OBJECTIVE AND SUBJECTIVE SLEEP AND COGNITIVE DYSFUNCTION IN WOMEN NEWLY DIAGNOSED WITH BREAST CANCER

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Abstract

Breast cancer is the most commonly diagnosed form of cancer in Canadian women. Cancer treatments such as endocrine therapy, radiation therapy, and chemotherapy are often associated with pervasive, negative side effects. One of the most prevalent barriers to resuming normal functioning following the completion of treatment is known as cancer-related cognitive dysfunction (CRCD). However, the factors that may influence the development of these cognitive impairments remain unclear. A potential underlying mechanism of CRCD that has not been well-studied is sleep quality. The present study sought to determine whether a patient's sleep quality prior to treatment is indicative of cognitive functioning four months following the initiation of treatment in a sample of 32 women with breast cancer, using both subjective and objective measures. We found that all patients experienced worsened cognitive function, sleep, and mood disturbance at four months on subjective measures compared to baseline. Our findings may indicate that women with insomnia symptoms prior to diagnosis may begin treatment with poorer cognition and thus be at a higher risk for further cognitive deterioration. Moreover, women that do not exhibit symptoms of insomnia prior to beginning treatment may have a buffer against a decline in cognition. Participants with insomnia symptoms at baseline may also be at an increased risk for worsened mood disturbance as their treatment regimen proceeds. Future research should examine the changes in cognition, sleep, and mood disturbance with longer follow ups and investigate whether sleep quality mediates or moderates the relationship between cancer treatment and CRCD.

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Background

Breast cancer is the most commonly diagnosed form of cancer in Canadian women, with one in nine Canadian females receiving a breast cancer diagnosis in their lifetime (Canadian Cancer Society, 2015). As of 2015, this disease is the second leading cause of death in females (Canadian Cancer Society, 2015). Fortunately, due to advances in cancer detection and treatment (Frank, Vance, Triebel, & Meneses, 2015; Tao, Visvanathan, & Wolff, 2015), women are now more likely to survive their diagnosis. However, cancer treatments such as endocrine therapy, radiation therapy, and chemotherapy are often associated with pervasive side effects that can be debilitating.

Cancer-Related Cognitive Dysfunction

One of the most prevalent barriers to resuming normal functioning following the completion of treatment is known as cancer-related cognitive dysfunction (CRCD). These impairments may include attention deficits, memory loss, and impairments in executive functioning, visuospatial skill, psychomotor speed, short term memory, and verbal memory (word retrieval and recall) (Bernstein, McCreath, Komeylian, Rich, 2017; Kanaskie & Loeb, 2015; Miao et al., 2016; Tao, Visvanathan, & Wolff, 2015). CRCD is one of the most frequently reported symptoms by patients, with as many as 75% of individuals endorsing some level of impairment during treatment (Boykoff, Moieni, & Subramanian, 2009; Kanaskie & Loeb, 2015; Tannock, Ahles, Ganz, van Dam, 2004). Furthermore, approximately 35% of patients continue to experience difficulties in cognitive domains, with some studies suggesting that these impairments may persist for at least 5-10 years post-treatment (Amidi et al., 2015; de Ruiter et al., 2011).

Unfortunately, physicians rarely discuss the potential for changes in cognition prior to initiating cancer treatment (Kanaskie & Loeb, 2015). These impairments can make it difficult for women to resume their daily routines, including work (Boykoff et al., 2009). Breast cancer survivors living with CRCD often face difficulty performing effectively in the workplace, with some women taking leaves of absence or even resorting to early retirement (Boykoff et al., 2009; Munir, Burrows, Yarker, Kalawsky, & Bains, 2010). Self-report measures and interviews with breast cancer survivors post-adjuvant treatment regarding their perceived cognitive impairments reveal that CRCD is one of their most distressing symptoms (Boykoff et al., 2009; Kanaskie & Loeb, 2015; Von Ah et al., 2013). CRCD has the potential to cause or exacerbate emotional and psychological distress, severely impacting quality of life (Downie et al., 2006; Mitchell, 2007).

Measuring Cognitive Impairments

It is important to consider subjective in addition to objective measures of cognitive functioning, since self-report may be the primary indicator of cognitive impairment in cancer patients.

Subjective cognitive assessment. Indices of subjective cognitive function can provide information that is not captured in objective assessments, such as personal experience of cognitive change following treatment, and how patients cope with these impairments (Kanaskie & Loeb, 2015). Kanaskie and Loeb (2015) interviewed a sample of seven women that had been treated with chemotherapy for breast cancer within the past twelve months regarding various domains of cognitive function (executive function, attention, concentration, memory and recall, and processing). Participants in this study were interviewed once per month for two months and kept a journal to note any experiences with cognitive difficulty during the time between interviews. Women in this study noted that they began experiencing cognitive changes during, as

well as months after beginning chemotherapy (Kanaskie & Loeb, 2015). Word retrieval was the most commonly described problem expressed by participants. Women also expressed severe difficulty with short-term memory, concentration, organization, and mental fatigue.

In a similar study, 22 breast cancer survivors that had completed chemotherapy a minimum of 12 months prior to recruitment were interviewed to assess perceived cognitive impairment (Von Ah et al., 2013). All women in this study reported problems with their memory since beginning treatment. Specifically, the common domains that exhibited impairment were short-term and long-term memory, processing speed, attention and concentration, language, and executive function. Moreover, women reported that their biggest concerns were related to their cognitive impairments. In a later study, Von Ah and Tallman (2015) examined the relationship between subjective cognitive impairment [Functional Assessment of Cancer Therapy-Cognitive scale (FACT-Cog)] and objective cognitive performance (neuropsychological tests) in women previously treated for breast cancer. The results of this study were novel, as it was one of the first to show a correlation between FACT-Cog scores and objective measures of immediate and delayed verbal memory, as well as executive function. Therefore, subjective measures of cognitive functioning may be an efficient way to identify cognitive impairments in breast cancer survivors (Von Ah & Tallman, 2015).

Though the results of these studies examining subjective cognitive impairment provide insight into women's perceived cognitive impairments, it is important to acknowledge their limitations. First, cognitive impairment as measured by subjective tests of cognitive function, does not always correlate with performance on objective measures (Von Ah et al., 2013). Second, these studies exclusively examined subjective cognitive functioning in women that had completed treatment up to a year or more prior to being recruited. This may have been

problematic because patients were often required to comment retrospectively about their perceived cognitive impairments, which is not always reliable.

Objective cognitive assessment. Cognitive impairments have also been observed in women receiving treatment for breast cancer by administering a series of objective neurocognitive measures. These studies have consistently shown that patients receiving various treatment regimens exhibit impairments in areas such as learning and memory, visual, verbal, and working memory, as well as processing speed and executive function (Meattini et al., 2017).

Particularly, many studies have examined the impact of adjuvant treatment (chemotherapy and endocrine therapy) on cognitive functioning by administering neurocognitive measures. One study compared neurocognitive test scores of 31 breast cancer patients undergoing adjuvant chemotherapy treatment, 40 breast cancer survivors two years adjuvant post-treatment, and 36 healthy controls. Both current and post-treatment groups experienced significantly more neurocognitive impairments than women in the healthy control group (Brezden et al., 2000). Corroborating these findings, patients receiving adjuvant therapy have performed worse on visual and verbal working memory tasks when compared with patients affected by ductal carcinoma not receiving adjuvant treatment (Bender et al., 2006). Additionally, a study examining cognitive function in 120 early-stage breast cancer patients receiving chemotherapy or tamoxifen provided evidence to support that patients treated with either chemotherapy *or* endocrine therapy are three times more likely than healthy controls to experience impairments six months following treatment (Debess, Riis, Engebjerb, Ewertz, 2010).

Prospective studies examining the impact of treatment on cognition have revealed results that support previous findings. These studies provide evidence for declines in areas such as processing speed, verbal ability, and motor performance specific to women treated with adjuvant

therapy (Ahles et al., 2010; Tager et al., 2010). Many of these studies have consistently found that women treated with chemotherapy for breast cancer exhibit more cognitive impairment compared to other treatments (Ahles et al., 2010; Jansen, Cooper, Dodd, & Miaskowski, 2011; Tager et al., 2010). One prospective study compared the effects of treatment on cognitive function by recruiting 41 women receiving chemotherapy, and 40 women receiving radiation therapy in the absence of other treatment (Quesnel, Savard, & Ivers, 2009). Neurocognitive measures were administered at baseline, post-treatment, and at 3-month follow-up, revealing that women receiving chemotherapy exhibited more cognitive impairment than women receiving radiation therapy (Quesnel et al., 2009). Specifically, chemotherapy appeared to have a negative effect on verbal fluency. Similarly, Jansen et al. (2011) administered a battery of neuropsychological tests to a sample of 91 women at baseline in addition to three assessments following the initiation of chemotherapy. Consistent with previous findings (Bender et al., 2006; Collins et al., 2009), women in this study experienced a significant decline in areas such as attention, visuospatial skill, delayed memory, as well as motor function throughout the course of treatment.

However, there has also been evidence to suggest that neurocognitive impairments also exist in patients receiving endocrine treatment in the absence of chemotherapy. Palmer, Trotter, Joy, and Carlson (2008) compared 35 women receiving tamoxifen to healthy controls and found that patients being treated with tamoxifen showed impairments in areas similar to patients treated with adjuvant or chemotherapy treatment, such as visual and verbal memory, verbal fluency, visual-spatial ability, and processing speed. Despite the conflicting findings in the literature regarding the effects of specific treatment on cognition, it is clear that women receiving

treatment for breast cancer are at risk for developing cognitive impairments, regardless of treatment regimen.

