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MEDICAL QIGONG VERSUS EXERCISE ON SLEEP DISTURBANCE AND
QUALITY OF LIFE IN BREAST CANCER SURVIVORS

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

June 2020

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ABSTRACT

Sleep disturbance affects nearly 30 percent of breast cancer survivors and has consequences on quality of life. Pharmacologic treatment for sleep disturbance exists, however cancer survivors are seeking alternative ways to improve outcomes. There is a need to investigate treatment modalities for sleep disturbance and quality of life in this population. Qigong is a five-dimension-based mind-body therapy that has shown to improve sleep disturbance and quality of life. There has yet to be a randomized controlled trial comparing Qigong to an active control on sleep disturbance specifically for breast cancer survivors. **We propose that Qigong will be superior in improving sleep disturbance and quality of life in breast cancer survivors when compared to light exercise.** Participants will be randomized to either Qigong or light exercise over twelve weeks. The findings will inform healthcare providers and assist them in managing symptoms that may improve quality of life in this population.

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

Breast cancer is the most commonly diagnosed cancer in females in the United States and the second most common cause of cancer-related death in females in the United States.¹ With increasing early detection screening tools and successful treatment regimens, higher numbers of women are diagnosed with early-stage breast cancer every year and mortality rates are steadily declining.^{2,3} In developed nations, there is now a 90% 5-year survival rate for women with breast cancer and an almost 100% 5-year survival rate for those with localized disease.⁴ As of January 1, 2019, an estimated 8,781,580 female cancer survivors were living in the United States, with 3,861,520 of those being breast cancer survivors (BCS) specifically.⁴ Yet with this increase in survivorship comes an increase in patients presenting to their healthcare providers with side effects from treatment and long-term comorbidities.⁴

The choice of treatment for women diagnosed with breast cancer is dependent on cancer stage, tumor size and grade, number of involved lymph nodes, and status of hormone receptors.⁵ Surgery is usually the first choice of treatment for early-stage breast cancer and entails either breast-conserving therapy or mastectomy.⁶ Depending on the stage and extent of lymph node or other organ involvement, women may undergo adjuvant therapy or neoadjuvant therapy. Adjuvant therapy is systemic therapy using chemotherapy, endocrine therapy, and/or targeted therapy. Women with localized and earlier-staged disease are most likely to benefit from neoadjuvant therapy, therapy initiated before surgery; it has demonstrated better overall disease-free survival outcomes than surgery combined with adjuvant systemic therapy.⁶

With the treatment options available come multiple side effects including those affecting body physiology, mental health, and quality of life. Physiological side effects can include chronic pain, lymphedema, infertility, cognitive deficits, and cardiotoxicity.⁷⁻⁹ Depression, anxiety, fatigue, and sleep disturbance are particularly pervasive in this population both during and after treatment, and are a result of a combination of the malignancy itself, treatment, and effects of treatment.¹⁰ Women undergoing treatment may experience depression and anxiety due to fear of recurrence, uncertainty of disease prognosis, fears of experiencing side effects, and worry of career and financial implications of the prognosis.^{7,11} One study found that 4.6% of a sample of 153 BCS met diagnostic criteria for post-traumatic stress disorder (PTSD) related to their breast cancer treatment as long as 20 years after diagnosis.¹¹

Fatigue has an estimated prevalence of anywhere from 28 to 91% in cancer patients and approximately 30% will experience persistent symptoms for years after treatment.^{5,12} Fatigue in cancer patients is a subjective and persistent sense of exhaustion physically, emotionally, and/or cognitively that cannot be attributed to recent activity and is related to cancer or cancer treatment.¹² There are many treatable contributing factors to fatigue in this population, a major one of which is sleep disturbance.¹²

Sleep disturbance, the focus of this study, is nearly ubiquitous in the breast cancer population. Compared to patients with other forms of cancer, breast cancer patients tend to experience sleep disturbance more frequently, and the majority report it within the first year of diagnosis and treatment.^{13,14} In BCS, prevalence rates of sleep disturbance are estimated to be anywhere from 30 to 90%; close to that of fatigue rates in all cancer patients.¹³ Almost 30% of BCS meet the criteria for insomnia which is defined as difficulty initiating sleep,

frequent awakenings, and an inability to return to sleep.¹³ This is almost twice the rate of sleep disturbance as seen in the general population.¹³ The types of sleep disturbances in BCS can vary widely and may include difficulty falling asleep, difficulty staying asleep, non-restorative sleep, frequent nighttime awakenings, hypersomnolence, excessive daytime napping, sleep apnea, parasomnias, restless leg syndrome, and sleep-related movement disorders like sleepwalking.^{13,15,16} Untreated sleep disturbance in BCS has negative consequences on quality of life and well-being, and has been associated with comorbidities like hypertension.¹³ A 2014 study found that sleep disturbance in breast cancer patients with metastatic disease was associated with poorer survival outcomes and that participants reporting less objective sleep disturbance were found to have significantly lower mortality rates over six years.¹⁷

