 26 (IBM Corporation, USA). Data were analyzed for the intention-to-treat sample and for those that completed 8 or more MBSR sessions (i.e., the per-protocol sample).

Mediation analyses were conducted with the Mediation and Moderation for Repeated Measures (MEMORE) (Montoya & Hayes, 2017) using Monte Carlo simulation with 5,000 resamples. Sobel test was used to evaluate the significance of a mediation effect. Change in total mindfulness and individual mindfulness facets (observing, acting with awareness, describing, nonjudging and nonreactivity) were used as mediators. Change in pain-related severity (BPI severity scores) and pain-related interference (BPI interference scores) were entered as outcomes of interest. Results for indirect and direct effects for each outcome were reported with 95% confidence intervals. The intention of this study was to explore, a posteriori, the potential role of mindfulness, and its facets, in changes in MBSR associated changes in pain severity and interference. As these analyses were exploratory in nature, as such adjustment for inflation of error were not performed.

## 3.5 Results

A total of 78 women participated in the MBSR program (49 randomly assigned, 29 delayed MBSR group) and were used in these analyses. No differences were observed between groups (see chapter 2 for group comparison analyses). Among those who participated in MBSR treatment, 33 women attended 8+ MBSR sessions.

### *3.5.1 Total Mindfulness as a Potential Mediator of Change in Pain Severity and Pain Interference*

Mediation analyses revealed that changes in pain severity were not mediated by change in total mindfulness score among women who participated in the MBSR intervention (Table ).

Mediation analyses did reveal a significant indirect effect of change in total mindfulness score on change in pain-related interference, *b*= .161, 95% CI [.023 to .346]; Sobel test: z= .196, *p*= .050, indicating partial mediation (Table ).

Mediation analyses performed for women who participated in 8+ MBSR intervention sessions (per-protocol analyses) showed that change in pain severity and changes in pain-related interference were not mediated by change in total mindfulness score (Table 3).

### *3.5.2 Facets of Mindfulness as a potential mediator of change in pain severity and pain interference*

Change in individual facet scores (awareness, non-judging, non-reactivity, describing and observing) were analyzed separately to determine the potential mediating role of each individual facet on self-reported changes in pain severity and pain-related interference. Mediation analyses did not indicate mediating effects for any individual mindfulness facet on changes in pain severity or pain-related interference for intention-to-treat (Table ) or per-protocol analyses (Table 3).

## 3.6 Discussion

There is increasing evidence that mindfulness practice can significantly improve an individual's experience of pain and quality of life. Having previously identified a positive relationship between MBSR intervention and improvements in self-reported pain severity and pain-related interference among breast cancer survivors who developed CNP, we sought to better understand and characterize the role of mindfulness in this change process by looking at potential mediators of change. We chose to perform mediation analyses in order to evaluate how change in

self-reported pain occurs in response to MBSR intervention. As previously discussed, there is a growing body of literature to support a role of mindfulness-based interventions in the treatment of CNP; however, until we gain a better understanding of the mechanisms of change through which change occurs, we remain in the dark on how best to implement and optimize therapeutic/clinical change.

Data from seventy-eight women who were enrolled and allocated to an MBSR intervention group after having their medication optimized to coincide with clinical practice guidelines for the pharmacological management of CNP were used in this study. A subgroup of women who attended 8+ MBSR sessions were also used to determine whether session attendance informed pain-related outcomes in response to MBSR intervention. Mediation analyses were performed to determine the potential mediating effect of mindfulness and its individual facets (observing, describing, acting with awareness, non-judging and non-reactivity) on previously identified improvements in pain severity and pain interference.

Exploratory analyses did not reveal significant mediating effects for changes in individual mindfulness facet scores on previously identified self-reported changes in pain severity or pain-related interference. Change in total mindfulness scores also did not mediate changes in pain severity, however, changes in pain-related interference were shown to be partially mediated by change in total mindfulness scores. This suggests that self-reported improvements in pain-related interference among breast-cancer survivors with CNP after participating in a MBSR intervention program is partially mediated by changes in their FFMQ total mindfulness scores. These results indicate that change in total mindfulness would seem to play some role in ameliorating pain-related interference but fails to account for self-reported changes in pain severity.

There is evidence to suggest that pain interference may better reflect the overall goal of mindfulness-based interventions, i,e. to improve the psychological experience of living with pain (Veehof, Trompetter, Bohlmeijer, & Schreurs, 2016). A recent study by Nigol and Di Benedetto (2020) reported a greater effect of mindfulness and depression on pain interference than for pain severity among a sample of 190 Australian adults who experienced chronic pain for greater than a six-month period. They also reported that mindfulness facets correlated more strongly with depression than with pain measures, which suggests that reductions in self-reported pain could be attributed to reductions in negative mood symptoms (e.g., depression).

It is also important to consider that the FFMQ may not be an optimally sensitive marker of mindfulness among our population, where changes in pain severity and pain-related interference that occur during an 8-week MBSR intervention are influenced by additional factors. These may include the contribution of changes over time, patient history, placebo effects, patient expectation, and maturation. Interpretation of what accounts for or explains the relation between MBSR intervention and reduction in pain-related interference requires an in-depth exploration of multiple criterion that likely converge to achieve change. These factors are difficult to account for, particularly when working with a population that is compounded by chronic illness and differing medication protocols, a reflection of real-world clinical practice, and may contribute to the lack of effects found in this study. In addition, mindfulness interventions are readily accessible, and participant's prior experience with mindfulness was not collected in our sample. In turn, previous meditation experience can influence an individual's understanding of the mindfulness facets and therefore increase variability in interpretation when self-reporting using the FFMQ (Van Dam, Earleywine, & Danoff-Burg, 2009).