Previous studies have been effective in identifying neurocognitive impairments in women diagnosed with breast cancer. Prospective studies are especially beneficial, as they allow researchers to observe changes in cognition throughout the course of treatment. However, similar to subjective studies, objective studies examining cognitive impairments in this population also have limitations. Many objective studies administer different neurocognitive measures, which can lead to conflicting results between studies. To provide reliable findings, these studies should remain consistent with the measures that are administered, as some neurocognitive measures are more sensitive than others. Additionally, it is important to note that many of these studies have not detected changes in objective cognitive functioning until at least six months following treatment onset (Debess et al., 2010; Quesnel et al., 2009), whereas studies measuring cognitive impairment subjectively have concluded that women report changes in their cognitive functioning much earlier in their treatment trajectory (Kanaskie & Loeb, 2015; Von Ah et al., 2013).

Theories of Cancer-Related Cognitive Dysfunction

Though previous studies have provided comprehensive evidence for the development of CRCD after a woman begins treatment for breast cancer, the underlying mechanisms are still unclear. Based on previous findings, it is clear that these cognitive impairments are not isolated to a single treatment, and that there are still many conflicting findings. As a result, there have been several theories posited to explain the development of CRCD, as well as the mechanisms underlying CRCD.

Genetics. Some studies have suggested that genetic factors may influence the development of CRCD (Janelsins, Kesler, Ahles, Morrow, 2014). For instance, patients previously diagnosed with cancer carrying an E4 allele are at a greater risk for developing CRCD (Ahles et al., 2003; Ahles et al., 2010). These individuals scored lower on a variety of cognitive measures, such as visual memory, spatial ability, and executive function, compared to those without this allele (Ahles et al., 2003). Further, Ahles et al. (2010) found that individuals with lower pre-treatment cognitive capacity were at a greater risk for decline in processing speed post-chemotherapy treatment.

Neuroanatomy. There are substantial changes in neuroanatomy associated with cognitive impairment in patients treated with chemotherapy. Using magnetic resonance diffusion tensor imaging, Deprez et al. (2011) observed significantly lower white matter integrity in the temporal and parietal tracts in 17 women treated with chemotherapy, which were compared to 18 healthy controls and 10 non-chemotherapy treated breast cancer patients. Furthermore, tests of attention and processing speed in this sample were correlated with parietal and temporal white matter integrity (Deprez et al., 2011). In a similar study, McDonald et al. (2013) compared MRI scans of women being treated for breast cancer with and without chemotherapy, as well as healthy controls. Significant reductions in frontal grey matter were observed in patients being treated with chemotherapy approximately six months following baseline assessment (McDonald et al., 2013). These results suggest that the alterations in these brain regions are specific to chemotherapy treatment, and are significant since the frontal regions of the brain are important for executive function and memory processes (Deprez et al., 2011; McDonald et al., 2013).

Immune response. Investigators have also suggested that inflammation accompanying a patient's immune response may precipitate or promote the development of CRCD. Cytokines are

commonly recognized for their role in regulating inflammation; however, they are also central in the maintenance of cell functioning and repairing neurotransmitters, all of which are important for normal cognitive function (Wilson, Finch, & Cohen, 2002). Many neurodegenerative disorders (such as Alzheimer's disease and multiple sclerosis) have been associated with the deregulation of cytokines (Tonelli, Postolache, Sternberg, 2005).

The relationship between cytokines and cognitive function is evident in cancer patients receiving immunotherapy. Researchers have suggested that the deregulation of cytokines experienced by patients receiving immunotherapy is associated with symptoms such as fatigue and cognitive disruption (Scheibel, Valentine, O'Brien, & Meyers, 2004). Moreover, longitudinal studies examining the effect of particular immunotherapies on cognition have revealed that patients experience deficits in cognitive abilities such as processing speed, executive function, spatial ability, and reaction time (Capuron, Ravaud, & Dantzer, 2001; Scheibel et al., 2004). Though there have not been any studies examining the association between cytokines, cancer treatment, and cognition, researchers have speculated about these relationships. Higher levels of inflammatory cytokines have been observed in patients treated with chemotherapy, leading researchers to suggest that higher levels of inflammatory cytokines are associated with cognitive dysfunction (Ahles & Saykin, 2007; Cleeland et al., 2003).

Demographic and lifestyle factors. Many studies examining the impact of cancer treatment on cognitive function have consisted of samples of women from an older population. The mean age of women recruited in these studies are usually between 45-60 years of age (Ahles et al., 2010; Jansen et al., 2011; Palmer et al., 2008; Quesnel et al., 2009). One study examining the impact of age on cognitive functioning in women receiving adjuvant treatment for breast cancer revealed that post-treatment decline in processing speed was associated with age and pre-

treatment cognitive reserve, defined as an individual's innate and developed cognitive capacity (Ahles et al., 2010). Specifically, patients receiving chemotherapy who were older and had a lower pre-treatment cognitive reserve performed worse than patients who did not receive chemotherapy, as well as healthy controls, on measures of processing speed. These findings suggest that older patients exhibiting a lower pre-treatment cognitive reserve may be at a higher risk for developing problems with processing speed when receiving chemotherapy as part of their treatment regimen. Despite age being the most common explanation for cognitive decline, previous studies have also suggested that both younger and older patients experience CRCD (Janelsins et al., 2014).

Lifestyle factors such as physical activity, obesity, and sleep have also been associated with cognitive functioning in patients that have completed treatment for breast cancer. Hartman, Marinac, Natarajan, and Patterson (2015) assessed 136 post-menopausal breast cancer survivors on measures of neuropsychological functioning, height, weight, physical activity (Global Physical Activity Questionnaire), and sleep (duration per night). Women reporting higher levels of physical activity performed significantly better than women reporting lower levels of physical activity on measures of attention and executive functioning. Additionally, women who were obese were three times more likely to exhibit impairments on domains of processing speed than those who were not. Finally, women reporting more hours of sleep per night correlated with improved performance in verbal functioning. Unfortunately, this study was primarily based on women's self-report for physical activity and sleep measures. Moreover, the investigators only included one question about sleep, which was regarding the duration of sleep obtained per night.

Sleep as a Potential Mechanism of CRCD

Although there is evidence that women undergoing treatment for breast cancer exhibit CRCD, the factors that may influence the development of these cognitive impairments remain unclear. According to the International Cognition and Cancer Task Force, studies should focus on potential mechanisms that may underlie such impairments (Wefel, Vardy, Ahles, & Schagen, 2011). A potential underlying aspect of CRCD that has not been well-studied is sleep quality. The quality of sleep before, during, and after cancer treatment may influence the development of CRCD.

Cancer Treatment and Sleep Disturbances

In addition to CRCD, sleep disturbances are among the most highly reported side effects experienced by patients being treated for cancer, with as many as 30-50% of patients reporting sleep difficulties (Savard, Ivers, Villa, Caplette-Gingras, Morin, 2011). The prevalence of sleep disturbance in individuals diagnosed with cancer is two to three times greater than the general population (Berger et al., 2005). It appears that treatment-related sleep difficulties occur across various stages of cancer, with as many as 75% of early-stage patients and 72% of advanced stage patients reporting sleep difficulties (Fiorentino & Ancoli-Israel, 2006; Sela, Watanabe, & Nekolaichuk, 2005; Savard et al., 2011). Patients have reported that sleep disturbances are among their most distressing symptoms (Liu et al., 2012), and poor sleep can cause, and/or exacerbate, other medical and psychological conditions.

Causes of Sleep Disturbances

The disturbances in sleep that patients experience throughout the night can be due to physical side effects of treatment (Kim, McDermott, Barsevick, 2014; Lee, Cho, Miaskowski, & Dodd, 2004). For instance, one of the most prevalent side effects experienced by breast cancer patients receiving endocrine therapy is hot flashes (Engstrom, 2008; Savard, Hervouet, & Ivers,

2013), which can negatively impact a patients' sleep (Downie et al., 2006; Savard et al., 2013). In 2006, Downie et al. employed a variety of subjective and objective measures to collect data regarding the relationship between fatigue, menopausal symptoms, and cognitive performance in twenty-one women receiving adjuvant chemotherapy for breast cancer. Approximately half of their sample was awakened by hot flashes during the night, leading them to experience fatigue during the day that impacted their daily functioning (Downie et al., 2006).

In addition to hot flashes, patients experience pain that is cancer-related and treatment-related. Pain is one of the most common attributions to insomnia as identified by patients diagnosed with cancer (Davidson, MacLean, Brundage, & Schulze, 2002). Approximately 40-55% of early-stage patients and 60-95% at advanced stages report cancer-related pain (Davidson et al., 2002; Sela et al., 2005). Increases in pain are positively correlated with sleep disturbance, with as many as 59% of patients attending pain clinics reporting sleep disturbances (Lee, Cho, Miaskowski, 2004; Sela et al., 2005). Lewin and Dahl (1999) suggest that the relationship between pain and sleep disturbance operates similar to a feedback-loop, such that poor sleep impairs the body's ability to repair tissue, which increases pain. The increased pain further disrupts sleep and this poor sleep leads to a reduction in a patients' emotional capacity to successfully manage pain, increasing pain perception, thus creating a continuous cycle of poor sleep and pain (Lewin & Dahl, 1999). Another explanation underlying the relationship between sleep disturbance and pain involves opioid use. To help control pain, patients diagnosed with cancer are often prescribed opioids; however, opioids decrease rapid eye movement and slow-wave sleep and may actually contribute to sleep disturbances experienced by these patients (Dimsdale, Norman, DeJardin, & Wallace, 2007).

