THE IMPACT OF EXERCISE ON THE RELATIONSHIP BETWEEN SLEEP QUALITY AND CANCER-RELATED FATIGUE IN CANCER SURVIVOR

by

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Dalhousie University is located in Mi'kma'ki,

the ancestral and unceded territory of the Mi'kmaq.

We are all Treaty people.

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Abstract

Sleep problems have been linked to a variety of factors in cancer survivors (CS), including the disease itself and the treatment. The inability to sleep is strongly associated with cancer-related fatigue (CRF). CRF is a significant concern for CS as it can impair a person's ability to perform their daily life activities. Thus, interventions are needed to improve sleep quality, and thus, reduce CRF. Exercise, has been shown to be an effective non-pharmacologic method for reducing the side effects of cancer treatment, including improving patient-reported sleep quality and reduce CRF independent of one another. However, few studies have studied sleep and CRF together and how this relationship is impacted by exercise. The purpose of this study was to investigate the impact of a 12-week exercise program on the relationship between sleep quality and CRF in CS. The specific objectives were to determine whether the exercise program impacted sleep quality and CRF independently, and whether exercise-induced changes in sleep quality influenced CRF in CS. It was hypothesized that the exercise program would improve sleep quality and thereby decrease CRF. We conducted an analysis of data from the Activating Cancer Communities through an Exercise Strategy for Survivors (ACCESS) study, which included 89 participants that completed the study between September 2018 and March 2020. A paired sample t-test was used to assess the impact of exercise on sleep quality and CRF, while a repeated measure Analysis of Covariance (ANCOVA) was utilized to examine the effect of age and sex on sleep quality and CRF. Additionally, we conducted a correlation analysis to determine if improvements in sleep quality had an impact on CRF and a two-factor mixed ANOVA was conducted to examine the association between PSQI score and change in CRF following the exercise intervention. Study findings indicated that the exercise program had a significant impact in improving sleep quality (p=0.002) and decreasing CRF levels (p=0.001). The two-factor mixed ANOVA results reveal exercise's significant impact on reducing CRF irrespective of sleep quality, although participants with poor sleep quality exhibit higher CRF levels, underscoring the sleep-CRF association. Notably, the exercise intervention proved more effective in lowering CRF for all participants, with a particularly pronounced decrease in those with good sleep quality. These findings underscore the exercise program's efficacy in improving CRF, emphasizing its potential to ameliorate CRF through enhanced sleep quality, particularly for individuals with good sleep patterns. In conclusion, it is crucial to highlight the importance of exercise in improving sleep quality to reduce CRF among CS. It is imperative to conduct further research to explore the lasting effects of exercise on sleep quality and CRF in CS, and to analyze the fundamental mechanisms by which exercise impacts sleep quality and CRF.

List of Abbreviations and Symbols Used

CS - Cancer Survivors

CRF - Cancer-Related Fatigue

WHO - World Health Organization

ACCESS - Activating Cancer Communities through an Exercise Strategy for Survivors

GSQI - Global Sleep Quality Index

PSQI - Pittsburgh Sleep Quality Index

CEP - Clinical Exercise Physiologist

ANCOVA - Analysis of Covariance

QoL - Quality of Life

RCT- Randomized Control Trial

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Chapter 1 Introduction

It is expected that 2 in 5 Canadians will develop cancer sometime during their lifetime (D. Brenner et al., 2021). Due to improvements in the early detection and treatment of cancer, there has been an increase in survival rate (D. Brenner et al., 2021). Regrettably, these treatments can have numerous side effects, such as sleep disturbances and fatigue (Johdi & Sukor, 2020a; Santos & Pyter, 2018). While some side effects are acute and short-lived, others linger and become chronic, while others may appear months or years after therapy is completed (DeSantis et al., 2014a).

Poor sleep, which includes sleep disturbances and/or sleep disorders (e.g., insomnia), is a common side effect among cancer survivors (CS) (Büttner-Teleagă et al., 2021; Mogavero et al., 2021; Strik et al., 2021). Poor sleep is the inability to get enough quality or quantity of sleep to maintain reasonable levels of alertness, performance, and health (Clark et al., 2004a). Poor sleep is the second most bothersome side effect in CS and studies have shown that it affects 20% to 78% of CS (Mogavero et al., 2021). The prevalence of sleep disturbances is markedly higher in CS in comparison to what is reported in the general population, 15% to 25% (Endeshaw et al., 2022). Getting a sufficient amount of sleep is an important part of maintaining health as it plays a vital role in maintaining mental and physical well-being (Franken et al., 2009a). Studies have shown that poor sleep can have negative health consequences, such as decreased physical and psychological functioning, mood, and health-related quality of life (QoL) as well as increased symptom distress (Cleeland et al., 2013a). Additionally, poor sleep has been linked to poor healing, increased pain, and risk of cancer recurrence, reduced cognitive functioning, decreased work productivity, increased safety concerns, drug misuse and abuse, poor relationships, and higher healthcare expenses (Carpenter et al., 2004a; Cheung et al., 2016a; Cleeland et al., 2013a; C. Engstrom et al., n.d.; Franken et al., 2009a).

Poor sleep also has been identified as a potential contributor to cancer-related fatigue (CRF). CRF is a significant side-effect of cancer therapy, affecting physical, mental, and emotional functioning (Campos et al., 2011). CRF is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion that is unrelated to recent activity and interferes with normal function (Curt, 2000). CRF is prevalent in CS and has a significant negative impact on QoL (Ma et al., 2020; Thong et al., 2020). The prevalence of CRF varies, depending on whether it is assessed during active treatment or after treatment is completed (Ma et al., 2020). CRF rates among CS receiving active treatment range from 62% to 85%, with 9% to 45% of those reporting moderate-to-severe CRF. Between 21% to 52% of CS continue to experience severe CRF up to three years after diagnosis. In the long-term (> 3 years), 23% to 49% of CS report chronic CRF (Ma et al., 2020). It's important to recognize that there is a strong correlation between poor sleep and CRF. When sleep quality declines, CRF levels

tend to increase (Charalambous et al., 2019a). This suggests that poor sleep may have a direct impact on CRF in CS. Therefore, improving poor sleep may represent an intervention that can be used to reduce CRF in CS.

Pharmacotherapy is the most widely used treatment to improve sleep in both the general population and CS (Savard & Morin, 2001). However, sleep medications can have significant side effects, including drowsiness, dizziness, headache, cognitive impairment, loss of motor coordination, and risk of dependency (Cheung et al., 2016a; Mercier et al., 2017a; Savard & Morin, 2001). As a result of the potential side effects, many CS prefer not to take sleep aid medications (Mercier et al., 2017). Thus, many CS seek non-pharmacological interventions (Mercier et al., 2017a). An expanding amount of evidence has shown that exercise has a positive effect on CS sleep (Campbell et al., 2019; Courneya et al., 2014a; Mercier et al., 2017a). Therefore, exercise represents a potential intervention to improve sleep quality and subsequently reduce CRF, providing a comprehensive approach to addressing the side effects of cancer survivorship.

Unfortunately, limited research has been conducted to examine the impact of exercise on the relationship between poor sleep and CRF. Furthermore, of the studies that have been published the results are inconsistent (Al-Majid & Gray, 2009; Linden & Satin, 2007; Puetz & Herring, 2012; Rogers, 2012; Speck et al., 2010). For example, one study found that in individuals with high- and low-grade glioma, that those with low exercise tolerance had more sleep disturbances and higher levels of CRF in comparison to those with high tolerance to exercise (Miklja et al., 2022). Similarly, Berger (2009) reported that CS that were inactive during the day had experienced more restless sleep and more intense fatigue compared to those that were active. Interestingly, studies that have used exercise interventions to improve sleep and CRF together have reported that while exercise improves one of the variables, it did not have a significant impact on the other variable (Coleman et al., 2012; Dodd et al., 2010). For example, one study found that 15 weeks of aerobic and strength resistance training exercise had no impact on CRF in CS. In fact, the CS became significantly progressively more fatigued, and experienced a decline in performance as the intervention progressed but experienced improved sleep (Coleman et al., 2012). Similarly, another study showed that a home-based exercise program did not improve either sleep or CRF in CS (Dodd et al., 2010). Thus, more research is needed to understand the relationship between exercise, sleep, and CRF.

This study aims to address the above gap in the literature which is to investigate the impact of exercise on the relationship between poor sleep and CRF. Specifically, the purpose of this study is to determine whether a 12-week tailored exercise program for CS affects the relationship between sleep quality and CRF. The objectives of the study determined if: 1) the exercise intervention improves sleep quality in CS; 2) the exercise intervention improves CRF in CS; 3) age and sex have impact on sleep quality and CRF; and 4) there is correlation between sleep quality and CRF such that exercise-induced changes in sleep quality influence CRF in CS. It was hypothesized that engaging in an exercise program would enhance both sleep quality and CRF, with age and sex potentially

influencing their level. Additionally, a correlation between sleep quality and CRF was hypothesized, suggesting that improved sleep could lead to a significant decrease in CRF.