Our previous findings suggest that mindfulness has some meaningful role in the pain experience among breast cancer survivors with CNP. The fundamental drivers of this relationship and mechanism through which changes occur remain unclear. Previous literature has identified individual facets of mindfulness and groupings of facets as having an integral role in improving well-being, psychological symptoms (depression, anxiety, and stress) and pain severity and interference (Baer et al., 2008). Yet, there is an ongoing debate among researchers as to which of these facets are key contributors to the change process (Van Dam et al., 2018). The lack of a normative definition and agreement in how mindfulness is best measured may explain discrepancies in the role that facets of mindfulness play on outcomes following the implementation of mindfulness-based interventions. Bednar, Voracek & Tran (2020) highlight the ambiguity of mindfulness as a construct and sought to address this by exploring common factors underlying the mindfulness facets assessed by the FFMQ. Data was collected from a general population sample of 3265 individuals who provided information relevant to meditation experience, mindfulness (FFMQ), attention regulation, body awareness, emotional regulation, decentering, nonattachment, anxiety, depression, somatization and perceived stress. These mechanisms have been previously proposed to explain the beneficial effects of mindfulness-based interventions (Brown, Ryan, & Creswell, 2007; Gu, Strauss, Bond, & Cavanagh, 2015; Hölzel et al., 2011; Shapiro, Carlson, Astin, & Freedman, 2006), however, as discussed by Bednar et al., (2020), no prior studies have explored whether mindfulness constructs are distinct from self-report measures of mindfulness, such as the FFMQ. Multigroup exploratory structural equation modeling identified five common factors underlying mindfulness facets that centered on attention/focusing, body sensations, feelings, emotions and dealing with distress (Bednar, Voracek, & Tran, 2020). They proposed that the aforementioned five underlying factors may

better account for mindfulness-related changes, and that the FFMQ may not adequately capture these elements.

## 3.7 Limitations

The limitations of the current study need to be considered. Limitation regarding the population sampled are presented elsewhere (*refer to Chapter* 2). This study was exploratory in nature and does not account for inflations in error due to performing multiple statistical tests. Relatedly, interpretations of mediation studies require replication and, thus, the partial mediation of total mindfulness on pain-related interference identified here should be further explored. This study sought to probe specific aspects of mindfulness that may play a contributing role in mediating changes in an individual's self-reported pain experience to inform future studies directed towards better characterizing the relationship between mindfulness and improvements in self-reported pain. What was not captured in this study is an established timeline between mindfulness and self-reported changes in pain. Pre- to post-changes in mindfulness may not capture the dynamic nature of change or indicate that change in mindfulness preceded identified changes in pain. The analyses presented here do not capture the potential mediating role of grouped facets, nor do they capture all aspects of mindfulness as a construct. Rather, the results of this study serve to inform what remains elusive - the mechanism of change through which mindfulness exerts its beneficial effects. Future studies directed towards this endeavor are central in understanding how an individual's pain experience is mitigated through mindfulness interventions. Replication of mediation studies that identify and explore mediators of mindfulness and pain-related outcomes across settings, conditions, medication regiments (e.g., dosing) and include additional methods of measurement should be further explored in order to

allow for examination of consistencies across studies. In line with the Bednar et al. (2020) approach, specificity of how mindfulness is assessed, in particular through exploring common factors, may help to identify more specific constructs attributable to therapeutic change. Lastly, participation in mindfulness-based interventions varies greatly both across studies, but also within individual treatment groups based on number of sessions, duration and participant engagement. Future studies may benefit from exploring a 'dose-dependent' gradient of mindfulness intervention to determine whether there is a relation between degree of mindfulness intervention and associated changes in pain-related outcomes.

## 3.8 Conclusions

Mindfulness-based interventions have shown significant promise for improving quality of life among individuals who suffer from medical illness, such as chronic pain. Despite supporting evidence from theory and research for a role of mindfulness in the change process, the nature of this role remains unclear. Mindfulness is a broadly defined construct comprised of five individual facets that encompass theoretical constructs that can be challenging to capture in populations reflecting real-world clinical practice. We have shown that participation in MBSR yields significant reductions in self-reported pain severity and pain-related interference. Individual facets of mindfulness, or FFMQ total mindfulness scores, do not appear to explain the effect of an MBSR intervention on change in self-reported pain. The preliminary observation that change in total mindfulness partially mediated change in pain-related interference is an initial step in providing an evidence-based explanation for how MBSR intervention produces change. The complexities of studying clinical populations with complex and comorbid illness and disease suggests that the mechanism through which effective interventions improve clinical outcomes is

likely equally complex. It is these complexities that are critical to our understanding of how to effectively treat these populations, and future studies directed towards building this understanding are required for the identification of clinical populations who may best benefit from particular interventions and subsequently in developing individualized and empirically supported treatment plans.

**Total Effects**

| | *b* | SE | df | *t* | *p* | 95% [CI] Lower | 95% [CI] Upper |
|---|---|---|---|---|---|---|---|
| MBSR → ΔBPI Severity | .519 | .168 | 77 | 3.518 | <.001*** | .257 | .927 |
| MBSR → ΔBPI Interference | .565 | .180 | 77 | 3.132 | <.01** | .206 | .924 |

**Indirect Effects**

| Mediator | *BPI Severity* | | | | | | *BPI Interference* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% [CI] | | | | | | 95% [CI] | |
| | *b* | SE | *z* | *p* | Lower | Upper | *b* | SE | *z* | *p* | Lower | Upper |
| Observing | .007 | .056 | .130 | .896 | -.112 | .136 | .098 | .068 | 1.434 | .151 | -.021 | .254 |
| Describing | .097 | .064 | 1.610 | .107 | .001 | .246 | .117 | .068 | 1.714 | .087 | .006 | .279 |
| Awareness | .065 | .055 | 1.182 | .237 | -.031 | .198 | .069 | .059 | 1.178 | .239 | -.031 | .207 |
| Non-judgment | -.130 | .117 | -1.120 | .263 | -.378 | .093 | -.163 | .126 | -1.290 | .197 | -.419 | .074 |
| Non-reactivity | .054 | .088 | .614 | .539 | -.124 | .244 | .096 | .095 | 1.016 | .310 | -.088 | .302 |
| Total Mindfulness | .053 | .065 | .813 | .416 | -.069 | .202 | .1601 | .082 | 1.958 | .050* | .0226 | .346 |

* $p \leq .05$
** $p < .01$
*** $p < .001$

*Table 2. Intention to treat mediation analyses: FFMQ individual facets scores and FFMQ total mindfulness scores (mediators) on changes in pain severity and pain-related interference (outcome measures) among breast-cancer survivors with CNP (intention-to-treat, n= 78).*

**Total Effects**

| | *b* | SE | df | *t* | *p* | 95% [CI] Lower | 95% [CI] Upper |
|---|---|---|---|---|---|---|---|
| MBSR → ΔBPI Severity | .926 | .309 | 32 | 2.996 | .0053** | .296 | 1.556 |
| MBSR → ΔBPI Interference | 1.209 | .331 | 32 | 3.655 | <.001*** | .535 | 1.882 |