The etiology of sleep disturbance in this population is multifactorial and not completely understood. The stress and anxiety associated with a cancer diagnosis in combination with the side effects of treatment are thought to be the primary precipitating factors.¹⁷ Physiologically, chronic low-grade inflammation and altered regulation of the autonomic nervous system have been implicated.¹⁸ The diagnosis of cancer itself has also been shown to alter the circadian rest-activity rhythm that normally dictates the sleep-wake cycle due to changes in rhythmic secretions of cortisol.¹⁸ Additionally, recent evidence has found that sleep disturbance, fatigue, and depression tend to co-occur.¹⁶ One study found that insomnia was related to higher levels of fatigue, with a higher degree of insomnia predicting a higher level of fatigue.¹⁹ Because sleep disturbance is a strong contributing factor of fatigue, and because of the intertwining nature of these disorders,

treating sleep disturbance has implications for concurrent treatment of fatigue, anxiety, and depression as well.

First-line treatment for sleep disturbance in BCS is usually either pharmaceutical therapy or psychotherapy, specifically Cognitive Behavioral Therapy for Insomnia (CBT-I).¹⁵ Yet many cancer survivors have an increased desire to use complementary medicine (CM) therapies. Eighty-three percent of American cancer patients have reported the use of CM in addition to their standard medical therapies after diagnosis, and nearly 50% of BCS report annual use of mind-body interventions to improve their health.^{20,21} Exercise is an alternative treatment modality recommended by the National Comprehensive Cancer Network (NCCN) which has published guidelines for improvement in general sleep hygiene measures for cancer patients.¹⁴ Exercise has been shown to improve perceived global sleep quality in BCS and endometrial cancer survivors and has demonstrated improved outcomes of better sleep including fatigue, physical function, and quality of life in patients with multiple forms of cancer.^{14,22,23} Although the benefits of exercise are apparent, exercise is considered a unimodal intervention and lacks multimodality unique to meditative movement exercises such as Qigong, Tai Chi, and yoga that could have more extensive indications for the myriad of symptoms that contribute to sleep disturbance.²⁴

Medical Qigong is a traditional Chinese medicine practice that could serve as a CM modality option for BCS experiencing sleep disturbance. As a form of CM, Qigong is widely used in China in conjunction with traditional healing modalities like pharmaceuticals or surgery, working best through this synergy.²⁵ The practice combines breathing, exercise, meditation, and body movements with the primary goal of manipulating the body's energy, or "qi," to improve physical, psychological, and spiritual health.^{26,27}

Though the exact mechanisms of Qigong remain unknown, it is thought to improve homeostasis of the autonomic nervous system and to increase the production of endogenous melatonin, a hormone for sleep and circadian rhythms in the body.^{13,21,28} Slow, deep breathing has been implicated in reductions in oxidative stress, blood pressure, and bringing balance to the autonomic nervous system.²⁹ Further, the combination of breathing with mindfulness and movement may contribute to improvement in emotional state, anxiety, and depression.²⁹ Tai Chi is one of the most widely known forms of Qigong especially in the United States, but it differs from pure Qigong in that it is more choreographed and complex, while Qigong is traditionally more repetitive, gentler, and easier to learn.²⁹

Qigong is an accessible modality for both healthy adults and those living with chronic disease and the benefits appear to be widespread. The exercise component of Qigong is gentle and easy to learn, and requires less physical capacity when compared to traditional aerobic exercise, yoga, and even Tai Chi.¹³ Thus, it may be more accessible to our population who often suffer from multiple treatment effects and comorbidities, as well as those in our population who are older and would benefit from exercise that corresponds to age-related changes.²⁶ Previous research has demonstrated adherence to conventional exercise being as low as 39% in cancer patients; while in the Women's Healthy Eating and Living study, 70% of BCS adhered to Tai Chi or Qigong.²⁹ Comparing the benefits of Qigong's multimodal framework to the unimodal framework of aerobic exercise and exploring implications of its effects on sleep disturbance and quality of life could both add to the knowledge of this eastern-medicine practice and give BCS a more accessible treatment option to sustain a healthy life.

1.2 STATEMENT OF THE PROBLEM

Sleep disturbance is reported as a major source of distress in BCS and has negative effects on quality of life.³⁰ Due to sleep disturbance being a result of multiple possible etiologies, it is difficult to identify the most effective method to manage it. CM modalities for treating sleep disturbance are becoming more desirable to BCS. Yet efficacy trials of alternative modalities are lacking to inform both patients and providers.²¹ Exercise is a unimodal non-pharmaceutical treatment option for sleep disturbance that has been shown to improve sleep and quality of life in BCS; however, for BCS with multiple comorbidities and increasing age, exercise is not always accessible and adherence may prove difficult.^{26,29} Qigong may be a more accessible and effective alternative.