Chapter 2 Literature Review

Sleep in the General Population

Good sleep is when a person falls asleep quite easily, does not fully wake up during the night, does not wake up too early, and feels refreshed, rested, and restored in the morning (Franken et al., 2009a). Good sleep, plays a vital role in maintaining mental and physical well-being (Franken et al., 2009a). Getting enough sleep makes one feel and function better in every way. It leads to improvements in productivity, better immune function, blood pressure, and cholesterol levels (Xie et al., 2013). To obtain these benefits it is recommended that individuals obtain a minimum of 7 hours of sleep each night to maintain optimal health.

Regrettably, in the United States, a substantial portion of the population experiences poor sleep patterns. Poor sleep is often defined as a dissatisfaction with sleep quantity or quality. Poor sleep is characterized as at least 3 months of difficulty in initiating and/or maintaining sleep, frequent awakenings or problems returning to sleep after waking (De Crescenzo et al., 2022). This can result in sleepiness and/or hyperactivity during the waking period (De Crescenzo et al., 2022). Specifically, approximately one-third of the population sleeps less than 7 hours per night on average, with 50% sleeping less than 6 hours each night, and 10% obtaining less than 5 hours of sleep nightly (Grigg Damberger & Ianakieva., 2017). Several studies have shown that poor sleep or lack of sleep can negatively impact bodily processes and thus impact health (Carpenter et al., 2004a; C. Engstrom et al., n.d.; Medic et al., 2017; Mogavero et al., 2021). Research indicates that individuals who consistently sleep less than 7 hours hours per night are more prone to experiencing weight gain. Conversely, those who achieve an average of 7 hours of sleep per night tend to have lower relative body fat compared to individuals with shorter sleep. (Doo & Kim, 2017; Kohatsu et al., 2006a; Medic et al., 2017). Sleeping five or fewer hours per night increases the risk of heart attack by 90 % (Nagai et al., 2010). Similarly, it has been reported that consistently losing a full six hours of sleep per night over an extended period of time is associated with an increased risk of developing type 2 diabetes. (Tasali et al., 2008; Knutson et al., 2016; Gottlieb et al., 2005). Lack of sleep also can lead to elevated stress levels increased risk of stroke, and death (Chatto et al., 2018). In fact, over 100,000 deaths world-wide are attributed to poor sleep each year. Furthermore, poor sleep has been linked to poor healing by the weakening of the immune system and increased pain or discomfort caused by the presence of disease and its treatment (Cheung et al., 2016a). More so, it can lead to an increase the risk of cancer, reduced cognitive functioning, decreased work productivity, increased risk of accidents, drug misuse and abuse, poor relationships, and higher healthcare expenses. Together, the adverse effects of lack of sleep can lead to morbidity as well as the reduction of health-related QoL (Carpenter et al., 2004a; Cleeland et al., 2013a; C. Engstrom et al., n.d.; Franken et al., 2009a; J, 2001).

Poor Sleep in Cancer Survivors

Poor sleep is a common side effect among CS (J, 2001). The prevalence ranges from 20% to 78% across a variety of CS (Endeshaw et al., 2022). Poor sleep in CS includes difficulty falling asleep and/or staying asleep, waking up early, obstructive sleep apnea, restless legs syndrome, periodic limb movement disorder, and excessive daytime sleepiness (Clark et al., 2004a). Poor sleep may be an acute issue or may become chronic, lasting months or years after cancer treatment has ended (Büttner-Teleagă et al., 2021; Mogavero et al., 2021; Strik et al., 2021). Sleep is impacted by a range of factors in CS, including biochemical changes related to neoplastic growth and anticancer therapy, as well as symptoms that commonly accompany cancer, such as pain, fatigue, anxiety, and depression (Roscoe et al., 2007a). Several studies have found that poor sleep among CS is correlated with fatigue, frustration, aggression, and reduced pain tolerance (Engstrom et al., 2022). Sela et al. (2005) found that 72% of advanced CS had sleep difficulties and the most prevalent complaints were having trouble getting to sleep (40%), staying asleep (63%), and not feeling rested in the morning (72%). Similarly, a sleep study conducted by Ashraf and colleagues (2021) showed that 70% of patients on treatment (n=212) had trouble getting asleep, remaining asleep, or waking up too early. In addition, Sixty-five percent (n=202 patients) were reported to snore or stop breathing while sleeping, which also impacts sleep quality (Ashraf et al., 2021a). It is evident that poor sleep is highly prevalent among CS, putting CS at risk of the adverse effects associated with poor sleep. Thus, it is important to address sleep disturbances and promote healthy sleep habits in CS to mitigate the potential adverse effects on their overall well-being and health outcomes.

Cancer-Related Fatigue in the Cancer Survivor

CRF is a prevalent symptom in the CS population. It is a complex phenomenon with a direct negative impact on one's QoL (D'Silva et al., 2022a). CRF is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that significantly interferes with usual functioning (Ebede et al., 2017a). Fatigue also is an umbrella term for a variety of symptoms, including muscle weakness and lack of energy, which are common in CS (Herschel et al., 2022). CRF can negatively affect physical and emotional health, leading to depression and anxiety disorders as well as poor performance at work or school and social isolation (Charalambous & Kouta, 2016). Furthermore, fatigue experienced at least six months after cancer treatment is linked with decreased cognitive performance (Joly et al., 2019). Several studies have shown that fatigue experienced after cancer treatment is correlated with a lower overall QoL, (Bower 2014; Karthikeyan et al., 2012; Kim et al., 2019; Mustian et al., 2012). Other evidence indicates that while fatigue can affect anyone after cancer treatment, it may be more problematic for older adults that have experienced cancer (Karthikeyan et al., 2012). Since CRF can significantly impact the health of CS it is necessary to understand factors that contribute CRF and how to manage it in order to help CS maintain their health and QoL.

One of the factors shown to influence CRF is poor sleep. The relationship between sleep, CRF, cancer treatment, and health outcomes is complex (Weber & O'Brien., 2016). A study showed that of approximately 60% of CS report severe daytime fatigue; 55% experienced severe insomnia; 20% experienced hypersomnia; and 10% experienced both insomnia and hypersomnia (Maski et al., 2017). Several studies have reported a correlation between sleep and CRF in CS; specifically, studies have shown that those who suffer from the most severe cases of insomnia also typically suffer from severe levels of CRF, while those with milder levels of insomnia may experience less severe CRF (Ancoli et al., 2001; Zhu et al., 2021). Research has also shown that poor sleep is strongly correlated with CRF such that poor sleep is more severe in fatigued CS (Humpel & Iverson, 2010a; Rogers et al., 2014a; Roscoe et al., 2007a). It has also been shown that people with more restorative sleep experience significantly less fatigue than those who reported being woken during the night by noise or by other factors (Arnal. et al.,2015). While CS who experience fatigue reported sleeping approximately 6.5 hours a night, studies suggest that most CS need at least 8 hours of sleep each night to achieve optimal QoL (Fox et al., 2019). As CRF represents a major challenge for many CS, efforts are needed to develop and evaluate interventions that can effectively reduce the CRF burden. One potential way to reduce CFR during and after cancer treatment is to improve sleep.

Medications to Improve Sleep

Medications are the most frequently used intervention to treat poor sleep. For example, CS who were identified as poor sleepers based on the Global Sleep Quality Index (GSQL- a measure of global sleep quality from the Pittsburgh sleep quality index (PSQI) reported using sleep medication 59% of the time in the previous month and 30% used sleep medication at least 3 times per-week (Lowery-Allison et al., 2018). Similarly, it has been reported that 37% of women with metastatic breast cancer that experience sleep disturbances have used sleep medications in the previous 30 days (Koopman et al., 2002). Several different medications, as well as natural products such as melatonin, are used to treat sleep disorders in CS. However, it is important to note that while these medications may provide relief, they can also be associated with negative side effects such as: (1) drowsiness and diminished motor skills; (2) potential drug interactions with other medications; (3) cardiac side effects; (4) anticholinergic side effects (such as dry mouth); (5) suppression of rapid eyes movement sleep; (6) rebound sleep problems; and (7) cognitive impairment. In addition to the potential side effects mentioned, it is worth noting that melatonin supplementation may have some limitations even as a natural product. One issue is the lack of regulation and standardization in the production of melatonin supplements, which can lead to variations in potency and quality which is harmful (Altun & Ugur-Altun, 2007). Furthermore, melatonin may not be suitable for everyone, particularly individuals with specific medical conditions or those taking certain medications such as diabetes medication. This is due to the potential impact it may have on their blood sugar levels. (Gooneratne, 2008).