**Indirect Effects**

| Mediator | *BPI Severity* | | | | | | *BPI Interference* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 95% [CI] | | | | | | 95% [CI] | |
| | *b* | SE | *z* | *p* | Lower | Upper | *b* | SE | *z* | *p* | Lower | Upper |
| Observing | .226 | .231 | .976 | .323 | -.212 | .726 | .440 | .255 | 1.725 | .085 | -.012 | 1.05 |
| Describing | .178 | .138 | 1.285 | .199 | -.042 | .552 | .207 | .151 | 1.370 | .171 | -.034 | .594 |
| Awareness | .093 | .103 | .902 | .367 | -.084 | .378 | 1.37 | .135 | 1.015 | .310 | -.092 | .485 |
| Non-judgment | -.142 | .204 | -.698 | .485 | -.593 | .249 | -.169 | .220 | -.768 | .442 | -.664 | .250 |
| Non-reactivity | .075 | .228 | .327 | .744 | -.407 | .584 | .060 | .241 | .250 | .803 | -.436 | .573 |
| Total Mindfulness | .056 | .181 | .309 | .757 | -.312 | .446 | .278 | .205 | 1.356 | .175 | -.083 | .748 |

* $p \leq .05$
** $p < .01$
*** $p < .001$

*Table 3. Per protocol mediation analyses: FFMQ individual facets scores and FFMQ total mindfulness scores (mediators) on changes in pain severity and pain-related interference (outcome measures) among breast-cancer survivors with CNP (per-protocol, n= 33).*

# Chapter 4 Discussion

MBSR is based on mindfulness practice with core tenets centred on faculties of purposeful attention, awareness and nonjudgment (Van Dam et al., 2018). Originally designed for treatment resistant chronic pain, MBSR aims to cultivate healthy adaptive responses to stress through skill acquisition developed from mindfulness practices/exercises (Kabat-Zinn et al., 1985). Studies designed to evaluate the effectiveness of mindfulness interventions across diverse populations are fundamental in validating mindfulness as an efficacious psychological intervention. However, there is limited understanding of how mindfulness interventions, such as MBSR, effect positive change. Thus, equally important, and perhaps less well understood, is a second fundamental question in understanding the role of mindfulness-based interventions: what works for whom, when, and why?

Mindfulness interventions influence the pain experience through integrative processes involving biological and psychological systems (Guendelman, Medeiros, & Rampes, 2017). The purpose of this study was to explore the relationship between mindfulness and the biological correlates of stress, immune function and cellular aging among breast cancer survivors living with CNP. Specifically, we were interested in examining whether participation in an 8-week MBSR treatment program, adjuvant to pharmacological pain management, was associated with preferential changes in biomarker expression representative of self-reported improvements in pain, physical function and emotional function. Further, we sought to better understand how mindfulness works, by identifying and evaluating potential mediators of change.

We conducted a double-blind (care providers and outcome assessors) randomized waitlist controlled trial. Our study was pragmatic, as it was designed to evaluate the effects of MBSR

treatment among a pre-existing clinical patient population. While this approach garners the benefits of external validity, it is also complicated by varying histories of cancer severity and cancer-related treatment, variability in the pain experience, and exposure to various concurrent treatments for pain management (e.g., pharmacological interventions). These factors can modify the effects of the MBSR intervention, making it more difficult to detect treatment effects of clinical significance.

Overall, we found that the MBSR intervention was associated with increasing mindfulness; however, contrary to our hypotheses, we did not attain the anticipated self-reported reductions in stress that are typically associated with mindfulness-based intervention. Thus, it was not surprising that we did not find any associated changes in biomarker expression consistent with our primary hypothesis. While broader studies have shown preferential improvements in stress in response to mindfulness interventions (*see review* Alsubaie et al., 2017), and the literature supports a role for mindfulness in reducing CNP in breast cancer survivors (*see review* Ngamkham, Holden, & Smith, 2019), this is the first study to investigate the efficacy of MBSR among breast cancer survivors living with CNP after guideline-based medical optimization (best-practice pain management).

Translating empirically supported treatment interventions into clinical practice requires rigorously controlled clinical trials across diverse populations. Critically evaluating the effectiveness of a treatment intervention in our population of interest, breast cancer survivors living with CNP, is complicated by the heterogeneity that inherently accompanies clinically representative populations reflecting real-world clinical practice. The complexity in empirically studying treatment interventions among highly heterogeneous populations highlights both the need for well-designed RCTs but also the challenges in identifying meaningful change that can

be obscured by patient heterogeneity. Moreover, heterogeneity among clinical populations can lead to negative findings despite encouraging results identified in earlier studies. RCTs report statistical analyses that represent an estimate of effect averaged across groups. This operates under the assumption that every individual in that group will have the same average response to treatment (Van Der Leeuw, Ridker, Van Der Graaf, & Visseren, 2014). However, we know from analgesic studies that this is not the case (Edwards et al., 2016). The complexity of our population is embedded in interpatient variability and thus, null findings may underrepresent important clinical effects at an individual level.

## 4.1. Influence of Guideline-Based Medical Optimization

The goal of pain management is to reduce the severity and intensity of the pain experience, minimize pain-related interference, enhance functional abilities/restoration of function, improve physical and psychological well-being while minimizing adverse/secondary outcomes, and enhance quality of life (American Society of Anesthesiologists Task Force on Chronic Pain Management, 2010). Consistent with the goals of pain management, pharmacological interventions are critical in this process. Identifying and tailoring which course of medication works best for each patient is individualized based on efficacy, side effects and accessibility (Moulin et al., 2007). It is unclear how long medical optimization takes to reach the correct therapeutic window. This means that the side effects and degree of efficacy (degree of pain management achieved) will also vary for each patient.

The effect of optimizing pharmacological interventions undoubtedly yields influential changes in our outcomes of interest, as the intended effects of the MBSR intervention are embedded in the goals of pain management. The trajectory towards achieving the optimal

therapeutic window is unknown, and thus it is possible that initial preferential changes in the pain experience attributable to pharmacological intervention may make MBSR-related changes undetectable. It also bears the question as to whether the MBSR intervention yields reliable additional effects on pain management above and beyond those achieved by medication alone.