Another potential underlying mechanism of sleep disturbances that warrants attention are the psychological side effects experienced by patients undergoing treatment for cancer. Previous studies have reported that many of the difficulties falling and staying asleep that patients experience throughout the night are due to psychological factors such as anxiety and depression (Clevenger et al., 2013; Downie et al., 2006; Trill, 2013). One study examined the contribution of depression and anxiety to sleep disturbance in women with ovarian cancer during the first year of diagnosis. Women in this study had higher depressive symptoms, which was associated with greater sleep disturbance (Clevenger et al., 2013). In a similar study, the relationship between sleep disturbance (measured by the Athens Sleep Insomnia Scale) and psychological distress (measured by the Hospital Anxiety and Depression Scale) was examined in a sample of 50 patients diagnosed with lung cancer (Nishiura, Tamura, Nagai, & Matsushima, 2015). In this sample 56% of patients experienced sleep disturbance. Moreover, patients with sleep disturbance had higher scores on the HADS, and all patients with sleep disturbance met criteria for subclinical or clinically significant depression/anxiety (Nishiura et al., 2015). It is important to consider anxiety and depression as an underlying contributor to sleep disturbance, as these psychological comorbidities often appear at the outset of a cancer diagnosis, and can persist even after a patient is cancer-free (Trill, 2013).

Objective Sleep Disturbance

The most common method of measuring objective sleep in patients diagnosed with cancer has been through actigraphy. When compared to healthy controls, cancer patients have consistently exhibited less contrast between day and night activity, which is indicative of circadian rhythm disruption (Fernandes et al., 2006; Levin et al., 2005). In one study, patients diagnosed with stage I-III breast cancer receiving chemotherapy-based treatment wore a wrist

actigraph for 72 hours prior to the administration of treatment, and for three weeks during cycles one and four of treatment (Savard et al., 2009). Disruptions of sleep-wake rhythms were observed following the first administration of chemotherapy, with progressively worse disruptions occurring with each consecutive cycle of chemotherapy.

Similarly, Liu et al. (2012) recruited 97 women scheduled to receive chemotherapy for breast cancer to examine the relationship between fatigue and sleep by administering objective and subjective measurements of sleep at baseline, and for three weeks during both cycles one and four of treatment. These measures were obtained using actigraphy, as well as the Pittsburgh Sleep Quality Index and the Multidimensional Fatigue Symptom Inventory-Short Form. Patients experienced worsened fatigue, and spent more time sleeping during the night and day when undergoing chemotherapy (Liu et al., 2012).

Patients undergoing other methods of treatment besides chemotherapy also experience sleep disturbance. Using measures of objective and subjective sleep disturbance, Dhruva et al. (2012) carried out a longitudinal study examining sleep disturbance prior to, during, and following radiation therapy in 73 women diagnosed with breast cancer. Upon beginning RT, the majority of women experienced a high number of night time awakenings which was classified as abnormal. Additionally, patients were awake for 11% of the time following sleep onset, which exceeds the cut-off of 10% for healthy adults (Dhruva et al., 2012).

Subjective Sleep Disturbance

It is also important to consider a patient's perception of their sleep quality. Self-report measures have revealed that patients being treated for various types of cancer experience difficulties with sleep. A cross-sectional survey examining sleep disturbance in a heterogeneous sample of 1000 patients revealed that of all cancer types included in the sample, women with

breast cancer present the highest prevalence of sleep disturbances (Davidson et al., 2002). Additionally, 76% of this sample reported experiencing multiple awakenings throughout the night, with nearly 31% meeting the criteria for insomnia disorder. Moreover, patients treated with radiation therapy, chemotherapy, or surgery in the past six months were more likely than those not treated in the past six months to report sleep problems, as well as excessive sleepiness, fatigue, and hypersomnolence (Davidson et al., 2002).

Prospective longitudinal studies have also revealed that patients with cancer report sleep difficulties prior to, as well as throughout the course of their treatment (Savard et al., 2011). Savard et al. (2011) interviewed 962 patients diagnosed with cancer using an insomnia diagnostic interview at six time points over the course of eighteen months (including a baseline assessment). At baseline 31% of their sample exhibited symptoms of insomnia and 28% met diagnostic criteria for an insomnia syndrome. Patients with symptoms of insomnia at baseline were more likely to have insomnia eighteen months later. By the sixth assessment, 21% of their sample had insomnia syndrome and 15% exhibited symptoms of insomnia. Of note, patients diagnosed with breast cancer exhibited the highest prevalence of insomnia throughout the study, with 42-69% of breast cancer patients meeting criteria for insomnia. Based on these findings, it may also be imperative to consider whether patients experience symptoms of insomnia at baseline, as these patients may be at further risk for developing an insomnia disorder as their treatment regimen proceeds.

The Impact of Poor Sleep on Cognition

Even partial sleep loss accumulated over a few days can have negative impacts on a variety of cognitive functions such as attention, memory, executive function, and behavioural alertness, all of which are imperative for proper daytime functioning (Gobin, Banks, Fins, &

Tartar, 2015; Van Dongen, Maislin, Mullington, & Dinges, 2003). Moreover, individuals that repeatedly obtain less than 7 hours of sleep per night demonstrate increased lapses of attention, and are at a higher risk for developing cognitive dysfunction (Belenky et al., 2013; Van Dongen et al., 2003). Van Dongen et al. (2003) randomly assigned 48 healthy adults to one of three varying time-in-bed conditions (eight hours, six hours, and four hours per night) and assessed their performance on neurocognitive measures. This study revealed impairments in working memory performance that were dependent on the amount of time-in-bed permitted. Participants in the eight-hour time-in-bed group performed best on the task, and those in the four-hour time-in-bed group performed worst on the task (Van Dongen et al., 2003). Additionally, it was apparent that individuals in this study had a tendency to overestimate their performance on tasks that required vigilance, and underestimated the impact that sleep restriction had on their cognitive abilities (Van Dongen et al., 2003). This is especially of concern, as individuals may attempt every-day tasks that require attention and reactivity (such as operating a motor-vehicle) without realizing their level of impairment.

Though these studies effectively demonstrate the short-term effects of sleep-related cognitive impairment, it is important to consider the long-term consequences of sleep disruption on cognitive functioning. In humans, prolonged sleep disruption can lead to the inability to detect changes in the surrounding environment, slower reaction times, and, in severe cases, hallucinations (Alkadhi et al., 2013; Reynolds et al., 2013). Additionally, chronic sleep disruption may negatively impact the functioning of the prefrontal cortex, impairing an individual's attention and ability to make executive decisions (Boonstra et al., 2007). The effects of long-term sleep disruption have been linked to neurodegenerative diseases such as dementia and Alzheimer's disease (Xie et al., 2013). This is explained by the accumulation of β-amyloid

that destroys neurons as a result of chronic sleep loss (Xie et al., 2013). The potential impacts of poor sleep are vast and have the potential for life-long consequences.

Sleep Disturbance and CRCD in Women with Breast Cancer

Compared to other cancer types, women with breast cancer are the most at risk for sleep disturbance (Savard et al., 2009; Servaes & Bleijenberg, 2002). However, the impact that poor sleep quality has on cognition in breast cancer patients receiving treatment has not been studied. The quality of sleep that a patient experiences before, as well as throughout the duration of their treatment may have the potential to contribute to the development of CRCD, as well as further exacerbate symptoms of cognitive impairment. Since previous studies have shown that cancer treatments can negatively impact sleep, poor sleep may further increase an individual's risk of developing CRCD (Servaes & Bleijenberg, 2002). Addressing the underlying causes of CRCD is crucial in order to develop effective prevention, early intervention, and treatment regimens.

Research that attempts to delineate the underlying causes of cognitive dysfunction in cancer patients has been growing. However, many of these studies have focused solely on cognitive impairments that arise during treatment or post-treatment, or have only used self-report measures of sleep and cognition (Bower, 2008; Hutchinson, Hosking, Kichenadasse, Mattiske, & Wilson, 2012; Von Ah et al., 2013). The present study sought to determine whether a patient's sleep at baseline (prior to beginning treatment) is indicative of cognitive functioning four months following the initiation of treatment in a sample of women with breast cancer using both subjective and objective measures of cognitive functioning and sleep to better understand the changes in cognitive functioning during the early stages of treatment.

In conducting this research, we answered the following questions in a sample of newly diagnosed women with breast cancer: (1) Is there a change in objective and subjective sleep,

cognitive functioning, and mood disturbance from pre-treatment to four months in women with and without insomnia symptoms (2) Is change in sleep associated with cognitive impairment and psychological disorders?

We hypothesized that (1) patients will exhibit worse cognitive function, sleep, and mood disturbance on subjective measures, and not on objective measures, at four months compared to baseline measures, and (2) that poor sleep is associated with more subjective cognitive impairment at four months, as well as higher scores on measures of anxiety and depression.

Methods

Participants

Participants were recruited from the Dr. H. Bliss Murphy Cancer Center in St. John's, Newfoundland. Patients were informed of the study by their treating oncologist during their appointment at the Cancer Centre. Patients were eligible for the study if they had recently received a diagnosis of stage I-III breast cancer, and were scheduled to receive chemotherapy, hormonal therapy, or radiation therapy. Patients were ineligible for the study if they had been previously treated for cancer or were presently undergoing cancer treatment. Moreover, patients were ineligible if they had a sleep disorder besides insomnia that was not adequately treated, a psychological disorder that was not currently stable or would impair their ability to participate, or if they scored lower than 24 on the Mini-Mental State Examination (suggesting the presence of a severe cognitive impairment). Patients were also ineligible to participate if they had an existing medical condition that would impair their cognition and/or ability to participate, such as Parkinson's disease, or Alzheimer's Disease, or previous history of a stroke.