The primary classes of the medications to manage sleep disorders include, but are not limited to, 1) non-benzodiazepines; 2) benzodiazepines; and 3) anti-Parkinsonian medications. Non-benzodiazepines are a first-line drug therapy for sleep disorders and improve the onset and duration of sleep (Wu A et al., 2020). While these drugs can improve the onset and duration of sleep, they have adverse side effects which include the next-day hangover of residual drowsiness, dizziness, and ataxia as well the risk of dependence and abuse (Bond et al., 2012). Other side effects include parasomnias and vivid dreams (Wu A et al., 2020). Benzodiazepines are widely used sedative-hypnotics (Pagel et al., 2018). They produce drowsiness which promotes the onset and maintenance of a state of sleep (Trevor, 2021). However, individuals can develop a tolerance to the medication as well as dependence (Pagel et al., 2018) Anti-Parkinsonian medications (dopamine agonists), such as gabapentin enacarbil (Horizant), pramipexole (Mirapex), ropinirole (Requip), and rotigotine (Neupro) are used to treat restless legs syndrome and periodic limb movement disorder (also called nocturnal myoclonus syndrome) (Trevor, 2021). Risks include the potential for addiction, which makes this medication unsuitable for long-term use, as well as the high degree of rebound poor sleep associated when the medication is stopped (Roehrs & Roth, 2010). So, although each type of medication has the potential to improve sleep, there are also significant downsides to their use. Thus, more non-pharmacological interventions are required to improve sleep.

Exercise Intervention on Sleep Problems

Exercise is a non-pharmacological intervention that has been shown to have a positive impact on sleep (Cramp & Byron-Daniel., 2012; Eyigor., 2014). According to Campbell. (2019) on the exercise guidelines for CS, there was strong evidence that low to moderate aerobic exercises which includes walking as well as resistance exercises is beneficial to improve sleep quality in CS(Campbell et al., 2019) . Similar to that, a meta-analysis conducted by Chiu and colleagues (2015) found that a moderate intensity exercise intervention (e.g., walking) significantly improved sleep in all cancer and breast CS (Chiu et al., 2015). Other research has shown that regardless of treatment status, aerobic and strength exercises can improve CS sleep (Kwekkeboom et al., 2010). Insomnia, poor sleep quality and short sleep durations are the most common problems seen in cancer survivors. More studies are needed about sleep disorders in cancer patients. In our study, we aimed to investigate the prevalence of sleep disorders and the impact of these problems on the quality of life in cancer patients. Pittsburgh Sleep Quality Index (PSQI) was given to a total of 314 patients. The psychometric evaluation of the Turkish version of PSQI in cancer patients revealed that 127 (40.4%) patients had global PSQI scores >5, indicating poor sleep quality. There was no statistically significant relationship between PSQI scores and sexuality, marital status, cancer stage and chemotherapy type ($p > 0.05$); while the patients with bone and visceral metastasis had much lower PSQI scores ($p = 0.006$). Patients with Eastern Cooperative Oncology Group performance scores of 3 or more had also significantly lower PSQI scores ($p = 0.02$). Also, CS who completed 12 weeks of a twice-weekly exercise program (90-minutes/session), that included resistance and aerobic exercise, reported improved sleep (Rajotte et al., 2012a). Furthermore, as little as 20 minutes of moderate intensity walking, four times per week, has been shown to improve

sleep in CS (Payne et al., 2008). It also has been shown that moderate to vigorous exercise in the evening, at least three times per week, a minimum of 20 minutes per session, may help ease nighttime symptoms associated with poor sleep, such as waking up in the middle of the night (Wang & Boros, 2019a). Thus, a growing body of evidence suggests that exercise might be an effective non-pharmacological intervention to improve the quantity and quality of sleep in CS who experience insomnia as a result of their cancer treatment (Dolezal et al., 2017).

Impact of Exercise on Cancer-Related Fatigue

The impact of exercise on CRF has been the subject of extensive research, aiming to explore the potential benefits of exercise interventions on CRF in CS. Unfortunately, the findings have been inconsistent (Zhang et al., 2023). Some studies have reported significant reductions in CRF following exercise interventions, for example Engaging in moderate-intensity aerobic training three times per week for training programs lasting at least 12 weeks has been shown to significantly reduce cancer-related fatigue during and after treatment. Additionally, combining moderate-intensity aerobic and resistance training two to three times per week, or engaging in twice-weekly moderate-intensity resistance training, can also be effective, with the strongest impact observed for moderate- to vigorous-intensity exercise; however, the effect of low-intensity training on fatigue reduction is limited (Campbell et al., 2019) while others have found no significant improvements (LaVoy et al., 2016). In a meta-analysis conducted by Rogers et al. (2012), exercise interventions were found to be effective in reducing CRF. However, only half of the included exercise trials demonstrated a significant reduction in fatigue, indicating that exercise may not be universally beneficial for all CS (Rogers, 2012). This can be attributed to the heterogeneous nature of CS, individual differences in severity and response, potential exacerbation of symptoms like post-exertional malaise, varying psychological factors, and the complexity of underlying mechanisms, highlighting the need for personalized treatment approaches. Similarly, Speck et al. (2010) conducted a meta-analysis and reported that while exercise interventions had a small to moderate effect on reducing CRF, not all participants experienced a decrease in fatigue following the exercise intervention. The inconsistency between studies may be attributed to various factors, including variations in the assessment tools used to measure CRF, differences in exercise protocols and prescriptions, variations in baseline fatigue levels, and the failure to tailor interventions based on the multifactorial biobehavioral mechanisms underlying fatigue such as sleep disorder, medication and treatment and other lifestyle factors and habit (Al-Majid & Gray, 2009; Linden & Satin, 2007; Puetz & Herring, 2012). To enhance the effectiveness of exercise as a treatment for CRF, it is crucial to consider the choice of CRF measurement tools. Different assessment tools may capture different dimensions of CRF, and the selection of an appropriate tool can influence the outcomes of exercise interventions. Moreover, understanding the underlying mechanisms through which exercise impacts fatigue is essential. By identifying the most influential mediators (sleep) of exercise effects on fatigue, interventions can be tailored to target these specific factors, potentially leading to more favorable outcomes. Despite the inconsistencies in the literature, exercise is still recommended as a potential treatment option for CRF following a cancer diagnosis. The American Society of Clinical Oncology (ASCO) recommends exercise

for reducing CRF in CS, emphasizing the importance of individualized exercise prescriptions and the consideration of patient preferences and capabilities (K. Mustian et al., 2012).

Exercise Intervention on Poor sleep and Fatigue

Numerous studies have investigated the relationship between poor sleep and CRF, highlighting the strong correlation between the two (Ancoli et al., 2001; Roscoe et al., 2007a). Exercise has been recognized as a non-pharmacological intervention for improving sleep in the general healthy population (Rock et al., 2020) and shows potential benefits for reducing poor sleep in CS as well (Humpel & Iverson, 2010a). Additionally, research has revealed that lower physical activity levels during the day are associated with restless sleep and more severe fatigue (A. M. Berger, 2009a). However, limited studies have specifically examined the impact of exercise on both poor sleep and fatigue concurrently, highlighting a gap in the literature. A few studies have explored the effects of exercise on poor sleep and fatigue. One study identified psychosocial factors as predictors of fatigue response, while biobehavioral factors which is the physiological and behavioural or lifestyle components that influence fatigue mediated and enhanced intervention effects on CRF (Rogers et al., 2014a). Another study investigated the mediating role of exercise in the relationship between sleep quality, fatigue, and QoL, showing that exercise partially mediated the relationship between sleep quality and QoL, as well as between fatigue and QoL (Wu et al., 2019). However, these studies did not comprehensively analyze the biobehavioral mediator (sleep disorder) of exercise effects on fatigue, indicating the need for further research in this area. The current study aimed to investigate the impact of exercise on the relationship between sleep quality and CRF in CS. The specific objectives of the study were to determine if: 1) the exercise intervention improved sleep quality in CS; 2) the exercise intervention improved CRF in CS; 3) age and sex have impact on sleep quality and CRF; 4) there was correlation between sleep quality and CRF such that exercise-induced changes in sleep quality influence CRF in CS. It was hypothesized that engaging in an exercise program would enhance both sleep quality and CRF, with age and sex potentially influencing their level. Additionally, a correlation between sleep quality and CRF was hypothesized, suggesting that improved sleep could lead to a significant decrease in CRF. Understanding the impact of exercise in the relationship between sleep quality and CRF has important implications for developing effective interventions to alleviate fatigue in CS. Exercise interventions can be tailored to effectively target sleep problems and reduce CRF in individuals with CS.

Chapter 3 Methodology

Study Design and Procedures

This study used data from the Activating Cancer Communities through an Exercise Strategy for Survivors (ACCESS) dataset to investigate the impact of a 12-week exercise intervention (aerobic, resistance and mobility) on the relationship between sleep quality and CRF. ACCESS is an implementation-effectiveness study, that delivers an evidence-based exercise program designed to help CS address the physical, psychological, and social effects of a cancer diagnosis and its associated treatments. The study data was collected between September 2018 and March 2020. Outcome measures were assessed pre- and post-intervention. The ACCESS study is a registered clinical trial NCT03599843 and approved by the Nova Scotia Health Research Ethics Board ROMEO File #: 1023682. All participants consented to participate in the study.