The relation between depression and pain has been well characterized and it has been recognized that cancer patients with chronic pain have been shown to experience greater levels of depression compared to those without pain (Bamonti, Moye, & Naik, 2018). A review by Alsubaie et al. (2017) exploring the mechanisms of action in mindfulness interventions among populations with physical and/or psychological conditions identified six RCT's that report significant decreases in depressive symptoms in response to mindfulness-based cognitive therapy (MBCT), where reductions in symptomology were mediated by significant increase in mindfulness (*see review* Alsubaie et al., 2017). We found a significant decrease in self-reported depression symptomology across time when averaged across control and per-protocol treatment group. It is possible that greater participation in the MBSR intervention may influence depression symptomology to some extent; however, the degree of this influence may be unable to be characterized in our medically optimized sample.

Another important factor in studying the efficacy of any intervention, whether pharmacological or psychological, is the timing of that intervention. It is possible that the effects of MBSR intervention are better captured at a later point in time, once the therapeutic window has been fully established, and initial gains in pharmacological pain management have been achieved.

Alternatively, non-pharmacological interventions introduced earlier in survivorship trajectories should also be considered. Survivorship trajectories have become the focus of recent

studies, with the goal of establishing a better understanding of individual needs post-diagnosis and treatment. A recent longitudinal qualitative study by Ratcliff et al. (2018) examining cancer survivorship trajectories highlights the multifaceted impact of cancer diagnosis and treatment among cancer survivors. According to this study, psychosocial factors of cancer-related worry, depression and post-traumatic growth varied considerably among a sample of 170 veterans previously diagnosed with colorectal, head and neck, esophageal or stomach cancer, based on four identified survivorship trajectories (Moving On, Seeing the World Differently Now, Taking One Day at a Time, and Never the Same; Ratcliff et al., 2018). It is suggested that patients who fall along each of these paths have different psychosocial needs, which can be used to inform and tailor treatment planning to meet the unique needs of cancer survivors. This may suggest that, for example, patients falling on the Never the Same path may benefit from mindfulness-based interventions earlier in survivorship, as these individuals have been associated with relative high distress, and who perceive little positive change.

More recently, Voute and colleagues (2020) proposed a predictive psychosocial vulnerability marker for the development of chronic pain one year following breast cancer diagnosis that suggests breast cancer patients may follow different pain trajectories which can be characterized by their psychosocial vulnerability at the time of diagnosis. This psychosocial vulnerability marker was derived from cognitive, emotional and quality of life parameters that, if used at the time of diagnosis, may help to orient pain-related treatment planning in survivorship (Voute et al., 2020). Thus, mindfulness-based interventions, such as MBSR, may prove more beneficial if introduced earlier in the cancer-trajectory. This stage of survivorship may also be more amenable to skill acquisition, a requirement for mindfulness practice.

## 4.2. Complexity of Biomarkers and Biological Systems in Cancer

In contrast to our hypothesis, biological markers of stress, immune function and cellular aging did not significantly change in response to MBSR intervention. This stands in contrast to previous studies that have shown preferential changes in biomarkers expression after participation in mindfulness interventions (Sanada et al., 2016)

Biomarkers are used to aid in the screening, diagnosis and monitoring of disease progression (Mayeux, 2004). Biomarkers are becoming increasingly more commonplace in clinical research as they provide the advantage of reducing measurement bias typically associated with patient self-report by providing an objective measure of biological processes (Strimbu & Tavel, 2010). We used biomarkers to represent changes in biological systems in response to MBSR intervention. While this measure is objective, which helps to gain insight into the mechanism of action off MBSR, there is also considerable variability within biomarkers, and the biological systems in which they are expressed.

Although there is support for mindfulness-related changes in biomarker expression among cancer populations, the findings are mixed. For example, Bower and colleagues (2015) found no significant changes in cytokines IL-6 and TNF-RII, or CRP, despite finding significant reductions in perceived stress and marginal reductions in depressive symptomology after a 6-week Mindfulness Awareness Practices (MAP) intervention among women diagnosed with early-stage breast cancer compared to wait-list controls. Notably, they performed exploratory analyses that showed participants who practiced mindfulness more frequently (attending classes and home practice) had lower levels of IL-6 post-intervention (Bower et al., 2015). Carlson and colleagues (2003) report pre- to post-intervention changes in biomarkers of immune function in early-stage breast and prostate cancer patients after participation in an 8-week MBSR program.

They found increased T cell production of pro-inflammatory cytokines IL-4 and decreased IFN-γ, and decreased NK cell production of anti-inflammatory cytokine IL-10, reflecting a shift in immune function from one typically associated with depressive symptoms to a more normal profile (Carlson et al., 2003). One-year post-intervention follow-up supported continued reduction in pro-inflammatory cytokines (Carlson, Speca, Faris, & Patel, 2007). In contrast, Witek-Janusek et al. (2008) found, at 1-month post-MBSR intervention, MBSR participants (early-stage breast cancer) had increased IFN- γ and decreased IL-4 and IL-10 production compared to control (standard care) group. Lengacher and colleagues (2013) report no change in INF- γ, and decreased IL-4 production in individual diagnosed with Stage 0-III breast cancer who participated in a 6-week MBSR program compared to control (standard care) group.

There were several differences between these studies concerning the characteristics of the interventions, including methodological factors such as type of cancer, type of mindfulness intervention, duration and/or frequency of intervention, timing of intervention relative to cancer diagnosis, and/or data collection (time, sample type). These factors can serve to moderate empirical findings which may, or may not, fully capture the true effect of an intervention.

It is known that cancer treatment leads to immune dysregulation, with chemotherapy and radiation differentially affecting immune recovery. It is less clear how cancer-related treatment influences biological systems post-treatment and into survivorship, the implications of which can have significant influence on mechanism of action studies, particularly when we know that these effects are likely unique to each patient. A study by Lengacher et al. (2013) attempted to characterize the trajectory of immune recovery in a sample of breast cancer patients who completed treatment, after MBSR intervention. They found that participation in a 6-week MBSR intervention promoted a more rapid immune recovery, pre- to post-MBSR intervention,

compared to standard care controls. MBSR-related immune effects were characterized by a decrease in T cell activation and Th1/Th2 ratio (representative of cytokine production, IL-4, and IFN- γ). Importantly, time alone was found to have restorative effects of lymphocyte levels, represented by recovery of B cell (produces IL-6) and NK cells (NK cell recovery reflects a reduction in CRP), independent of MBSR intervention.