Procedure

Recruitment. Treating oncologists in the Dr. H. Bliss Murphy Cancer Centre cancer center identified eligible participants by examining their clinical charts. At the time of the patients' appointment, the treating oncologist informed them of the study by providing a brief description, and asked them if they would like to speak with a research assistant (RA) about the study. If the patient was agreeable, the RA met with the patient for approximately five minutes to provide the patient with information about the study. The RA described the study to the patient, including background information, objectives, a brief description of the assessment types, and frequency of assessment. If the patient was interested in participating, the RA obtained the patients' contact information. If the patient preferred to speak with someone at a later time, they were provided with an introduction letter which included a description of the study, and information to contact the RA or the principal investigator.

Screening. Once informed consent was obtained, the RA screened the participant for any sleep, psychological, or medical complications that would impair their ability to participate in the study. This included administering the Mini-Mental State Exam (MMSE), and a study developed sleep, psychological, and medical history screening questionnaire.

Baseline and Four-Month Follow-up Assessments. Informed consent to participate in the study was obtained at the beginning of the baseline assessment. Baseline and four-month follow-up assessments followed the same procedure and were scheduled at the convenience of the participants. Assessments consisted of cognitive assessments, self-report measures, as well as wearing an Actigraph and completing a Sleep Diary for one week (see measures). The total time to complete each assessment was approximately 45-60 minutes. At the end of each assessment,

participants were given the Actigraph and Sleep Diary, as well as a postage-paid envelope to return these items by mail.

These assessments were completed in-person or by telehealth at their local healthcare centre to complete the assessment. If a participant completed an assessment via Telehealth, the Actigraph, Sleep Diary, as well as the questionnaires were mailed to them with a postage-paid envelope to return the materials in following the Telehealth assessment. Participants were asked to begin wearing the Actigraph and begin the Sleep Diary as soon as they received it in the mail, and to complete the questionnaires at the earliest possible opportunity.

Measures

To provide an objective assessment of cognition, we included the neurocognitive measures recommended by the International Cognition and Cancer Task Force (Wefel et al., 2011).

Screening and demographics. Demographics information such as sex, age, ethnicity, marital status, and employment status was collected from all participants.

The sleep, psychological, and medical history screening questionnaire obtained information such as cancer type, diagnosis date, treatment date, and type of treatment received, sleep and psychiatric history, and current medication use.

To determine whether a participant exhibited a cognitive impairment that would impair their ability to participate in the study, the MMSE was administered. A score lower than 24 on the MMSE indicates a severe cognitive impairment. The MMSE demonstrates good reliability and construct validity when compared against gold standards that identify and measure cognitive impairment (Tombaugh & McIntyre, 1992).

Subjective Neurocognitive Assessments

The Functional Assessment of Cancer Therapy – Cognitive Function Version 3 (FACT-Cog V3). The FACT-Cog V3 is a 37-item self-report questionnaire consisting of four cognitive subscales: perceived cognitive impairments, impact on quality of life, comments from others, and perceived cognitive abilities (Jacobs, Jacobsen, Booth-Jones, Wagner, & Anasetti, 2007; Wagner, Sweet, Butt, Lai, & Cella, 2009). This questionnaire requires participants to reflect on these items regarding the past seven days. Responses may range from 0 (never) to 4 (several times a day). Perceived cognitive impairment and impact on quality of life subscales are reverse-scored, with higher scores indicating better cognitive functioning and that cognitive functioning has more of an impact on quality of life, respectively. Higher scores on the perceived cognitive ability subscale indicate better cognitive functioning.

Objective Neurocognitive Assessment

The Hopkins Verbal Learning Test-Revised (HVLT-R). The HVLT-R assesses verbal learning and memory, including immediate and delayed recall, as well as delayed recognition. Each version of the HVLT-R consists of a list of 12 nouns with four words drawn from each of three semantic categories (Brandt & Benedict, 2001). The HVLT-R exhibits high test-retest reliability, as well as construct, concurrent, and discriminant validity (Brandt & Benedict, 2001; Brandt, 1991). HVLT-R test booklets one and two were used for baseline and 4-month follow-up assessments, respectively. Higher scores indicate better cognitive functioning.

Letter-Number Sequencing (LNS). LNS is a supplemental subtest obtained from the Weschler Adult Intelligence Scale. This task requires participants to recall a series of numbers and letters by stating the numbers first, then the letters, in ascending order. LNS is a measure of

working memory, attention, and mental control (Wechsler, 2008). Higher scores indicate better cognitive functioning.

Subjective Sleep

Insomnia Severity Index. The Insomnia Severity Index (ISI) is a patient-reported outcome that assesses the impact that insomnia has on daytime functioning, as well as the amount of associated distress (Bastien, Vallieres, & Morin, 2001). Items are scored on a five-point scale ranging from 0 to 4 with higher scores representing more severe insomnia symptoms. The cut-off scores are 0-6 (no clinically significant sleep difficulties, 7-14 (sleep difficulties require further investigation) and 15+ (clinically significant insomnia) (Bastien et al., 2001). The ISI has demonstrated internal consistency, reliability, construct validity, specificity and sensitivity in a representative sample of 1670 cancer patients (Savard et al., 2005).

The Consensus Sleep Diary (CSD). A self-report measure of sleep which will be completed by participants for 7 consecutive days. Participants will report their sleep duration, perceived quality, and disruption. Sleep diaries are considered a reliable and valid patient self-report of nightly insomnia symptoms (Carney et al., 2012). The CSD collects information such as total sleep time, sleep onset latency, wakefulness after initial sleep onset, total time spent in bed, and sleep quality/satisfaction (Carney et al., 2012).

Objective Sleep Measure

Actigraphy monitoring provided objective information regarding a participant's sleep. An actigraph is a wrist-worn device similar to a watch that can record activity levels throughout the day and night. This information includes sleep efficiency, latency, total sleep time, as well as the frequency and number of awakenings. The type of actigraph that will be utilized in the present study is the Motionlogger, which is among the most accurate instruments for collecting objective

actigraphic data, having an approximate 90% accordance with polysomnography (Rupp & Balkin, 2011).

Comorbid Symptom Outcomes

The Hospital Anxiety and Depression Scale (HADS). The HADS is a 14-item, self-rated instrument for anxiety (7 items) and depression (7 items) symptoms in the past week and has been extensively used in people with cancer (Bjelland, Dahl, Haug, & Neckelmann, 2002; Mitchell, Meader, & Symonds, 2010). The following cut-offs have been established: 0–7 not significant; 8–10 subclinical; and 11-21 clinically significant depression/anxiety.

The Multidimensional Fatigue Inventory-Short Form (MFSI-SF). The MFSI-SF is a 30 item self-report measure consisting of five subscales (general, emotional, physical, mental, and vigor) and a total fatigue score. Internal consistency ranges from 0.87 to 0.92 with test-retest reliabilities ranging from 0.51 to 0.70. The MFSI-SF has demonstrated appropriate convergent and discriminant validity (Stein, Jacobsen, Blanchard, & Thors, 2004).

Statistical Methods

Descriptive statistics were generated for demographic, disease stage, and treatment characteristics. Paired samples t-tests were used to compare those with and without insomnia symptoms at baseline to determine whether there were any differences between the groups in terms of demographics, cognitive functioning, and mood disturbance.

Repeated measures Analysis of Variance (ANOVA) was used to assess change in subjective and objective cognitive functioning, sleep, and mood disturbance from pre-treatment to four months following the initiation of treatment. In this analysis, the between subjects factor was group (participants with insomnia symptoms and without insomnia symptoms), and the

within subjects factor was time (pre-treatment and four months following the initiation of treatment).

Finally, change scores were calculated on the ISI, FACT-Cog V3, and HADS by subtracting the baseline scores from the four-month follow-up scores. Correlational analyses were used to determine whether change in insomnia severity was associated with change in cognitive impairment, anxiety, and depression.

Results

Demographics

Thirty-eight women diagnosed with stage I-III breast cancer agreed to participate in this study. Of the 38 participants who consented to participate, 6 participants were lost-to-follow-up at 4-months. Health complications, inability to travel to the nearest telehealth location, and being too busy to commit to the study were the indicated reasons for withdrawal. Therefore, there were 32 participants that completed a 4-month follow-up assessment. Only participants with complete data (baseline and four months) were included in the analysis. The age of the participants ranged from 38 to 80 (M = 59.47, SD = 10.36), with the majority of participants being married (81.3%). The mean years of education completed in this sample were 14.06 years, and the majority of the sample identified as retired (65.6%). (See Table 1 for demographic information).

This sample was further divided into those with and without insomnia symptoms, which was determined by ISI score at baseline. An ISI score less than or equal to 7 represented no insomnia (N = 16), and a score greater than or equal to 8 was indicative of insomnia symptoms (N = 16). At baseline there were no significant differences between those with and without insomnia symptoms with respect to age, years of education completed, hours worked per week,

hours of physical activity per week, or number of caffeinated beverages consumed per day (see Table 1 for *p* values).