Participants that enrolled in the study completed a standardized set of questionnaires at baseline designed to assess sociodemographic characteristics, health status, disease history, lifestyle behaviors, sleep and CRF. The same set of questionnaires, minus the sociodemographic questionnaire, were completed again at the end of the intervention. Participants also underwent a pre- and post-intervention fitness evaluation, but that data was not used in this thesis. Once enrolled in the study participants attended a 12-week, twice weekly (~60 minutes/session) exercise program which included aerobic, strength, balance, and flexibility exercises. To accommodate the clinical population and maintain program adherence, participants in this study were given flexibility regarding attendance (e.g., missing and making up exercise sessions, completing more than 2 exercise sessions/week). Therefore, some participants completed the intervention is less than 12 weeks, whereas others took longer than the 12-weeks to complete. All participants that completed the intervention attended 24 exercise sessions in total. The tailored exercise program for each participant was developed Clinical Exercise Physiologist (CEP) based on their medical history and pre-intervention fitness testing. The CEP and/or trained staff supervised the program. Each exercise session began with a warm-up and ended with a cool-down. All exercise session were completed in a fitness facility located in a hospital setting or at a community partner facility.

Participants

Inclusion & exclusion criteria

To be eligible to participate in the ACCESS study individuals had to: (1) have received a cancer diagnosis; (2) be 18 years or older; (3) be able to participate in low to moderate levels of physical activity (at a minimum); (4) be pre-treatment, receiving active treatment, off-treatment or have received a cancer diagnosis within the last 5 years or have late occurring/ongoing side-effects as a result of the cancer diagnosis (e.g., fatigue); (5) have the

ability and willingness to participate in a twice-weekly in-person fitness program; and (6) provide written informed consent in English.

Participant Recruitment

Participants were recruited for the study through various methods, including self-referral and referrals from healthcare providers, using strategies such as posters and information sessions conducted with nurses and doctors in the Halifax Region Municipality in Nova Scotia.

Outcome Measures

Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI) (Akman et al., 2015). The PSQI is a 19-item self-report questionnaire evaluating sleep quality and quantity among adults. It consists of 19 questions evaluating the following 7 domains: subjective sleep quality (1 question), sleep latency (2 questions), sleep duration (1 question), habitual sleep efficiency (3 questions), sleep disturbances (9 questions), use of sleep medication (1 question) and daytime dysfunction (2 questions) as described in the Appendix B. Each question had a response scale with scores ranging from 0 to 3, where 0 is 'not during the past month', 1 'less than once a week', 2 'once or twice a week', and '3 or more times a week'. Using the question responses, a global subjective sleep quality score between 0 and 21 is calculated by adding the scores from all components as described in Appendix A. Higher scores indicate poorer sleep quality and a high level of sleep disorders. A global score of >6 is a clinical indicator that a patient's sleep quality is poor. The PSQI is a widely used assessment tool for evaluating sleep quality and has demonstrated high diagnostic sensitivity and specificity in various research studies (Agargun, 1996; Akman et al., 2015; Buysse et al., 1989). The diagnostic sensitivity of the PSQI refers to its ability to accurately identify individuals who have sleep problems or poor sleep quality. With a sensitivity of 89.6%, the PSQI demonstrates a high level of accuracy in correctly detecting individuals who are experiencing sleep difficulties. On the other hand, the diagnostic specificity of the PSQI indicates its ability to correctly identify individuals who do not have sleep problems or poor sleep quality. The PSQI shows a specificity of 86.5%, suggesting that it can effectively distinguish individuals without sleep issues. Thus, the PSQI is a valid and reliable diagnostic tool that can be used to assess sleep quality as described in appendix D.

The Functional Assessment of Cancer Therapy—Fatigue (FACIT-F) was used to assess fatigue. The FACIT-F is a widely used and well-validated measure of CRF in CS and others with chronic health conditions (Cella et al., 2011a). The FACIT-F is a 13-item questionnaire designed to assess self-reported tiredness, weakness, and difficulty performing daily activities due to fatigue. Each item has a graded response: 0, not severe at all; 1, a little bit severe; 2, somewhat severe; 3, quite a bit severe; and 4, very much severe as described in the Appendix C. The 13 items yield a single total score with a possible range of 13 to 52 where higher scores reflect higher levels of fatigue. This

scale has been shown to be valid [content validity (0.86–1.00), criterion-related validity, convergent validity, and consistency reliability (Cronbach's α range, .84–.87) (Tinsley et al., 2011).

Statistical Analysis

For data analysis, the statistical software IBM SPSS Version 28.0.1.1 was utilized. The normality of the data was assessed using Kurtosis and Skewness statistics. The results indicated that the data did not follow a normal distribution. Considering the application of the central limit theorem, which suggests that for a reasonably accurate normal approximation, a sample size of approximately 30 or more is often considered sufficient, as it allows the distribution of sample means to become approximately normal. (Kwak & Kim, 2017) thus parametric statistics were deemed appropriate for analysis. A significance level of $p < 0.05$ was used to determine statistical significance.

Descriptive statistics were calculated for the sample population (mean, standard deviation, frequency, and percentages). Variables included were age, sex, cancer type, income, employment status, education, program adherence, and health status.

For the first objective, paired sample t-tests were employed to assess the influence of exercise on sleep quality and CRF. In the case of sleep quality, the independent variable was exercise, while the dependent variable was the PSQI sleep and CRF score measured pre-and post- intervention. This t-test aimed to discern any significant changes in sleep quality resulting from the exercise program. A repeated measure Analysis of Covariance (ANCOVA) was conducted on sleep quality and fatigue measures to determine if these variables changed over the 12-week of exercise program. Covariates were accessed based on the age and sex of the participants to determine if they have an impact on the effect of exercise on sleep or CRF level of the CS. A two-factor mixed ANOVA was conducted to examine the association between exercise-induced PSQI score and CRF score. The dependent variable is the CRF score, and independent variable is the pre- post PSQI score grouped into good and poor sleep. Correlation analysis using Pearson's correlation coefficient was conducted between change in sleep score and change in CRF to determine if changes in sleep influenced CRF. Effect size (Cohen d) was calculated to quantify the magnitude of continuous variables. Effect size is interpreted as small ($d = 0.2$), medium ($d = 0.5$), or large ($d = 0.8$) (Cohen, 1988). Partial eta-squared (η^2) was also conducted to indicate the effect size of the ANOVA. A larger partial eta-squared value suggests a stronger influence of the independent variable on the dependent variable, with values typically ranging from 0 to 1. In general, a higher value indicates a more substantial effect of the independent variable on the outcome (Richardson, 2011)

Chapter 4 Results

The present study utilized data from 89 CS who completed the ACCESS exercise study between September 2018 and March 2020. Table 1 displays the demographic and medical characteristics of the study sample. Most of the participants were female (68.5%), and the mean age was 60.3+/-10.6 years old (range, 28-85 years). Breast CS comprised the largest proportion of the cohort (38.2%), followed by lymphoma (9%) and colorectal (9%) CS. The majority of the participants self-identified as Caucasian 97.8% and 22.5% of the cohort held a bachelor's degree and 23.6% held graduate degrees. Almost half of the participants were retired 40.4%, whereas only 19.1% still worked full-time. Prior to commencing the ACCESS intervention, 80% of participants reported their health to be good, very good, or excellent, while only 20% reported their health to be fair to poor.

Table 1: ACCESS Participant Characteristics

Variable		N =89	% of the total sample
Sex	Female	n = 61	68.5%
	Male	n= 28	31.5%
Age	18-39	n= 2	2.2%
	40-55	n= 24	27.0%
	56-75	n= 55	61.8%
	76-85	n= 2	2.2%
	Missing	n= 6	6.7%
Cancer Diagnosis	Breast	n= 34	38.2%
	Brain/CNS	n= 4	4.5%
	Colorectal	n= 8	9.0%
	Esophageal	n= 4	4.5%
	Lymphoma	n= 8	9.0%
	Lung	n= 4	4.5%
	Prostate	n= 6	6.7%
	Others	n= 19	21.4%
	Missing	n= 2	2.2%
Marital Status	Married	n= 62	69.7%
	Divorced	n= 11	12.4%
	Never Married	n= 10	11.2%
	Widowed	n= 5	5.6%
	Missing	n= 1	1.1%
Education	Highschool (or less)	n= 13	14.6%
	Trade, technical, or vocational school	n= 7	7.9%
	Diploma from a community college or non-university certificate	n= 15	16.9%
	University certificate below bachelor's level	n= 11	12.4%
	Bachelor's degree	n= 20	22.5%
	Graduate degree	n= 21	23.6%
	Missing	n= 2	2.2%
Employment	Retired	n= 36	40.4%
	On disability leave	n= 27	30.3%
	Full-time	n= 17	19.1%
	Part-time	n= 4	4.5%
	Homemaker	n= 2	2.2%
	Unemployed	n= 2	2.2%
	Missing	n= 1	1.1%
Income	Less than $24,999	n= 6	6.7%
	$25,000-$49,999	n= 18	20.2%
	$50,000-$74,999	n= 8	9.0%
	$75,000-$99,999	n= 20	22.5%
	$100,000-$149,999	n= 18	20.2%
	$150,000-more	n= 10	11.2%
	Prefer not to answer	n= 7	7.9%
	Missing	n= 2	2.2%
Health status	Excellent	n= 2	2.2%
	Very good	n= 24	27.0%
	Good	n= 46	51.7%
	Fair	n= 12	13.5%
	Poor	n= 4	4.5%
	Missing	n= 1	1.1%

To accommodate the clinical population and maintain program adherence, participants in this study were given flexibility regarding attendance. Therefore, participants had to attend 24 sessions to complete the program, which could take longer than the allotted 12 weeks. Participants were permitted to miss sessions due to illness or treatment-related symptoms, and any missed sessions were rescheduled to the end of the program, allowing participants to complete the full 24 sessions. Figure 1 displays the number of weeks it took participants to finish the program. The program's completion time varied between approximately 11 to 38 weeks. More specifically, 11% of participants finished the program in less than 12 weeks while 38% finished it between 13 and 16 weeks, and 47% finished it in 17 or more weeks. On average, participants completed the program over 17 ± 40.94 weeks.