We did not find changes in immune function in response to MBSR intervention; however, time-related effects were reported, with IL-6 expression decreasing significantly across time when collapsed across groups. There are several biological markers of immune function that are involved in various biological processes and thus the effects of our MBSR program may not be captured by the biological markers proposed and predicted here. We did not measure all biomarkers of stress and immune function, making this a logical inquiry for future study.

Long-term effects of biological processes post-cancer treatment and into survivorship are not well understood. The effects of cancer treatment on telomere length may differ by cancer type and treatment, and the trajectory of telomere length recovery has not been well understood (Gallicchio, Gadalla, Murphy, & Simonds, 2018). A five-year longitudinal prospective biobehavioral study by Anderson et al. (2017) evaluating changes in levels of stress, depression and immune function in patient with stage I-III breast cancer from time of surgery, showed two distinct phases of recovery. The change point varied between cancer stress, depressive symptoms and immunity. Cancer stress was reported that how two distinct phases, with a rapid decline occurring within the first 12 months post-surgery, and which continued to decline at a less rapid rate through the next 4 years. Depressive symptomology followed a similar trajectory, with an initial steep decline within the first 7 months, with gradual improvements thereafter. With regards to immune function, Natural killer cell cytotoxicity (NKCC) increased steadily through

the first 18 months, with upper limit stability thereafter, and T-cell blastogenesis showed no reliable trajectory. Significant variability in T-cell blastogenesis was identified, making it difficult to detect a trajectory of change (Andersen, Goyal, Westbrook, Bishop, & Carson, 2017).

While further study is required to better understand the nature of these trajectories, these studies hold important considerations when interpreting biobehavioural findings in cancer survivor populations. It is possible that our findings are influenced by time-related changes in biomarker expression that occur naturally post-cancer treatment. In our study population, both the average time post-diagnosis and post-treatment was less than five-years. Relatedly, our participants endorsed, on average, approximately 3 years living with CNP. Thus, it is suggested that treatment timing, and elapsed time since cancer completion of treatment, be considered when exploring the effects of a stress-reducing interventions on biological markers in cancer survivors.

## 4.3. Mediators and Mechanisms of Change

We found significant improvements in pain severity among breast cancer survivors who participated in an MBSR intervention compared to waitlist controls, with significant improvement in pain-related interference among those whose participation in the MBSR intervention was optimal (evidenced by attendance of 8+ MBSR sessions). Improvements in pain severity and interference are consistent with reports from previous RCTs that similarly report preferential improvements in self-reported pain experience after a mindfulness intervention (Gardner-Nix et al., 2008; Kabat-Zinn et al., 1985; Kaplan et al., 1993; Veehof et al., 2011). MBSR-related improvements in CNP adds to the growing body of literature suggesting MBSR as effective in improving CNP in breast cancer survivors.

In addition to understanding the clinical utility and efficacy of MBSR in the treatment of CNP, there is also a need to understand the mechanism of actions through which MBSR interventions bring about change. We identified the facets of mindfulness as a proposed mediator of change after demonstrating preferential improvements pain severity and pain-related interference after MBSR intervention. Subsequent analysis did not identify individual facets of mindfulness that mediated these self-reported changes in pain severity or pain-related interference, suggesting that there are other mediators involved in this change process that are not captured within the individual facets of mindfulness as we have defined them here.

Investigating mechanisms of action of underlying mindfulness interventions is important in understanding how change comes about. Mediators and mechanisms of change in psychotherapy has recently emerged as a topic of interest across mindfulness literature, as understanding the processes that effect clinical outcomes can be used to optimize therapeutic change. A conceptual framework has been established by Kazdin (2007) that proposes a set of recommendations for demonstrating mediators and mechanisms of change in scientific study. The first criteria stipulates the need for a clear association between change in the proposed mediator and the proposed outcome of interest (e.g., therapeutic change). Additionally, manipulation studies should be utilized to demonstrate specificity of the association between the intervention, proposed mediator and outcome of interest (specificity criterion), and this relation should be replicated across studies (consistency criterion). Outcomes of interest and proposed mediating variable(s) need to be measured across multiple timepoints (timeline criterion). Further, demonstrating a gradient (dose-response) relationship can support plausibility for causality (Kazdin, 2007). Alsubaie et al. (2017) conducted a recent systematic review to explore the evidence on the mechanisms of action in MBCT and MBSR in individuals with physical

and/or psychological conditions using a conceptual framework derived from Kazdin's (2007) recommendations. They report few studies to have met the suggested criteria outlined by Kazdin for establishing mediators and mechanisms in psychological treatment (Alsubaie et al., 2017). While global changes in mindfulness were associated with better outcomes, lack of methodological rigor precluded definitive conclusions from being able to be made based on reported findings.

Notably, there is an overarching challenge specific to mindfulness interventions that impacts studies of this nature, being that there is no universally agreed upon definition of mindfulness. Without an operational definition, specificity and consistency across studies is impaired. It is therefore important to interpret clinical findings within the context in which mindfulness was designed and measured within a particular study. Here, we defined mindfulness according to the Five Factor Mindfulness Questionnaire, proposing that total mindfulness is derived from five individual facets (observing, describing, awareness, non-judgment and non-reactivity). Further examination of the 18 studies reviewed by Alsubaie et al. (2017) highlights the discrepancy across mindfulness research as mindfulness was assessed using one of four different self-report mindfulness questionnaires, and measures of emotional function and factors associated with mindfulness also varied considerably across studies. Bednar et al. (2020) investigated the common factors underlying mindfulness facets assessed by the FFMQ in a sample of meditators and non-meditators. They identified five common factors to underlie the mechanisms and facets of mindfulness, which included emotion regulation strategies, attentional control, distanced perspective (separation from thoughts, feelings and emotions), body awareness and body association (Bednar et al., 2020). These findings suggest that some of the proposed mechanisms of mindfulness are among the defining features of the mindfulness construct.

Moreover, the lack of a universally agreed upon operational framework for defining mindfulness means that we do not yet have consensus on how to observe and measure mindfulness across studies. Differentiating mediators of change is challenged when the basis from which change is attributed is not clearly defined. Thus, the extent to which empirical findings can be deemed as supportive or contradictive of a proposed theory depend largely on the definition of mindfulness used in the study.