Participants with and without insomnia symptoms at baseline were compared to determine whether there was a difference between the groups in terms of subjective cognitive functioning and mood disturbance. Participants with insomnia symptoms ($M = 50.63$, $SD = 11.00$) scored lower on the perceived cognitive impairment subscale than those without insomnia symptoms ($M = 58.89$, $SD = 11.08$), $t\ (1,30) = 2.118$, $p = .043$. Participants with insomnia symptoms ($M = 18.88$, $SD = 5.41$) also scored lower on the perceived cognitive ability subscale at baseline compared to those without insomnia symptoms ($M = 22.88$, $SD = 4.81$), $t\ (1,30) = 2.208$, $p = .035$. Additionally, participants without insomnia symptoms ($M = 14.31$, $SD = 3.61$) exhibited higher scores on the impact of cognitive impairment on quality of life subscale compared to those with insomnia symptoms ($M = 10.38$, $SD = 5.01$), $t\ (1,30) = 2.552$, $p = .022$. Participants with insomnia symptoms ($M = 5.06$, $SD = 3.34$) scored higher on the depression subscale of the HADS compared to those without insomnia symptoms ($M = 2.19$, $SD = 2.64$), $t\ (1,30) = 2.704$, $p = .011$. Participants with insomnia symptoms ($M = 9.19$, $SD = 3.76$) also scored higher on the anxiety subscale of the HADS compared to those without insomnia symptoms ($M = 4.56$, $SD = 4.55$), $t\ (1,30) = 3.135$, $p = .004$. Refer to Figure 1 and Figure 2 for baseline scores on subjective cognitive functioning and mood disturbance measures.

Cognitive Functioning

Subjective. When examining the perceived cognitive impairment subscale of the FACT-Cog V3, a significant effect of time was observed, $F\ (1,30) = 13.089$, $p = .001$, $\eta^2 = .304$. This indicates that both groups had significantly more perceived cognitive impairment four months following the initiation of treatment compared to baseline (refer to Figure 3). A significant effect

of time was also observed for the perceived cognitive ability subscale of the FACT-Cog V3, F (1,30) = 4.780, p = .037, η^2 = .137, indicating that both groups perceived less cognitive ability four months following the start of treatment compared to baseline (refer to Figure 4). A significant effect of group was observed for the perceived impact that cognitive impairment has on quality of life subscale of the FACT-Cog V3, F (1,30) = 5.076, p = .032, η^2 = .145. Participants without insomnia symptoms (M = 14.00, SE = .765) indicated that their cognitive impairment had more of an impact on their quality of life compared to those with insomnia symptoms (M = 11.56, SE = .765) (refer to Figure 5).

Objective. There were no significant time or group differences observed on baseline to four-month follow-up for those with or without insomnia symptoms on the HVLT-R (including measures of total recall, delayed recall, retention, and recognition). There were also no significant time or group differences observed from baseline to four-month follow-up for those with or without insomnia symptoms on LNS scores. See Table 2 for objective cognitive measure values.

Subjective Sleep Measures

Consensus Sleep Diary. When examining the number of minutes awake after sleep onset, a significant effect of group was observed, F (1,28) = 7.551, p = .010, η^2 = .212. Participants with insomnia symptoms (M = 44.90, SE = 5.764) spent more time awake after sleep onset than those without insomnia symptoms (M = 22.50, SE = 5.764) (refer to Figure 6). In terms of sleep efficiency, there was a significant effect of group, F (1,28) = 7.842, p = .009, η^2 = .219. Participants without insomnia symptoms (M = 84.60, SD = 2.079) had better sleep efficiency than those with insomnia symptoms (M = 76.37, SD = 2.079) (refer to Figure 7).

Additionally, there was a significant interaction of group and time in terms of sleep efficiency, F (1,28) = 6.295, p = .018, η^2 = .018.

There was no significant main effect of group or time, and there was no significant interaction for sleep diary measures of sleep onset latency, number of awakenings, total sleep time, or time spent in bed.

Insomnia Severity Index. A repeated measures ANOVA revealed a significant effect of time, F (1,30) = 9.789, p = .004, η^2 = .246, indicating that both groups exhibited more symptoms of insomnia four months following the initiation of treatment compared to baseline. There was also a significant effect of group, F (1,30) = 44.352, p = .000. Participants with insomnia symptoms (M = 14.63, SE = .982) exhibited more symptoms of insomnia compared to those that did not have insomnia symptoms (M = 5.38, SE = .982) (refer to Figure 8).

Mood Disturbance

Hospital Anxiety and Depression Scale. A repeated measures ANOVA revealed a significant effect of time on the depression subscale of the HADS, F (1,30) = 8.236, p = .007, η^2 = .215. Both groups experienced more symptoms of depression four months following the start of treatment compared to baseline. Additionally, there was a significant effect of group for the depression subscale of the HADS, F (1,30) = 5.672, p = .024, η^2 = .159, indicating that participants with insomnia symptoms (M = 5.66, SE = .798) exhibited more symptoms of depression than those without symptoms of insomnia (M = 2.97, SE = .798). There was no significant interaction of group x time (p = .698). See Figure 9 for details.

There was a significant effect of group on the anxiety subscale of the HADS, F (1,30) = 9.164, p = .005, η^2 = .234, indicating that participants with insomnia symptoms (M = 8.25, SD = .854) exhibited more symptoms of anxiety compared to those without insomnia symptoms (M =

4.59, *SD* = .854). There was no significant effect of time (p = .110) or group x time interaction (p = .089). See Figure 10 for details.

Associations between Change Scores

When change in insomnia severity was correlated with change in cognitive impairment, anxiety, and depression, we found that change in insomnia severity was only associated with the perceived cognitive ability subscale of the FACT-Cog V3, r = -.391, p = 016. Increases in insomnia symptoms was associated with worsened perceived cognitive ability.

Our correlational analyses also revealed that the depression subscale of the HADS was associated with the perceived cognitive impairment, perceived cognitive ability, and impact on quality of life subscales of the FACT-Cog V3. Increases in symptoms of depression was associated with more cognitive impairment. Additionally, the anxiety subscale of the HADS was associated with the impact on quality of life subscale of the FACT-Cog V3. Women with higher anxiety symptoms reported that their cognitive functioning had more of an impact on their quality of life. Finally, the perceived cognitive impairment subscale of the FACT-Cog V3 was associated with the perceived cognitive ability and impact on quality of life subscale of the FACT-Cog V3. Having less perceived cognitive impairment was associated with a higher perceived cognitive ability and less of an impact that cognitive functioning has on quality of life. See Table 5 for correlations.

Discussion

In conducting this research, we sought to investigate change in cognitive functioning, sleep quality, and mood disturbance from pre-treatment to four months following the initiation of treatment in a sample of newly diagnosed women with breast cancer. In doing so, we divided our sample into two groups; women with and without insomnia symptoms at baseline. Upon dividing

our sample into these groups, we assessed whether they differed at baseline in terms of their cognitive functioning and mood disturbance. We expected that patients would exhibit worse cognitive function, sleep, and mood disturbance at four months on subjective measures, and not on objective measures, compared to baseline. We also questioned whether change in sleep would be associated with subjective cognitive impairment and psychological disorders. We predicted that poor sleep would be associated with more subjective cognitive impairment at four months, as well as higher scores on measures of anxiety and depression.

Corroborating our first hypothesis, all patients exhibited worse cognitive function, sleep, and mood disturbance at four months on subjective, but not objective, measures compared to baseline. However, women with insomnia symptoms exhibited more cognitive impairment at baseline compared to women that did not have insomnia symptoms. As previous research suggests that poor sleep is associated with cognitive decline (Gobin et al., 2015; Van Dongen et al., 2003), our findings may indicate that women with insomnia symptoms prior to diagnosis may enter treatment with worse cognition and thus be at a higher risk for further cognitive deterioration. Moreover, women that do not exhibit symptoms of insomnia prior to beginning treatment may have a buffer against a decline in cognition. Our findings are consistent with previous findings that women report experiencing cognitive deficits after treatment onset, as well as throughout the duration of treatment (Kanaskie & Loeb, 2015; Von Ah et al., 2013). However, these aforementioned studies did not assess pre-treatment sleep quality. Since women in such studies reported cognitive impairments as their biggest concerns, it is especially important to consider patient-reported symptoms of cognitive decline during the early stages of treatment.

Our results also suggest that four months following the onset of treatment may be too early to detect changes in cognitive domains such as working memory, attention, and mental

control using objective measures. Previous longitudinal studies have not detected changes in objective cognitive functioning in patients receiving cancer treatment until at least six months following treatment onset (Debess et al., 2010; Quesnel et al., 2009). Studies that have detected specific objective deficits in cognitive domains have utilized a group comparison approach (patients currently undergoing treatment, post-treatment, and healthy controls), rather than a longitudinal approach, or have not included a pre-treatment assessment (Bender et al., 2006; Brezden et al., 2000; Palmer et al., 2008). Excluding a baseline assessment prevents researchers from knowing how patients would have performed on these measures prior to beginning treatment. Related, there may be pre-existing group differences in cognitive functioning. Additionally, patients in the cancer treatment group may have started their treatment at various times. Our findings support the need for longitudinal repeated assessment when assessing the development of symptoms such as insomnia and cognitive impairment, which may both present at varying times and have different individual presentations (Jansen et al., 2011; Von Ah et al., 2013; Savard et al., 2009; Savard et al., 2011).

Our results also strengthen previous research suggesting that women being treated for breast cancer experience poor sleep and are, subsequently, at an increased risk for developing insomnia (Savard et al., 2009; Servaes & Bleijenberg, 2002). In the present study, women experienced more symptoms of insomnia four months following treatment onset compared to pre-treatment, regardless of whether they experienced symptoms of insomnia at baseline.