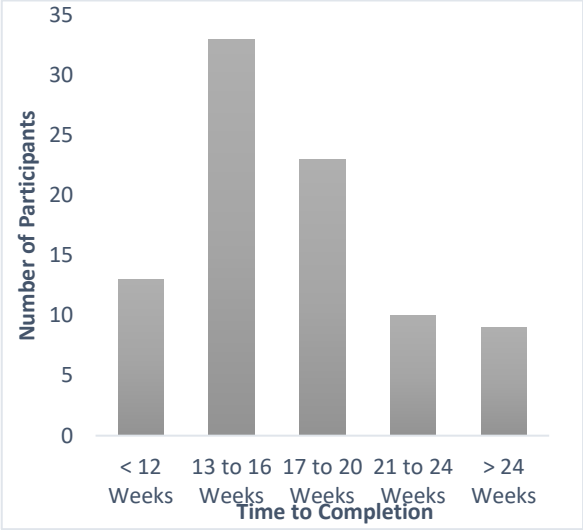

Figure 1: Time required to complete the 24 exercise sessions.

The Impact of Exercise on Sleep Quality

A paired sample t-test was conducted to assess the differences in sleep quality between the pre-intervention and post-intervention phases. The independent variable under investigation was exercise, and the dependent variable comprised the pre- and post-intervention sleep quality scores. The analysis revealed a significant decrease in the PSQI scores from pre-intervention ($M = 6.54$, $SD = 3.09$) to post-intervention ($M = 6.01$, $SD = 3.12$), $t(88) = 2.32$, $p = 0.01$; $d = 0.2$. The graphical representation of the mean PSQI scores before and after the exercise intervention is depicted in Figure 2. These findings indicate a noteworthy enhancement in sleep quality among CS as a result of their participation in the exercise program.

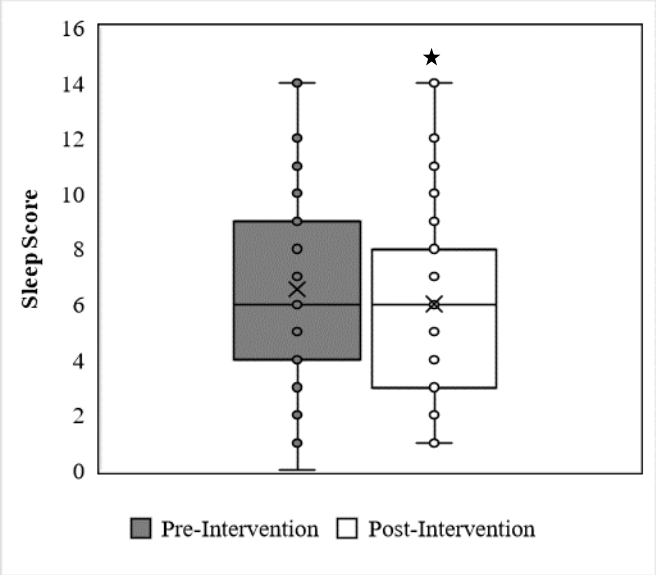

Figure 2: Change in sleep quality before and after the exercise intervention.

The impact of Exercise on Cancer-related Fatigue

A paired sample t-test was employed to compare CRF scores before and after the intervention. The independent variable considered was exercise, while the dependent variable encompassed pre- and post-intervention CRF scores. The analysis demonstrated a statistically significant reduction in CRF scores from pre-intervention ($M = 19.47$, $SD = 9.15$) to post-intervention ($M = 16.70$, $SD = 8.53$), $t(88) = 3.42$, $p < 0.001$; $d = 0.4$. This decrease in CRF scores suggests a meaningful improvement in CRF following the exercise intervention. The graphical depiction of the mean CRF scores before and after the exercise intervention is presented in Figure 3. These findings suggest that

participation in the exercise program led to a notable reduction in CRF in CS.

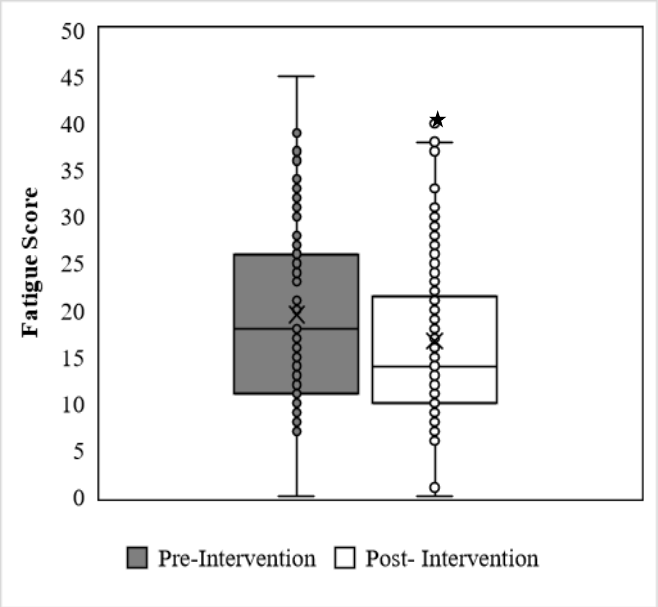

Figure 3: Change in CRF level before and after the exercise intervention.

Relationship between Sleep Quality and Cancer-related Fatigue

A Pearson correlation analysis was performed to explore the relationship between sleep quality and CRF among CS. The objective was to ascertain whether changes in sleep quality were associated with changes in CRF scores from pre to post intervention. To this end, the analysis utilized the difference between pre-intervention and post-intervention scores for both sleep quality and CRF. The results of the Pearson correlation analysis revealed a significant positive correlation between sleep quality and CRF $r(87) = 0.31$, $p = 0.004$. This indicates that as sleep quality improved, there was a corresponding improvement in CRF. Figure 4 graphically illustrates the relationship between sleep quality and CRF, depicting how changes in sleep quality are linked to changes in CRF.

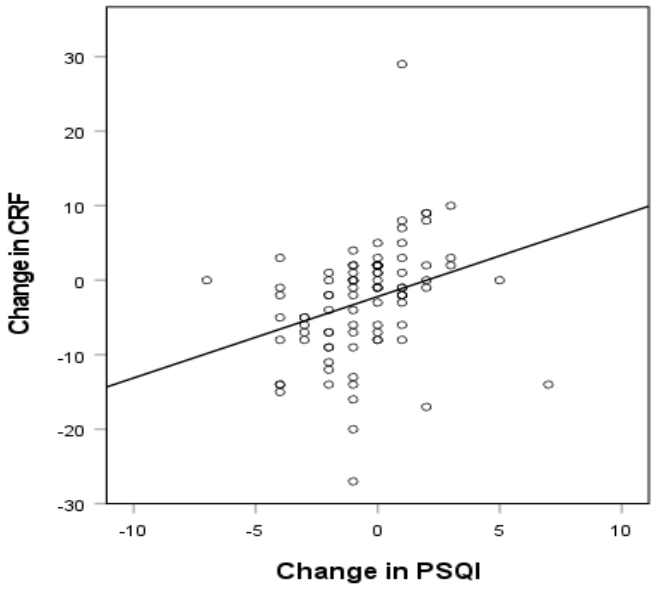

Figure 4: Correlation between sleep quality and CRF

Factors Affecting Sleep Quality and Fatigue

A repeated measure ANCOVA was conducted to examine the relationship between sleep quality, age, and sex of the participants post intervention. The analysis indicated that the main effect of exercise was statistically significant, $f(1, 84) = 1.53$, $p = 0.03$, $\eta^2 = 0.33$, and the main effect of age also demonstrated significance, $f(1, 84) = 0.60$, $p = 0.004$, $\eta^2 = 0.08$. However, there was no significant interaction effect observed between exercise and age, $f(1, 84) = 0.49$, $p = 0.49$, $\eta^2 = 0.00$, nor between exercise and sex, $f(1, 84) = 2.93$, $p = 0.09$, $\eta^2 = 0.01$. This analysis suggests that after the intervention, the exercise had a significant main effect on the sleep quality outcome, indicating its influence on the observed changes. Additionally, the participants' age also exhibited a notable main effect, implying that age plays a role in the quality of sleep of participants. However, no significant interactions were found between exercise and either age or sex, suggesting that the relationship between exercise and the sleep quality did not vary significantly based on participants' age or sex.