## 4.4. Survivorship Needs and Clinical Implications

The overarching goal of studying mindfulness interventions in the treatment of CNP in cancer survivors is to improve the pain experience. While seemingly relatively straightforward in theory, mindfulness is not a panacea. Individual differences and individual pain experiences challenges the ability to identify a treatment that works for everyone. Thus, in an effort to tailor treatment interventions to the unique needs of cancer survivors, the role of patient preference is essential.

Participation in mindfulness intervention, however, requires the individual to acquire a new skill through repetition and practice and, as such, relies on the patient's willingness to engage in such practices. Studies exploring treatment planning in survivorship highlight the critical role for patient preference when developing and implementing long-term care plans (Marbach & Griffie, 2011; Smith, Singh-Carlson, Downie, Payeur, & Wai, 2011). Smith et al. (2011) facilitated focus-groups with 120 women previously diagnosed with non-metastatic invasive breast cancer who were 3-12 months post-treatment completion in order to explore their preferences when developing a post-cancer treatment plan. A total of 8 core components were identified. These preferences centered around a desire for a customized treatment plan to meet

the unique needs of each patient. Included in the identified core elements was information regarding lifestyle choices that can help reduce the risk of cancer recurrence and promote health, with a preference for recommendations/resources with specialized training in breast cancer care; information about expected side effects and recovery; knowledge of support groups and counselling services; and updated research findings related to recommendations for care (Smith et al., 2011). They also report that participants stated that the optimal time to introduce the concept of survivorship was around the end of the last phase of cancer treatment. Similar findings were reported by Marbach et al. (2001) after conducting a focus group with 40 cancer survivors after completion of initial cancer treatment, where information regarding late-effects of cancer treatment and a desire for additional supportive services such as meditation and yoga were identified as preferences to include when developing survivorship care plans. Relatedly, research has shown that both patient expectations for treatment success are predictors in treatment response (Witt, Schützler, Lüdtke, Wegscheider, & Willich, 2011).

Taken together, these studies demonstrate a role for mindfulness interventions in survivorship treatment planning. It also suggests that introducing mindfulness interventions closer to the late-phase of cancer treatment may help to improve buy-in for mindfulness intervention. In addition, early introduction to mindfulness practices can help with skill building that can later be utilized and tailored towards CNP if needed.

Patient phenotyping has become a recent focus for the treatment of persistent and treatment resistant pain as an avenue to help overcome the therapeutic challenges of treating chronic pain conditions. IMMPACT recommendations have recently been proposed for patient phenotyping in clinical trials for chronic pain (Edwards et al., 2016). Patient phenotyping involves identifying the characteristics of individual patients that increase or decrease their

response to a specific treatment or intervention. In our study, patient phenotyping could lead to the identification of individual who may be more likely to benefit from mindfulness intervention, which can be used to develop an individualized treatment plan. IMMPAC identified phenotypic domains include psychosocial factors, pain variability and quality, neuropathic pain symptom reporting, sleep and fatigue,

The characteristics of the individual patients that increase or decrease the response to a specific treatment need to be identified. The identified measurable phenotypic characteristics associated with treatment response can be used to predict individual response to treatment outcomes. This has the potential to tailor treatment interventions to the needs of the individual as opposed to the overall needs of a population.

## 4.5. Strengths

This study had a number of methodological strengths. Our population of interest is a clinically representative sample reflecting real-world clinical practice. Recruitment strategies were diverse, which included both physician referred and self-referred participants. As such, the results of the present studies may be more generalizable, which suggests that our sample population is representative of breast cancer survivors living with CNP within the larger community.

This is the first study to explore the adjuvant effects of MBSR after guideline-based medical optimization in a population of breast cancer survivors living with CNP. Pharmacological management was conducted using two recent evidenced-based consensus statements. Each participant met with a physician with expertise in chronic pain management to

ensure optimal pharmacological pain management. Medical optimization is consistent with guideline-based recommendations for the treatment and management of chronic pain. Additionally, MBSR intervention was conducted by senior clinical psychologist with specialized training.

This study followed IMMPACT recommended guidelines for conducting chronic pain clinical trials (Dworkin et al., 2009, 2008), which included the use of outcome measures for pain, physical functioning, emotional functioning and measures of overall satisfaction with treatment. In line with this, psychometrically sound self-report measures included BPI-SF pain severity and pain-related interference (Cleeland, 1989), Profile of Mood States (Heuchert & McNair, 2012), Patient Global Impression of Change (Ferguson & Scheman, 2009), and adverse events were recorded.

Additionally, methodological strengths include both the use of intention-to-treat and per-protocol analyses. Intention-to-treat principles included data from all randomized participants included in outcome analyses, and single imputation procedures were employed to provide an estimate for missing data. Further, biological samples and self-report measures were collected across multiple timepoints. We also know the level of participation in MBSR intervention for each participant, which allowed for per-protocol analyses (optimal treatment adherence) to assess a dose-response relationship of MBSR attendance and participation on our outcomes of interest, consistent with Kazdin's (2007) recommended guidelines for mediators and mechanisms of change.

Another notable strength of this study was the use of biomarkers. Biomarkers provide an objective marker for psychological outcomes of interest. Biological correlates of MBSR and

treatment outcomes provides a direct measure of psychological outcomes that typically rely on self-report and thus reduce the risk for bias.

## 4.6. Limitations

The findings presented here must be considered within the context of the study limitations. First, there is significant heterogeneity within our study population, which is further impacted by a small sample size. Further, although participants were all medically optimized prior to randomization, and a stable medication regiment was recommended, adjustments to medications were made where appropriate. Additionally, while recruitment strategies targeted community and physician-referrals, all participants were recruited within the same general area.

We did not obtain a measure of previous knowledge of, or prior experience with, mindfulness or meditative practices, nor were we able to ascertain whether participants engaged in mindfulness practices outside the parameters of the study. Future studies should be include data regarding mindfulness practice outside of the parameters of the program intervention to further inform a dose-response relationship and to reinforce the importance of continued practice.