The decline in sleep quality experienced by participants in the present study is consistent with previous research that has detected such changes in the early stages of treatment, using objective measures of sleep (Savard et al., 2009). Since the present study provides evidence that changes in sleep during the early stages of treatment are detectable using subjective measures, it

should be standard to administer subjective measures of sleep such as the ISI before, during, and after the completion of cancer treatment. By providing patients with self-report measures of sleep, physicians and healthcare providers can receive immediate feedback from patients about their symptoms. In turn, healthcare providers can identify patients that have, or are exhibiting symptoms of insomnia, and intervene to refer patients to appropriate intervention to avoid further decline in sleep quality. By implementing therapies to avoid decline in sleep, patients may also be able to avoid the decline in cognitive functioning that is experienced upon beginning treatment.

The present study revealed unique findings about mood disturbance in women with and without insomnia symptoms prior to beginning treatment. While previous research demonstrated an association between mood disturbance and sleep disruption after patients have begun treatment for cancer (Nishiura et al., 2015; Trill, 2013), we found that women experiencing symptoms of insomnia exhibited significantly more symptoms of depression and anxiety compared to women without symptoms of insomnia prior to starting treatment, and this persisted in the four months following the initiation of treatment. Regardless of insomnia symptom status, women receiving treatment for breast cancer are at risk for developing symptoms of depression during the early stages of treatment (Trill, 2013), but poor sleep appears to convey a greater risk. Since anxiety and depression have been documented as potential factors underlying a patient's sleep disruption (Clevenger et al., 2013; Downie et al., 2006; Trill, 2013), it is especially important to monitor symptoms of mood disturbance in addition to sleep, as mood disturbance may be a potential risk factor for developing sleep disturbance, or vice versa. By identifying patients that exhibit more symptoms of anxiety and depression, health care providers can intervene to provide appropriate treatment/therapy procedures to decrease symptoms of mood

disturbance. In turn, decreasing symptoms of mood disturbance may decrease symptoms of insomnia experienced by patients (Clevenger et al., 2013; Downie et al., 2006; Nishiura et al., 2013).

Our second hypothesis was partially supported, indicating that increases in insomnia severity were associated with worse perceived cognitive ability. Previous research has also shown a relationship between sleep quality and cognitive functioning (Belenky et al., 2013; Gobin et al., 2015; Van Dongen et al., 2003). Other subscales included in our analysis were approaching significance (such as the depression subscale of the HADS and the impact on quality of life subscale of the FACT-Cog V3). It is possible that a relationship between changes in insomnia severity and depression, or the impact that cognitive dysfunction has on quality of life, may be detected with a larger sample. Finally, of note is the significant relationship between the depression subscale of the HADS and all three subscales of the FACT-Cog V3. This finding indicates that as symptoms of depression increase, women experience worsened cognitive performance.

The current study presents many methodological strengths. First, this study provided both subjective and objective measures used to measure cognitive functioning and sleep, whereas many previous studies only included one or the other. By including both measures we were able to provide an objective, measurable component of cognitive function, as well as capture patient's personal experience of change in cognitive functioning and sleep. Second, participants in this study were recruited prior to treatment initiation, whereas many previous studies did not include a baseline assessment in their methodology. By providing a baseline assessment, we were able to determine whether there were any pre-treatment differences between groups of women in our sample. Additionally, providing a baseline assessment allowed us to measure cognitive

functioning, sleep, and mood disturbance before treatment began, as well as provide indications as to how these factors changed during the early stages of treatment. Finally, we rigorously screened for other disorders that could potentially account for changes in cognition, such as Alzheimer's Disease or a history of stroke.

Despite the many strengths this study presents, it is important to acknowledge its potential methodological limitations. Firstly, this study includes a small sample size which could have negatively impacted the power to detect differences. However, even with a small sample size we were able to detect strong signals that cancer treatment negatively impacts sleep, cognition, and mood disturbance during the early stages. Secondly, our study only included four-month follow-up data, whereas many previous studies have included assessments beyond this (such as eight-month, 12-month, and post-treatment follow-up). Though we were unable to include data beyond four months at this time, there will be eight and twelve-month data available in the future as the study continues.

Despite these limitations, the findings of the present study have a number of implications that could potentially help women receiving treatment for breast cancer in the future. Namely, health care providers should screen for symptoms of insomnia, depression, and anxiety prior to beginning treatment, as these symptoms are highly comorbid, have a reciprocal relationship with each other (Clevenger et al., 2013; Savard et al., 2011; Trill, 2013), and may place patients at an increased risk for developing CRCD. Additionally, since our study provided evidence that insomnia symptoms significantly increase during the early stages of treatment, it is important for health care providers to consider implementing sleep therapies as early as possible to avoid a decline in sleep quality, and, in turn, potentially avoid decline in mood and cognitive functioning. Future research should examine the changes in cognition, sleep, and mood

disturbance with longer follow ups and investigate whether sleep quality mediates or moderates the relationship between cancer treatment and CRCD.

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Table 1
Demographic Information

	Total Sample (N = 32)		No Insomnia Symptoms (N = 16)		Insomnia Symptoms (N = 16)		Good vs. Poor Sleepers
	M(SD)	Range	M(SD)	Range	M(SD)	Range	*p*
Age	59.47 (10.36)	38.00-80.00	60.00 (12.17)	38.00-80.00	58.94 (8.54)	44.00-74.00	.777
BMI	31.06 (7.98)	16.97-51.55	29.36 (5.85)	19.13-42.93	32.76 (9.55)	16.97-51.55	.234
# Hours worked per week	12.92 (20.30)	0-55.00	11.56 (21.03)	0-55.00	14.28 (20.13)	0-50.00	.711
Years of Education	14.06 (4.29)	7.00-25.00	14.03 (3.88)	7.00-19.00	14.08 (4.78)	7.00-25.00	.975
Hours of Physical Activity per week	2.68 (2.67)	0-10.00	3.14 (2.62)	0-10.00	2.48 (2.77)	0-9.50	.678

Table 2
Objective Cognitive Measures

	No Insomnia Symptoms M (SD)		Insomnia Symptoms M (SD)		Between (Group)		Within (Time)		Interaction (Group x Time)	
	Baseline	4 Months	Baseline	4 Months	F	*p*	F	*p*	F	*p*
HVLT-R										
Immediate Recall	46.69 (8.15)	45.50 (10.16)	46.13 (9.93)	47.81 (10.28)	.084	.774	.024	.877	.803	.377
Delayed Recall	48.44 (8.02)	44.19 (9.61)	47.06 (9.98)	47.56 (11.83)	.100	.753	1.447	.238	2.321	.138
Retention	51.25 (10.18)	49.88(7.08)	49.63 (9.20)	50.38(9.90)	.047	.830	.026	.874	.297	.590
Recognition	51.50 (6.29)	48.63 (9.60)	47.33 (10.67)	47.20 (10.74)	.923	.345	.735	.398	.611	.441
LNS	11.06 (2.98)	9.94 (2.86)	10.13 (1.36)	9.88 (3.44)	.363	.552	1.740	.197	.705	.408

Table 3
Subjective Cognitive Measures

Measure	No Insomnia Symptoms M (SD)		Insomnia Symptoms M (SD)		Between (Group)		Within (Time)		Interaction (Group x Time)	
	Baseline	4 Months	Baseline	4 Months	F	*p*	F	*p*	F	*p*
FACT-Cog V3										
Perceived Cognitive Impairment	58.89 (11.08)	53.06 (11.08)	50.63 (11.00)	46.31 (11.83)	4.066	.053	13.089	.001	.292	.593
Perceived Cognitive Ability	22.88 (4.81)	19.94 (6.19)	18.88 (5.41)	17.94 (5.74)	2.918	.098	4.780	.037	1.273	.268
Impact on Quality of Life	14.31 (3.61)	13.69 (2.70)	10.38 (5.00)	12.75 (4.52)	5.076	.032	.863	.360	2.537	.122

Table 4
Sleep Measures

Measure	Good Sleepers M(SD)		Poor Sleepers M(SD)		Between		Within		Interaction	
	Baseline	4 Months	Baseline	4 Months	F	*p*	F	*p*	F	*p*
Sleep Diaries										
Sleep Onset Latency	20.40 (14.86)	29.53 (25.40)	34.07 (26.08)	33.80 (25.52)	1.683	.205	.772	.387	.867	.360
Number of Awakenings	2.17 (1.16)	2.22 (1.25)	2.59 (1.06)	2.64 (0.95)	2.684	.266	.111	.741	.001	.982
Minutes Awake	19.60 (16.80)	25.40 (19.69)	52.33 (35.30)	37.47 (30.10)	7.551	.010	.744	.396	3.868	.059
Total Sleep Time (hours)	7.45 (0.91)	7.67 (1.01)	6.57 (1.67)	7.14 (1.51)	2.720	.110	3.153	.087	.622	.437
Time in Bed (hours)	8.76 (0.92)	9.13 (1.18)	8.82 (1.31)	8.97 (0.93)	.017	.896	1.737	.198	.289	.595
Sleep Efficiency (%)	85.20 (7.40)	84.00 (4.44)	73.80 (10.77)	78.93 (10.80)	7.842	.009	2.428	.130	6.295	.018
ISI	3.06 (1.95)	7.69 (6.25)	13.88 (4.84)	15.38 (5.11)	44.352	.000	9.789	.004	2.548	.121