Similarly, the study also employed a repeated measures ANCOVA to explore the relationships between age, sex, and CRF. The analysis revealed a statistically significant main effect of exercise, $f(1, 84) = 1.53$, $p = 0.03$, $\eta^2 = 0.14$, as well as a significant main effect of age, $f(1, 84) = 0.60$, $p = 0.004$, $\eta^2 = 0.17$. However, the main effect of sex was not statistically significant, $f(1, 84) = 3.91$, $p = 0.14$, $\eta^2 = 0.57$. Additionally, a significant interaction effect emerged between exercise and age, $f(1, 84) = 0.83$, $p = 0.004$, $\eta^2 = 0.22$, while no significant interaction was observed between exercise and sex, $f(1, 84) = 0.001$, $p = 0.98$, $\eta^2 = 0.000$. The significant main effect of exercise suggests that exercise has a notable impact on CRF levels. Additionally, the significant main effect of age indicates that age plays a significant role in influencing CRF. However, the main effect of sex was not found to be statistically significant, suggesting that sex may not be a major factor in predicting CRF. Importantly, the significant interaction effect

between exercise and age underscores that the relationship between exercise and CRF is influenced by the participants' age. Conversely, the lack of a significant interaction between exercise and sex suggests that the impact of exercise on CRF is not significantly influenced by sex. These findings collectively contribute to a deeper understanding of how exercise, age, and sex collectively influence CRF.

The Impact of Exercise Induced sleep quality on CRF.

A two-factor mixed analysis of variance (ANOVA) was conducted to examine the effect of PSQI sleep score group on CRF score. The mean and standard deviation of pre and post CRF scores were calculated for each level of the PSQI sleep score group. For participants in the 'Good Sleep' group, the mean pre CRF score was M = 15.67, SD = 7.22, and the mean post CRF score was M = 12.08, SD = 6.54. For participants in the 'Poor Sleep' group, the mean pre CRF score was M = 22.44, SD = 9.46, and the mean post CRF score was M = 20.30, SD = 8.19. Mauchly's test indicated that the assumption of sphericity had been met ($\chi^2 = 1.00$, $p = 0.49$). The main effect of exercise revealed a significant difference in CRF levels following the exercise intervention, $f(1, 85) = 12.22$, $p < 0.001$, $\eta^2 = 0.12$. Additionally, the main effect of PSQI group demonstrated that CRF was higher in the poor sleep quality group compared to the good sleep quality group, $f(1, 85) = 24.60$, $p < 0.001$, $\eta^2 = 0.22$. However, the non-significant interaction indicated that the effect of exercise on CRF did not differ significantly between the two sleep quality groups, $f(1, 85) = 0.78$, $p = 0.38$, $\eta^2 = 0.01$. Notably, the good sleep quality group exhibited a significant decreased in CRF levels.

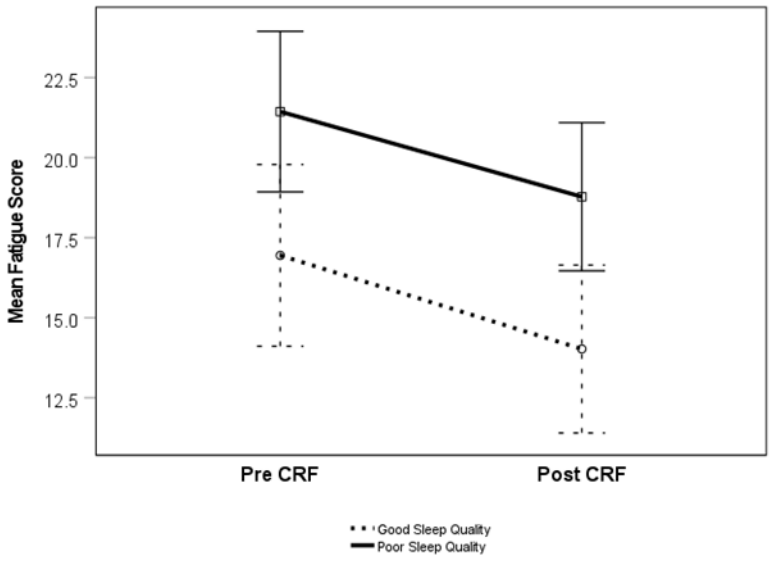

Figure 5: Examining the Impact of Exercise-Induced Sleep Improvement on Cancer-Related Fatigue Levels

This result indicates that the exercise intervention had a notable impact on reducing CRF, as reflected by the significant main effect of exercise. Moreover, it underscores the association between sleep quality and CRF, as the main effect of group revealed that individuals with poor sleep quality experienced higher CRF levels compared

to those with good sleep quality. However, the absence of a significant interaction suggests that the effect of exercise on CRF was consistent across both sleep quality groups. The significant decrease in CRF levels observed in the good sleep quality group further highlights the potential benefits of exercise in improving CRF outcomes.

Chapter 5 Discussion

CRF and sleep problems are prevalent and debilitating issues experienced by CS. CRF negatively impacts the physical, cognitive, and emotional well-being of CS while poor sleep quality further exacerbates these challenges(Wu et al., 2019). Exercise has emerged as a promising non-pharmacological intervention to address both CRF and sleep problems in various populations(Campbell et al., 2019)(Zhang et al., 2023). However, studies examining the impact of exercise on the relationship between sleep quality and CRF in CS have produced inconsistent findings (Al-Majid & Gray, 2009; Linden & Satin, 2007; Puetz & Herring, 2012; Rogers, 2012; Speck et al., 2010). As a result, there remains a need to understand this relationship and the potential impact of exercise. Therefore, the primary purpose of this study is to determine whether a 12-week tailored exercise program for CS affects the relationship between sleep quality and CRF. The objectives of the study determined if: 1) the exercise intervention improves sleep quality in CS; 2) the exercise intervention improves CRF in CS; 3) age and sex have impact on sleep quality and CRF; and 4) there is correlation between sleep quality and CRF such that exercise-induced changes in sleep quality influence CRF in CS. Overall, our findings provide evidence that participation in an exercise program improves sleep quality and reduces CRF in CS. The study also showed that exercise induced improvements in sleep lead to a reduction in CRF.

As previously discussed, sleep problems are a significant concern for CS as it can profoundly impact their physical and psychological well-being. Building upon previous research that has explored the impact of exercise on sleep quality, the present study adds to the existing literature by demonstrating the effectiveness of a multi-modal exercise program in improving sleep among CS. These findings align with and further support the results of other studies conducted on various cancer types, including the studies by Chandwani et al. (2014), Cheville et al. (2013), and Cormie et al. (2014), which have shown exercise to be beneficial in improving sleep quality. In the study conducted by Courneya et al. (2012) on lymphoma survivors, a combination of aerobic, strength training, and flexibility exercise was shown to improve sleep quality (Courneya e et al., 2012). Similarly, studies involving mixed CS populations, including Kampshoff et al. (2015), Lin et al. (2015), and Rajotte et al. (2012), have reported positive impacts of exercise on sleep quality. For instance, CS that completed a supervised 12-week exercise program consisting of 90-minute resistance and aerobic exercise sessions, twice per week reported improved sleep (Rajotte et al., 2012). Together, these collective findings strongly indicate that exercise is an effective method for improving sleep in individuals living with or beyond a cancer diagnosis. By incorporating exercise interventions into the treatment and survivorship care plans, healthcare professionals can potentially enhance the sleep quality and overall well-being of individuals affected by cancer.

Results from this study also showed that the exercise program significantly improved CRF among CS. This aligns with previous studies that have investigated the impact of exercise on CRF in survivors with different cancer types. Meta-analysis conducted by Kangas et al. (2008) and another study examining the effects of exercise on CRF, collectively reinforce the efficacy of regular exercise in reducing CRF and improving the quality of life for

CS. Kangas et al.'s comprehensive analysis of multiple studies provides strong evidence supporting the positive impact of exercise on CRF during and after treatment, they analyzed a total of 119 randomized controlled trials (RCTs) and non-RCT studies to evaluate the effectiveness of exercise. Their meta-analyses, based on 57 RCTs, revealed that exercise intervention showed reductions in CRF. The authors identified several specific interventions, such as multimodal exercise and walking programs that showed promising potential for alleviating CRF (Kangas et al., 2008a). Likewise, the findings from the other meta-analyses highlight the importance of exercise, particularly resistance exercise, and its potential benefits in reducing CRF and improving health outcomes among cancer survivors, including older individuals (J. Meneses-Echávez et al., 2015; K. Mustian et al., 2012; Tomlinson et al., 2014). Based on the results from this study and the literature it is clear that exercise represents an effective intervention to manage CRF in CS.