Relatedly, a common criticism of mindfulness interventions is the lack of an agreed upon operational definition of mindfulness (Van Dam, van Vugt, Vago, Schmalzl, Saron, Olendzki, Meissner, Lazar, Kerr, Gorchov, R Fox, et al., 2018). We defined mindfulness within the conceptual framework adopted by the FFMQ, which defines mindfulness based on five individual facets. Several studies have attempted to characterize the common factors assessed by the FFMQ and other commonly used self-report questionnaires to assess trait mindfulness.

Biomarkers studies are not exhaustive of biological processes involved in our outcomes of interest. Thus, our findings should be interpreted within the context of the specific biomarkers used here, which may not reflect an accurate depiction of the involvement of these biological processes based on one of several markers involved in each biological system. Relatedly, while we did obtain samples across multiple timepoints, these timepoints also may not depict the full involvement of MBSR intervention on biological systems. Findings should be interpreted with this in mind. Further, cancer and cancer-treatment are known to cause immune dysregulation. We do not have a marker for immune function prior to study participation which makes it difficult to determine whether observed changes are related to MBSR intervention or natural trajectory over time. This also means that the timeframe for baseline expression of biological markers unoccluded by medication is small. This is further impacted by residual effects of cancer treatment, which studies have shown extend to at minimum five years post-cancer treatment (Andersen, Goyal, et al., 2017).

## 4.7. Directions for Future Research

Despite a growing interest in exploring mindfulness-based interventions in chronic illness and disease, our understanding the mechanism through which these interventions exert their effects is still in its infancy. Biomarker studies have been instrumental in helping gain insight into potential mediatory and mechanisms of action, however, these studies are limited by inter-individual differences that challenge even the most rigorously designed clinical trials. This is further complicated by the substantial heterogeneity inherent in complex clinical populations.

Precision medicine and patient phenotyping provide an opportunity to study the effect of an intervention on outcomes of interest in a given individual rather than a across a group of

individuals who have unique individual needs. We have discussed the individuality of survivorship needs within breast cancer populations, which further demonstrates the importance of directing future research towards better understanding the unique needs of cancer survivors. Guidelines for patient phenotyping in clinical trials of chronic pain treatments have been proposed (Edwards et al., 2016) and should be considered in the development of future clinical trials seeking to explore mindfulness interventions in chronic pain in cancer populations. Doing this can allow for a more targeted approaches to treatment by directing specific treatment interventions towards those who have been identified as having the most favorable outcomes.

Future research should also be directed towards the development of a universally agreed upon operational definition of mindfulness. This will help facilitate translating empirical findings across studies and provide a foundational framework and language from communicating clinical findings. Until such a definition is developed, caution should be taken when interpreting data derived from mindfulness-based intervention, and future studies should proceed with caution when interpreting and translating empirical findings, as this needs to be done within the conceptual framework and operating definition of mindfulness used.

Additionally, Kazdin's (2007) recommended guidelines for mediation and mechanisms studies should be followed when designing and implement RCTs for chronic pain. Tracking participant engagement in MBSR intervention both within the study design (e.g., number of sessions attended) and at home should be considered, and prior understanding, knowledge and practice of mindfulness should also be documented, which can be used to inform patient phenotyping and dose-response relationships.

## 4.8. Conclusions

This study provides important data relating to biological markers of an MBSR intervention in a clinically representative sample of cancer survivors with CNP. Although the results of these studies failed to show the anticipated stress reducing effects of mindfulness interventions and was subsequently unsuccessful in identifying biological markers of change, we did show support for MBSR in reducing pain severity and pain-related interference.

Given that pain is a subjective experience, and a therapeutic challenge, there is a need to study and characterize more objective measures of pain in order to truly understand the mechanism by which these interventions exert their effects in this change process. Only then will we be able to better understand the true efficacy of mindfulness interventions across populations, and perhaps more importantly, who may benefit from these interventions.

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# Appendix A: Per-protocol results: Manipulation check evaluating change in mindfulness and stress over time (T2 and T3)

*Per-protocol (8+ MBSR sessions attended) results: Manipulation Check*

| | *df* | *F* | *p* | $\eta^2$ |
|---|---|---|---|---|
| FFMQ total | | | | |
| Group | 1 | .260 | 611 | .003 |
| Time | 1 | 14.903 | .000** | .160 |
| Time x Covariate | 1 | 13.638 | .000** | .149 |
| Group x Time | 1 | 9.467 | .003* | .108 |
| Error | 78 | | | |
| PSS | | | | |
| Group | 1 | .001 | .970 | .000 |
| Time | 1 | 21.972 | .000** | .220 |
| Time x Covariate | 1 | 3.960 | .050* | .048 |
| Group x Time | 1 | . 794 | .376 | .010 |
| Error | 78 | | | |

*Covariate – Medical optimization*
*$p < .05$.
**$p < .001$

# Appendix B: Per-protocol results: ANCOVA evaluating change in biological markers over time (T2 and T3)

*Per-protocol (8+ MBSR sessions attended) results: Biomarkers*

| | *df* | *F* | *p* | $\eta^2$ |
|---|---|---|---|---|
| CRP | | | | |
| Group | 1 | 1.384 | .244 | .020 |
| Time | 1 | .889 | .349 | .013 |
| Time x Covariate | 1 | 4.368 | .040* | .060 |
| Group x Time | 1 | .084 | .773 | .001 |
| Error | 78 | | | |
| IL-6 | | | | |
| Group | 1 | .227 | .635 | .003 |
| Time | 1 | 4.115 | .046* | .050 |
| Time x Covariate | 1 | 6.936 | .010* | .082 |
| Group x Time | 1 | .394 | .532 | .005 |
| Error | 78 | | | |
| Cortisol | | | | |
| Group | 1 | .283 | .596 | .968 |
| Time | 1 | 12.870 | .001** | .139 |
| Group x Time | 1 | .149 | .701 | .002 |
| Error | 78 | | | |

| | *t* | *df* | *p* |
|---|---|---|---|
| Telomere Fold Change | | | |
| Pre-Medical Optimization relative Pre-MBSR | 1.717 | 70 | .090 |
| Pre-MBSR relative Post-MBSR | -.836 | 70 | .406 |