Table 5
Change Score Correlations

	ISI	HADS Depression	HADS Anxiety	FACT-Cog PCI	FACT-Cog PCA
HADS Depression					
r	.263				
p	.080				
HADS Anxiety					
r	-.046	.301			
p	.404	.053			
FACT-Cog PCI					
r	-.181	-.460	-.006		
p	.169	.005	.488		
FACT-Cog PCA					
r	-.391	-.315	.122	.661	
p	.016	.045	.260	.000	
FACT-Cog QOL					
R	-.281	-.307	-.584	.323	.295
p	.066	.049	.000	.041	.057

Acronym definitions. PCI: perceived cognitive impairment, PCA: perceived cognitive ability, QOL: quality of life

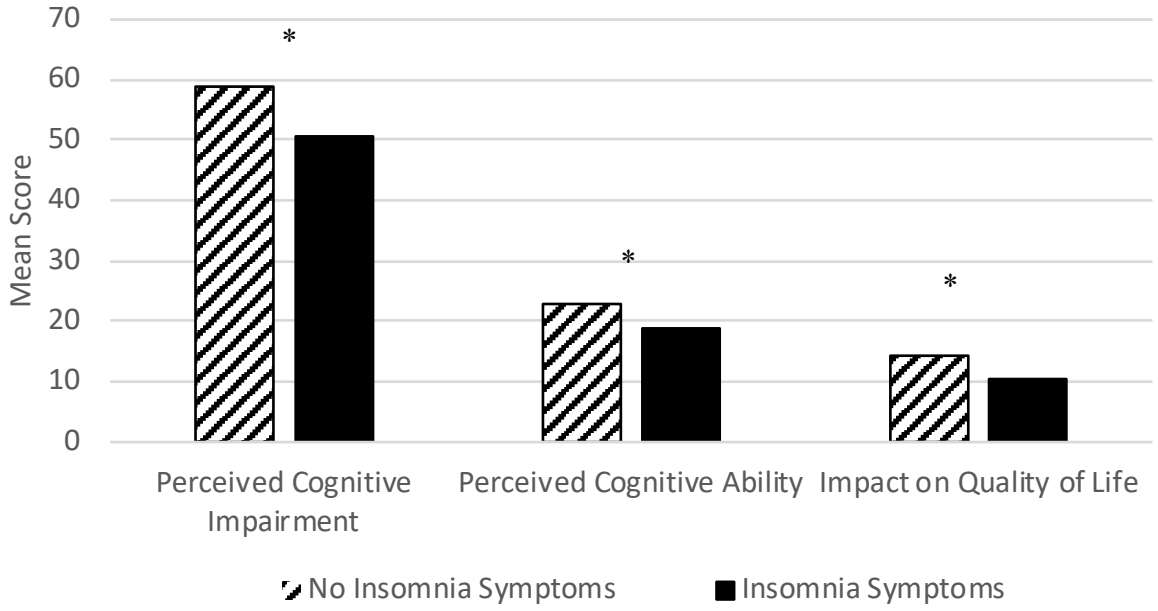

***Figure 1*. Baseline FACT-Cog V3 scores of participants with and without insomnia symptoms, *$p < .05$.**

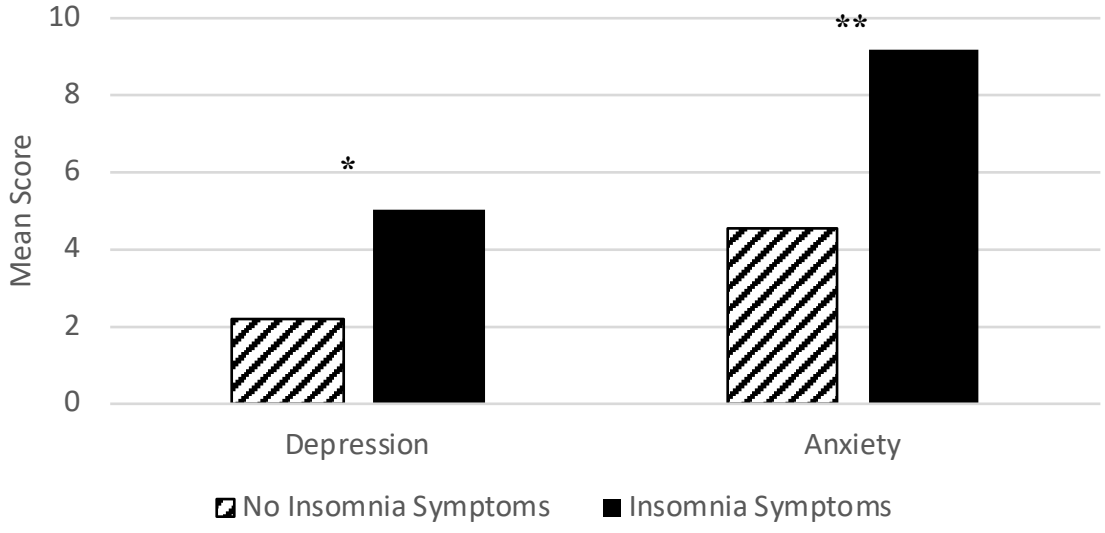

***Figure 2*. Baseline HADS scores of participants with and without insomnia symptoms, *$p < .05$, **$p < .01$.**

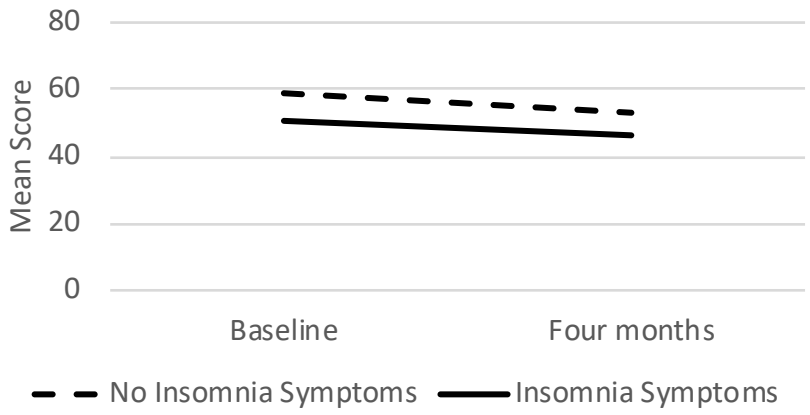

***Figure 3*. FACT-Cog V3 perceived cognitive impairment subscale. both groups had significantly more perceived cognitive impairment four months following the initiation of treatment compared to baseline, $p = .001$.**

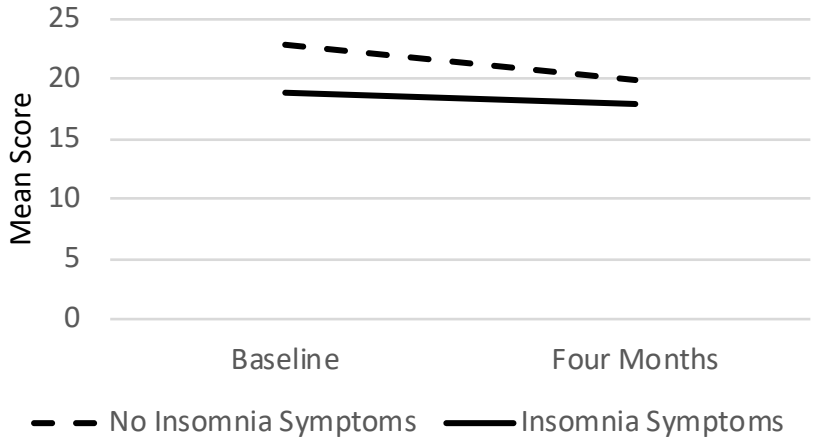

***Figure 4*. FACT-Cog V3 perceived cognitive ability subscale. Both groups perceived less cognitive ability four months following the start of treatment compared to baseline, $p < .05$.**

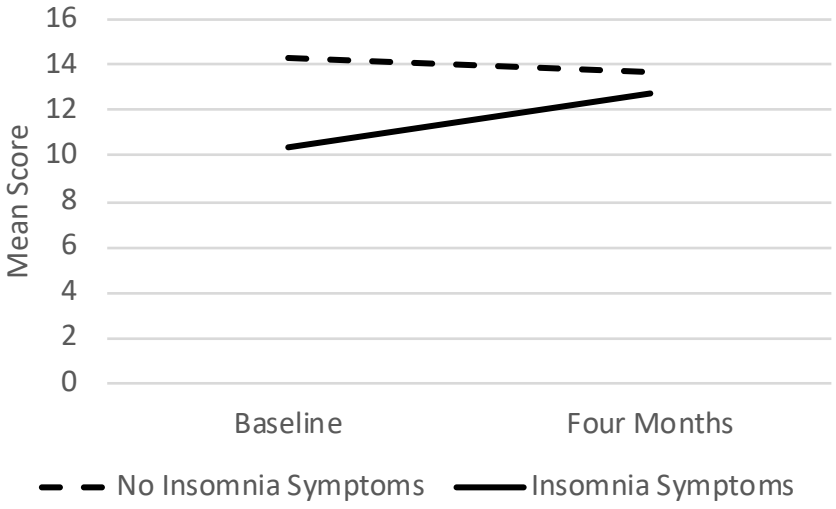

***Figure 5*. FACT-Cog V3 impact on quality of life subscale. Participants without insomnia symptoms indicated that their cognitive impairment had more of an impact on their quality of life compared to those with insomnia symptoms, $p < .05$.**