Importantly, a significant correlation between sleep quality and CRF was found after the intervention. The positive correlation indicates that as sleep quality improves (higher change in PSQI scores, indicating better sleep), CRF also tends to improve (higher change in CRF scores, indicating reduced fatigue). These findings are consistent with previous research demonstrating the strong relationship between sleep quality and CRF in CS (Berger et al., 2018; Wang et al., 2016). Similarly, a recent study by Momayyezi et al. (2021) found a strong link between sleep disturbance and increased levels of CRF in CS. The research showed that individuals with poor sleep quality experienced more severe fatigue, with 63% of those experiencing sleep disturbance also reporting CRF. These consistent findings across multiple studies highlight the critical role of sleep quality in influencing CRF among CS. Addressing sleep disturbances through interventions targeting sleep quality may prove beneficial in alleviating CRF and improving the overall well-being of CS.

The study also aimed to explore the relationship between sleep quality and various demographic factors, specifically sex and age, among CS. The findings align with previous research that has explored the complex relationship between exercise, sleep quality, and demographic factors (Garfield et al., 2019; Ruggiero et al., 2019; W. Zhu et al., 2022). Similar to this study results, a study observed a significant main effect of exercise on sleep quality among CS post-intervention, indicating that exercise interventions can lead to improvements in sleep outcomes (Takemura et al., 2020). This consistency suggests a robust connection between exercise and sleep quality enhancement, emphasizing the potential of exercise interventions to positively influence sleep patterns in various populations. Furthermore, the identification of age as a significant factor influencing sleep quality is in line with the work of Zhu et al. (2022), Gonzalez et al. (2021) who reported that older adults experienced more sleep disturbances. This concurrence highlights the role of age-related physiological changes in sleep patterns and quality. By corroborating these findings, this study contributes to the broader understanding of how age interacts with exercise interventions to impact sleep quality outcomes. While our results did not reveal significant interaction effects between exercise and age or sex, this is consistent with the study which also did not find significant moderating effects of age or sex on the relationship between exercise and sleep quality(Zimmer et al., 2018). These

parallel outcomes underscore the robustness of the exercise-sleep quality relationship, suggesting that the positive impact of exercise on sleep quality is relatively consistent across different age groups and genders(Langford et al., 2012). In contrast, the lack of significant interaction effects contrasts with the study which identified sex as a moderating factor in the relationship between exercise and sleep quality(Kampshoff et al., 2015). It is important to note that while our study did not find a significant interaction, the underlying mechanisms may be influenced by various contextual factors unique to each study. Further exploration into the interplay of exercise, sex, and sleep quality is warranted to better understand potential nuances.

Additionally, this study also examined the relationship between CRF and demographic factors, specifically sex and age, among CS. The obtained outcomes align with prior research investigations that have explored the intricate relationships between exercise, age, sex, and CRF among diverse populations of CS. Notably, the finding of a significant main effect of exercise on CRF levels is consistent with a study which observed similar exercise-induced reductions in CRF among breast cancer survivors participating in a structured exercise program (Mijwel et al., 2019). This correspondence underscores the robustness of exercise as an effective intervention for ameliorating CRF, transcending different cohorts and intervention modalities. The identification of a significant main effect of age on CRF is congruent with the findings who reported that advanced age was associated with increased CRF severity among CS (Nowe et al., 2019). This congruence further solidifies the role of age as a pivotal determinant of CRF and supports the notion that aging may exacerbate CRF, potentially due to cumulative physiological effects of cancer treatment. Conversely, the lack of a statistically significant main effect of sex in predicting CRF echoes the results of a recent study which synthesized data from various studies and indicated that sex may not be a predominant factor influencing CRF levels in CS (Makhoul et al., 2015). This finding underscores the need to consider multifaceted factors beyond sex when addressing CRF-related concerns in clinical practice. The significant interaction effect between exercise and age in our study echoes the nuanced findings of studies who demonstrated that the impact of exercise on CRF reduction may vary based on participants' age groups, signifying the importance of age-specific exercise prescription for optimizing CRF outcomes (Minton et al., 2013; Schmitz et al., 2011). Similarly, the non-significant interaction between exercise and sex aligns with the results of a study indicating that the relationship between exercise and CRF remains consistent irrespective of sex (Vear et al., 2020). The significant relationship between CRF and age highlights the potential influence of age-related factors on the experience of fatigue among CS.

Furthermore, the study findings align with previous investigations that have explored the relationship between exercise-induced sleep quality and CRF among CS. In congruence with the study by Zhang et al. (2023), our results underscore the significant impact of exercise on CRF reduction. Zhang and colleagues demonstrated similar exercise-induced reductions in CRF, highlighting the effect of exercise as an effective intervention for ameliorating CRF across diverse samples of cancer survivors (Zhang et al., 2023). Furthermore, the observed association between sleep quality and CRF corroborates the outcomes of a study which reported that poor sleep quality was

linked to elevated CRF levels (Papadopoulos et al., 2019a) . The congruence of these findings accentuates the significance of sleep quality as a potential mediator of CRF, suggesting that poor sleep quality might exacerbate CRF severity, possibly due to the cumulative physiological toll of cancer and its treatment (Dun et al., 2022). Our results also resonate with the work of Dirksen et al. (2008), Heckler et al. (2016), Lin et al. (2019), Poier et al. (2019), Savard et al. (2015), Yeh et al. (2016), and Zengin et al. (2019), who explored the impact of sleep quality on CRF and identified a significant relationship between sleep disturbances and heightened CRF. These findings reinforce the notion that individuals with poor sleep quality may experience a higher burden of CRF, providing additional support to our observed main effect of PSQI sleep score group on CRF. While this study aligns with prior research, it contributes unique insights by revealing a significant decrease in CRF levels specifically within the 'Good Sleep' group following the exercise intervention. This resonates with a study that demonstrated that exercise interventions can lead to substantial CRF reductions, particularly in individuals with improved sleep quality (P.-J. Lin et al., 2019a). This results further emphasize the potential of exercise as an impactful strategy to alleviate CRF, offering potential avenues for tailored interventions targeting individuals with varying sleep qualities. In conclusion, the study's outcomes align with existing research, highlighting the influential role of exercise-induced sleep quality on CRF reduction. This aligns with prior investigations and underscores the importance of considering sleep quality as a modifiable factor in managing CRF among cancer survivors. The observed significant decrease in CRF levels within the 'Good Sleep' group provides further impetus for incorporating exercise interventions to improve sleep quality and mitigate CRF, ultimately enhancing the well-being and quality of life for cancer survivors.

Strengths and Limitations

The present study possesses several notable strengths that contribute to its significance and credibility. Firstly, the utilization of data from the ACCESS program, an evidence-based and pragmatic exercise program implemented across multiple locations in Nova Scotia, is a notable strength. The program's pragmatic approach, characterized by individualized programming, flexible program duration, and a less structured format, deviates from the typical RCT design, making it more applicable to real-world settings. This pragmatic nature enhances the study's external validity and allows for a broader generalization of the findings. The inclusion of a heterogenous sample population is another key strength of this study. By including participants with diverse cancer types and treatment histories, the findings are more representative of the larger CS population, further increasing the generalizability of the study. However, several limitations should be acknowledged in interpreting the findings of this study. Firstly, ACCESS did not incorporate a control group. Therefore, direct comparisons between groups could not be made, and the study's conclusions are primarily based on correlational relationships. The absence of a control group diminishes the ability to determine whether the observed changes in outcomes resulted from the intervention itself or potential confounding variables such as lifestyle habits, psychological factors, or concurrent treatments. Another limitation of this study is the lack of diversity in terms of ethnicity and socioeconomic status among the participants. The study primarily consisted of individuals from white and higher-income demographics, which

limits the generalizability of the findings to more diverse populations. Ethnicity and socioeconomic status can play significant roles in health outcomes, including sleep quality and CRF. Therefore, the results of this study may not fully represent the experiences and needs of individuals from different ethnic backgrounds or lower-income groups. The underrepresentation of diverse populations in research studies is a common issue that hinders the understanding of health disparities and the effectiveness of interventions across different demographic groups (Polite et al., 2017). In order to address this limitation and enhance the external validity of future studies, it is crucial to include a more diverse range of participants that reflect the ethnic and socioeconomic diversity of the target population. This will allow for a comprehensive exploration of the impact of exercise interventions on sleep quality and CRF among individuals from various backgrounds. Moreover, reliance on self-reported measures of sleep quality and exercise constitutes another limitation. Self-report measures are subject to recall bias and measurement errors, which could affect the accuracy and reliability of the data collected (C. Yu, 2010). Lastly, the study's lack of follow-up assessments is a notable limitation. Long-term follow-up assessments would provide valuable insights into the effects of sustained exercise interventions on sleep quality and fatigue outcomes among CS. Understanding the durability and long-lasting effects of the exercise program would enhance the overall understanding of its effectiveness in improving sleep quality and reducing CRF over an extended period. Therefore, future studies should consider incorporating follow-up assessments to investigate the long-term impact of exercise interventions on sleep and CRF in this population. This would provide a more comprehensive evaluation of the intervention's efficacy and inform the development of effective long-term management strategies for poor sleep quality and CRF in CS.