*Covariate – Medical optimization*
*$p < .05$.
**$p < .001$

# Appendix C: Per-protocol ANCOVA evaluating change in psychosocial outcomes over time (T2 and T3)

*Per-protocol (8+ MBSR sessions attended) 2x2 ANCOVA results: Measures*

| | *df* | *F* | *p* | $\eta^2$ |
|---|---|---|---|---|
| BPI (Severity) | | | | |
| Group | 1 | .083 | .775 | .001 |
| Time | 1 | 5.118 | .026* | .062 |
| Time x Covariate | 1 | 7.021 | .010* | .083 |
| Group x Time | 1 | 5.547 | .021* | .066 |
| Error | 78 | | | |
| BPI (Interference) | | | | |
| Group | 1 | .692 | .408 | .009 |
| Time | 1 | 14.980 | .000** | .161 |
| Time x Covariate | 1 | 5.266 | .024* | .063 |
| Group x Time | 1 | 4.009 | .049* | .049 |
| Error | 78 | | | |
| NPSI | | | | |
| Group | 1 | .107 | .744 | .001 |
| Time | 1 | 11.778 | .001** | .131 |
| Time x Covariate | 1 | 7.668 | .007* | .090 |
| Group x Time | 1 | .791 | .377 | .010 |
| Error | 78 | | | |
| PCS | | | | |
| Group | 1 | .046 | .830 | .001 |
| Time | 1 | 10.603 | .002* | .120 |
| Time x Covariate | 1 | .764 | .385 | .010 |
| Group x Time | 1 | 2.618 | .110 | .032 |
| Error | 78 | | | |
| PHQ9 | | | | |
| Group | 1 | .001 | .979 | .000 |
| Time | 1 | 4.926 | .029* | .059 |
| Time x Covariate | 1 | .114 | .737 | .001 |
| Group x Time | 1 | .125 | .725 | .002 |
| Error | 78 | | | |
| POMS2A | | | | |
| Group | 1 | .013 | .908 | .000 |
| Time | 1 | 4.916 | .030* | .059 |
| Time x Covariate | 1 | 5.451 | .022* | .065 |
| Group x Time | 1 | 2.547 | .115 | .032 |
| Error | 78 | | | |
| PGIC | | | | |
| Group | 1 | 5.308 | .024* | ,063 |
| Time | 1 | 11.340 | .001** | .126 |
| Group x Time | 1 | 5.791 | .018* | .068 |
| Error | 78 | | | |

*Covariate – Medical optimization*
*$p < .05$.
**$p < .001$

# Appendix D: Comparison of completers versus non-completers on baseline outcomes of interest

| | MBSR | | | WLC | | |
|---|---|---|---|---|---|---|
| | *Completed (n= 31)* | Withdrew (n= 18) | *p* | Completed (n= 33) | Withdrew (n=16) | *p* |
| **Patient Demographics** | | | | | | |
| *Age (Mean, SE)* | 55.67 (1.75) | 54.06 (2.37) | .586 | 52.67 (2.06) | 48.44 (2.55) | .227 |
| *Years with Pain (Mean, SE)* | 3.66 (.54) | 2.68 (.41) | .206 | 2.92 (.35) | 2.66 (.35) | .631 |
| *Years post BC Diagnosis (Mean, SE)* | 3.49 (.40) | 3.25 (.44) | .694 | 3.35 (.38) | 3.53 (.58) | .788 |
| *Years post BC Treatment (Mean, SE)* | 2.69 (.31) | 2.54 (.42) | .765 | 2.43 (.37) | 2.69 (.43) | .657 |
| *Time (days) Post-Medical Optimization and Intervention Start (Mean, SE)* | 16.55 (1.87) | 14.67 (1.62) | .452 | 15.27 (1.37) | 15.13 (2.56) | .956 |
| *Ethnicity (n)* | 31 | 17 | .468 | 33 | 16 | .656 |
| *Employment (n)* | 31 | 17 | .092 | 33 | 16 | .522 |
| *Education (n)* | 31 | 17 | .146 | 33 | 16 | .377 |
| *Type of Cancer Treatment* | | | | | | |
| *Chemotherapy (n, %)* | 25 (80.6%) | 14 (77.8%) | .810 | 30 (90.9%) | 12 (75%) | .136 |
| *Radiation (n, %)* | 28 (90.3%) | 15 (83.3%) | .472 | 31 (93.9%) | 16 (100%) | .315 |
| **Psychological Measures** | | | | | | |
| *BPI Severity (Mean, SE)* | 4.02 (.31) | 4.67 (.40) | .211 | 4.58(.30) | 4.67(.47) | .850 |
| *BPI Interference (Mean, SE)* | 3.90 (.45) | 4.16 (.55) | .719 | 4.20 (.41) | 4.29 (.61) | .892 |
| *NPSI (Mean, SE)* | .35 (.03) | .36 (.03) | .812 | .39 (.03) | .30 (.04) | .092 |
| *FFMQ (Mean, SE)* | 133.37 (4.50) | 125.65 (4.06) | .254 | 126.12 (4.02) | 127.91 (6.07) | .803 |
| *PCS (Mean, SE)* | 17.93 (2.20) | 21.39 (2.91) | .347 | 19.99 (1.91) | 19.59 (2.57) | .903 |
| *PHQ-9 (Mean, SE)* | 8.77 (.92) | 10.67 (.99) | .190 | 9.00 (1.05) | 9.35 (1.79) | .860 |
| *PSS (Mean, SE)* | 17.09 (1.59) | 20.44 (1.41) | .160 | 19.03 (1.26) | 19.77 (2.10) | .750 |
| *POMS2a (Mean, SE)* | 62.88 (2.82) | 63.57 (2.17) | .081 | 64.56 (2.50) | 64.47 (4.27) | .985 |
| *PGIC (Mean, SE)* | 4.02 (.285) | 3.69 (.226) | .438 | 4.10 (.267) | 3.76 (.360) | .467 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Biomarkers** | | | | | | |
| *CRP (Mean, SE)* | 2250.55 (350.63) | 2320.92 (359.05) | .896 | 2846.71 (437.51) | 2307.70 (495.42) | .457 |
| *IL6 (Mean, SE)* | 3.72 (.39) | 3.45 (.58) | .693 | 3.93 (.44) | 2.65 (.38) | .069 |

[a] Leave of absence, retired, disability, home maker
Continuous outcomes evaluated using independent samples t-test
Nominal variables evaluated using Chi-square.
*$p < .05$.
**$p < .001$

# Appendix E: Experimental Design and Timepoints of Sample Collection