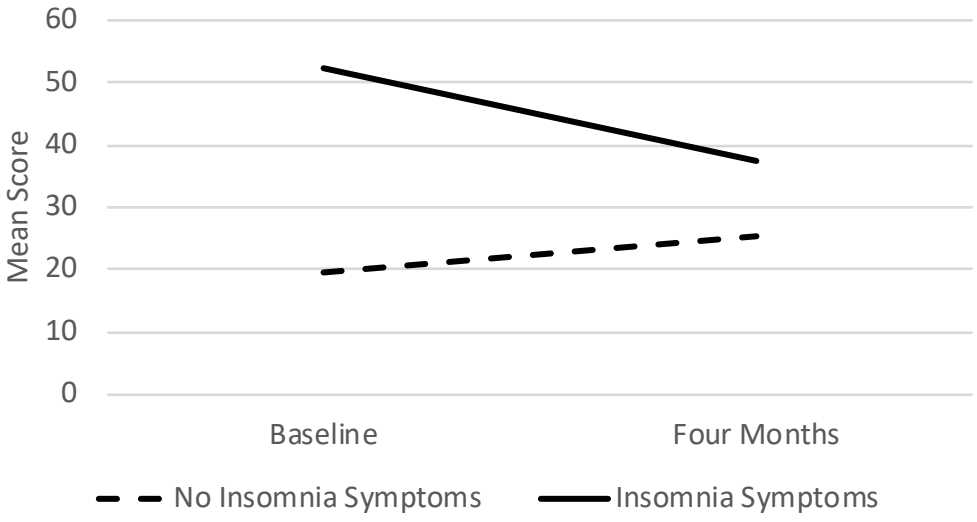

***Figure 6*. Number of minutes awake after sleep onset for participants with and without insomnia symptoms. Participants with insomnia symptoms spent more time awake after sleep onset than those without insomnia symptoms, $p = .010$.**

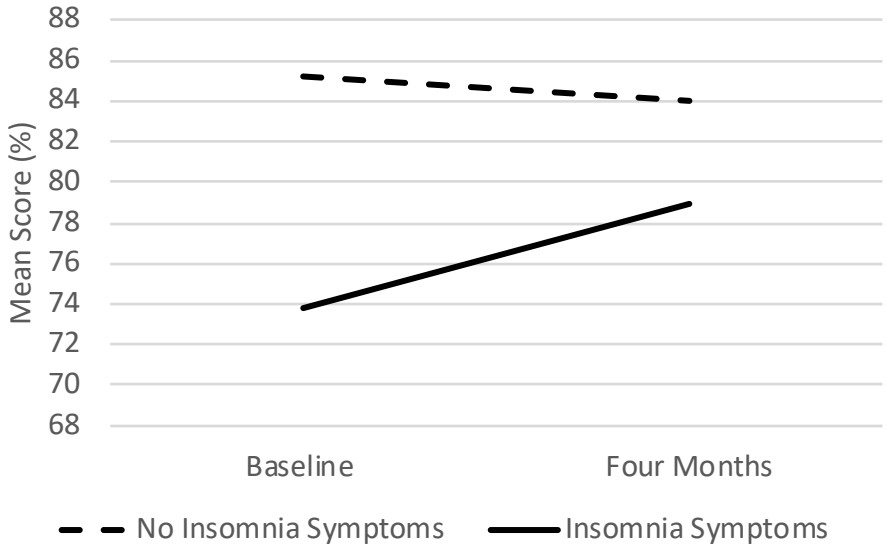

***Figure 7*. Sleep efficiency (%) for participants with and without insomnia symptoms. Participants without insomnia symptoms had a higher sleep efficiency than those with insomnia symptoms, $p < .010$.**

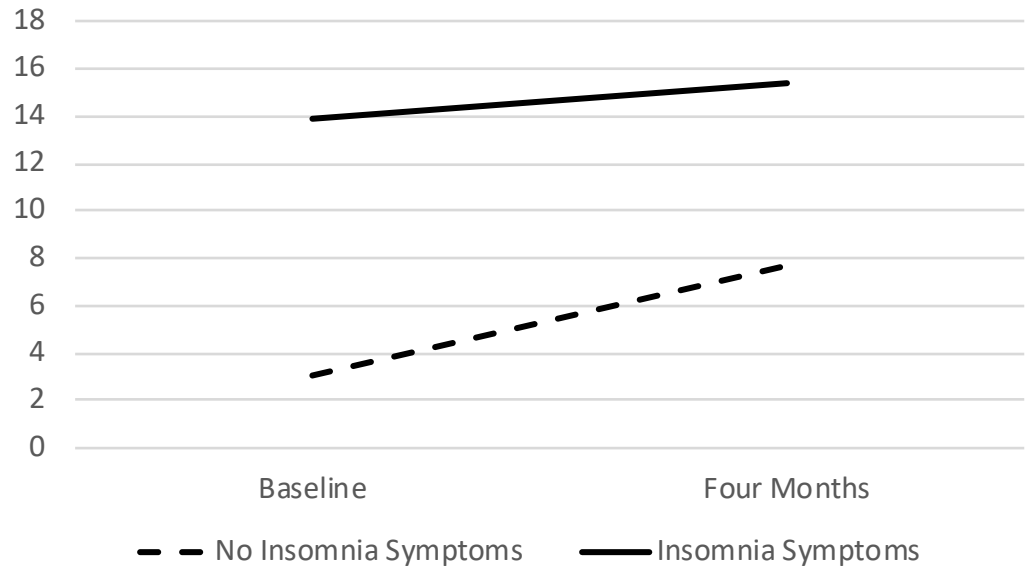

***Figure 8*. ISI scores for participants with and without insomnia symptoms. Participants in the insomnia symptoms group exhibited more symptoms of insomnia than the group without insomnia symptoms, $p < .001$. Both groups experienced more symptoms of insomnia at four months compared to baseline, $p < .005$.**

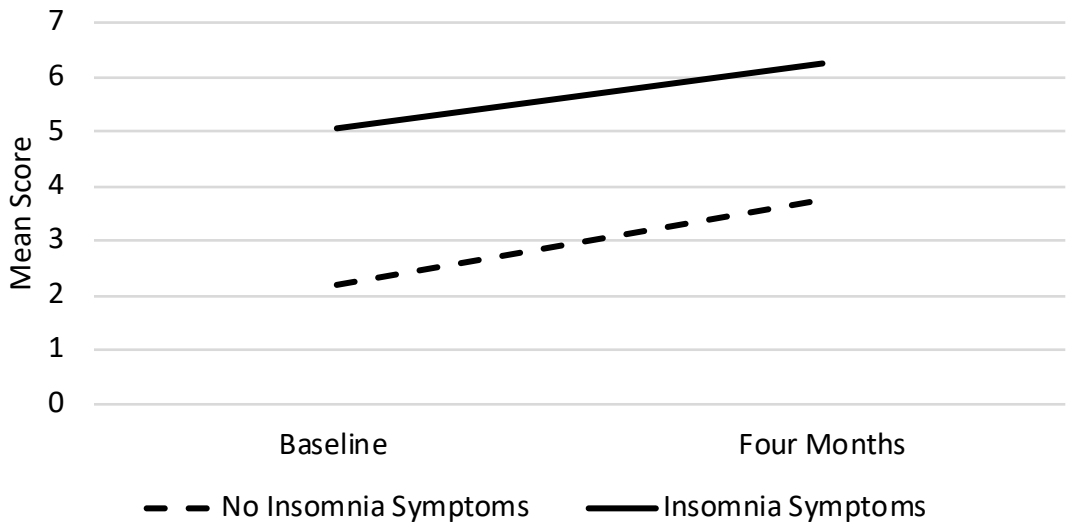

***Figure 9*. HADS depression subscale scores for participants with and without insomnia symptoms. Both groups experienced more symptoms of depression four months following the start of treatment compared to baseline, $p < .01$. Participants with insomnia symptoms exhibited more symptoms of depression than those without symptoms of insomnia, $p < .05$.**

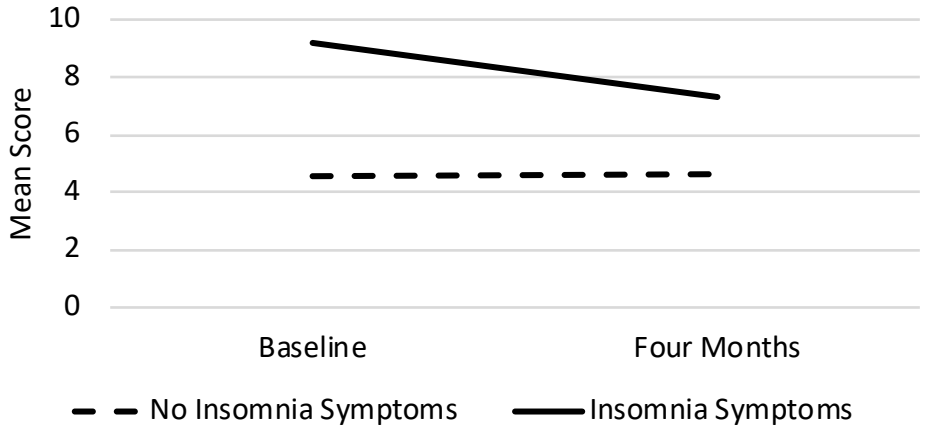

***Figure 10*. HADS anxiety subscale scores for participants with and without insomnia symptoms, participants with insomnia symptoms exhibited more symptoms of anxiety compared to those without insomnia symptoms, $p < .05$.**