Implications and Future Directions

The findings of this study have important implications for cancer care and survivorship. Healthcare providers must prioritize interventions to improve sleep quality, recognizing its impact on CRF. Encouraging regular exercise among this population can help improve sleep quality and reduce CRF. By incorporating evidence-based strategies for optimizing sleep, exercise, and fatigue management, the results of this research have the potential to inform clinical practice guidelines and enhance survivorship care. These interventions can improve the well-being and long-term outcomes of individuals living with or beyond cancer diagnosis.

In terms of future research, new studies should consider utilizing longitudinal designs to establish a clearer understanding of the causal relationship between sleep quality, exercise, and CRF. Long-term follow-up assessments are necessary to examine the effects of sustained exercise interventions on sleep quality and fatigue outcomes. Objective measures of sleep quality and exercise, such as actigraphy or accelerometry, should be incorporated to enhance the accuracy and reliability of future research. Replicating the current findings in larger and more diverse samples, particularly in terms of ethnicity and socioeconomic status, would enhance the generalizability of the results and allow for a better understanding of the moderating effects of these demographic factors. Additionally, several research studies have explored the potential relationships between sleep quality,

exercise, and CRF (Palesh et al., 2013; Wang et al., 2017; Mustian et al., 2017; Bower et al., 2014) however, exploring potential mediators or moderators, such as psychological distress, inflammation, or circadian rhythm disruptions, could provide deeper insights into the underlying mechanisms of the relationship between sleep quality, exercise, and CRF. Furthermore, future research should investigate the optimal timing, intensity, and type of exercise interventions for improving sleep quality and reducing CRF. Comparative effectiveness studies on different exercise modalities (e.g., aerobic exercise, resistance training, mind-body exercises) in relation to sleep quality and fatigue outcomes would inform the design of tailored exercise programs. The long-term sustainability of the observed improvements in sleep quality and CRF following exercise interventions should also be examined to develop strategies for lasting effects. Understanding the lived experiences, barriers, facilitators, and preferences of individuals in managing sleep disturbances and engaging in exercise programs is crucial for developing patient-centered interventions and supportive care strategies (Novak et al., 2013a). By addressing these research gaps, future studies can advance our knowledge of the complex relationship between sleep quality, exercise, and CRF, leading to more effective interventions and improved quality of life for CS.

Conclusion

The present study has yielded valuable insights into the relationship between sleep quality, exercise, and CRF symptoms among individuals living with or beyond a cancer diagnosis. The findings highlight the significance of promoting exercise and improving sleep quality as a strategy to alleviate CRF and enhance the QoL for individuals living with or beyond a cancer diagnosis. However, it is important to acknowledge the study's limitations and the need for further research to expand upon these findings. The study emphasizes the importance of incorporating exercise interventions and addressing sleep disturbances as integral components of comprehensive cancer care. Healthcare providers need to acknowledge the impact of sleep quality on CRF and integrate interventions targeting sleep quality into routine care for individuals affected by cancer, aiming to alleviate CRF symptoms and enhance well-being. By combining exercise interventions with interventions addressing poor sleep quality, healthcare providers can potentially reduce CRF and improve the overall quality of life for individuals affected by cancer. Future research should address the study's limitations, explore additional factors contributing to the complex relationship between sleep quality, exercise, and CRF, and inform comprehensive care provision for individuals living with or beyond a cancer diagnosis.

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Appendix A: PITSSBURGH SLEEP QUALITY INDEX SCORING

Component	Scoring
Component 1	Q9 score
Component 2	Q2 score (<15min=0, 16-30min=1, 31-60min=2, >60min=3) + Q5a score. If sum is equal 0=0, 1-2=1, 3-4=2, 5-6=3
Component 3	Q4 score (>7=0, 6-7=1, 5-6=2, <5=3)
Component 4	(total hours asleep)/(total hours in bed) * 100 (>85%=0, 75%-84%=1, 65%-74%=2, <65%=3)
Component 5	sum of scores Q5B to Q5J. (0=0, 1-9=1, 10-18=2, 19-27=3)
Component 6	Q6 score
Component 7	Q7 score + Q8 score. (0=0, 1-2=1, 3-4=2, 5-6=3)
Global PSQI	Sum of component 1 to component 7 (<6 = Good sleep quality, >6 = Poor sleep quality)

Appendix B: PITTSBURGH SLEEP QUALITY INDEX QUESTIONNAIRE

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answersshould indicate the most accurate reply for the majority of days and nights in the past month.
Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?NUMBER

OF MINUTES _____

3. During the past month, what time have you usually get up in the morning?

GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may bedifferent from the number of hours you spent in bed.)

HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
_____	_____	_____	_____

b) Wake up in the middle of the night or early morning

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
_____	_____	_____	_____

c) Have to get up to use the bathroom

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

d) Cannot breathe comfortably

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Cough or snore loudly

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

f) Feel too cold

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

g) Feel too hot

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

h) Had bad dreams

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

i) Have pain

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

j) Other reason(s), please describe_____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?Very good

_____

Fairly good _____

Fairly bad _____

Very bad _____

During the past month, how often have you taken medicine to help you sleep (prescribed or"over the counter")?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

7. During the past month, how often have you had trouble staying awake while driving, eatingmeals, or engaging in social activity?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

8. During the past month, how much of a problem has it been for you to keep up enoughenthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problemA _____

very big problem _____

9. Do you have a bed partner or room mate?

No bed partner or room mate Partner/room mate _____

in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a room mate or bed partner, ask him/her how often in the past month youhave had . . .

a) Loud snoring

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
_____	_____	_____	_____

b) Long pauses between breaths while asleep

Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
_____	_____	_____	_____

c) Legs twitching or jerking while you sleep

Not during the	Less than	Once or twice	Three or more

Appendix C: FACIT-F QUESTIONNAIRE

Please circle or mark one number per line to indicate your response as it applies to the past 7days.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
HI 7	I feel fatigued	0	1	2	3	4
HI 12	I feel weak all over	0	1	2	3	4
An 1	I feel listless ("washed out")	0	1	2	3	4
An 2	I feel tired	0	1	2	3	4
An 3	I have trouble starting things because I am tired	0	1	2	3	4
An 4	I have trouble finishing things because I am tired	0	1	2	3	4
An 5	I have energy	0	1	2	3	4
An 7	I am able to do my usual activities	0	1	2	3	4
An 8	I need to sleep during the day	0	1	2	3	4
An 12	I am too tired to eat	0	1	2	3	4
An 14	I need help doing my usual activities	0	1	2	3	4
An 15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An 16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix D: PSQI SCORING AND REFERENCES

Reference

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: The Pittsburgh Sleep Quality Index: A newinstrument for psychiatric practice and research. *Psychiatry Research* 28:193-213, 1989.

Notes on data entry

The range of values for questions 5 through 10 are all 0 to 3.

Questions 1 through 9 are not allowed to be missing except as noted below. If these questions are missing, then any scores calculated using missing questions are also missing. Thus, it is important tomake sure that all questions 1 through 9 have been answered.

In the event that a range is given for an answer (for example, '30 to 60' is written as the answer to Q2,minutes to fall asleep), split the difference and enter 45.

Scores – reportable in publications

On May 20, 2005, on the instruction of Dr. Daniel J. Buysse, the scoring of the PSQI was changed to set the score for Q5J to 0 if either the comment or the value was missing. This may reduce the DURAT scoreby 1 point and the PSQI Total Score by 1 point.

PSQIDURAT DURATION OF SLEEP
IF Q4 $\geq$ 7, THEN set value to 0
IF Q4 < 7 and $\geq$ 6, THEN set value to 1IF Q4 < 6 and $\geq$ 5,
THEN set value to 2IF Q4 < 5, THEN set value to 3
Minimum Score = 0 (better); Maximum Score = 3 (worse)

PSQIDISTB SLEEP DISTURBANCE
IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) = 0, THEN set value to 0

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 1 and < 9, THEN set value to 1

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 9 and $\leq$ 18, THEN set value to 2

IF Q5b + Q5c + Q5d + Q5e + Q5f + Q5g + Q5h + Q5i + Q5j (IF Q5JCOM is null or Q5j is null, set the value of Q5j to 0) > 18, THEN set value to 3Minimum Score = 0

(better); Maximum Score = 3 (worse)

PSQILATEN SLEEP LATENCY

First, recode Q2 into Q2new thusly:

IF Q2 $\geq$ 0 and $\leq$ 15, THEN set value of Q2new to 0 IF Q2 > 15 and $\leq$ 30, THEN set value of Q2new to 1IF Q2 > 30 and $\leq$ 60, THEN set value of Q2new to 2IF Q2 > 60, THEN set value of Q2new to 3