Because Qigong is based in Eastern medicine, some studies have lacked generalizability as samples have been restricted to locations in Asian countries.^{13,27} Sample sizes of trials have been small and some studies lacked effective control groups or the presence of control groups at all, which threaten the validity of results.^{13,29} Randomized controlled trials (RCT) comparing the multimodal benefits of Qigong compared to the unimodal benefits of exercise on sleep disturbance and quality of life are missing.²⁹ There is a need to extend the literature with an RCT comparing Qigong with an active control, such as light exercise, in BCS to add treatment options and improve survivorship outcomes in this population.

1.3 GOALS AND OBJECTIVES

In this RCT, we aim to investigate the multidimensional effects of Qigong compared to light exercise in female BCS. We will accomplish this by looking at the pre- and post-

intervention changes in five dimensions—physical, social, spiritual, emotional, and mental—with an emphasis on the physical dimension as measured by sleep disturbance. We hope to demonstrate the improved mind-body benefits of Qigong over conventional exercise and add to the literature regarding the efficacy of this more accessible option for mitigation of post-treatment sleep disturbance and decreased quality of life.

Only BCS who meet the eligibility criteria will be enrolled in the trial. Participants will be randomly assigned to one of two groups: Qigong or light exercise. They will be followed weekly for 12 weeks. The main objective is to determine differences in mean change from baseline in self-reported sleep scores as measured by the Pittsburg Sleep Quality Index (PSQI) between groups. Secondary objectives include: 1) determining differences in mean change from baseline between groups in objective sleep parameters using a Fitbit wristband, 2) determining differences in mean change from baseline between groups in the four other dimensions—social, spiritual, emotional, and mental—measured by the Functional Assessment of Cancer Therapy- Breast (FACT-B) and the spirituality subscale of the FACT-B, the Functional Assessment of Chronic Illness Therapy- Spiritual Well-Being Scale (FACIT-Sp).

1.4 HYPOTHESIS

Among adult females within six months to five years past completion of primary treatment for primary breast cancer stages 0-III, there will be a statistically significant difference in sleep disturbance measured by mean change in sleep quality scores on the PSQI after 12 weeks of an instructor-led group Qigong course, as compared to instructor-led light exercise through the integration of physical movement and meditative stress reduction, and results will be durable 6 months after intervention completion.

1.5 DEFINITIONS

Primary breast cancer treatment: Surgery, radiation, chemotherapy, or endocrine therapy.

Sleep disturbance: Difficulty initiating sleep, frequent awakenings, and an inability to return to sleep.¹³ A score of greater than 5 on the PSQI.³¹

Medical Qigong/ Qigong: “qi” -energy flow or life energy, “gong” -achievement, work, or skill.^{23,27} A movement-based mind-body practice originating in China that combines slow, low-impact movement with meditation, breathing techniques, and mindful focus on the body, with a goal of manipulating the body’s energy (qi) for the benefit of physical, psychological, and spiritual health.^{23,27}

Instructor-led light exercise: Classes led by exercise physiologists meeting at the same length and frequency as the Qigong group with focus on light resistance training, stretching, and a light aerobic component.

Pittsburg Sleep Quality Index (PSQI): a self-rated questionnaire that assesses sleep quality and disturbance through nineteen individual items that generate a global score and seven component scores.³¹

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CHAPTER 2: REVIEW OF THE LITERATURE

2.1 INTRODUCTION

A search of relevant medical literature was conducted between August 2019 and June 2020 using Ovid Medline, EMBASE, PsychINFO, AMED, Cochrane, and Scopus. Primary searches were performed using the combination of MeSH terms “breast neoplasms,” “cancer survivors,” “Qigong,” “medicine, Chinese traditional,” “sleep,” and “sleep initiation and maintenance disorders.” Additional search terms included Tai Chi, Tai Ji, mind-body therapies, mind-body intervention, exercise therapy, survivors, cancer survivors, neoplasms, Fitbit, accelerometry, quality of life, insomnia, and sleep-wake disorders. The search was limited to articles written in English and to those with human subjects. Articles were analyzed for relevance to the topic and clinical trials, systemic reviews, and meta-analyses were prioritized. Additional references were extracted from reference lists of primary articles if found to be pertinent to our study. The literature search and review demonstrate the prevalence of sleep disturbance in breast cancer patients undergoing treatment and the prevalence of symptoms that persist following treatment. It is evident through the search that many alternative therapies have been considered and studied for this issue, but there remains much to learn regarding Qigong and its efficacy in our population.

2.2 REVIEW OF EMPIRICAL STUDIES

2.2.1 Sleep Disturbance in Female Breast Cancer Survivors

Multiple studies have demonstrated the prevalence of sleep disturbance in female breast cancer patients both during and after treatment. One study investigated subjective sleep disturbance in women with breast cancer stages I-III undergoing four rounds of

chemotherapy compared to age-matched women without cancer.¹ They found that women with breast cancer experienced worse subjective sleep quality as measured by the PSQI than their non-cancer counterparts (p=0.011 at start of treatment T1, p<0.001 after four cycles of chemotherapy T2, and p=0.02 one year after treatment initiation T3).¹ Similarly, an observational study of women with stages I-IIIa breast cancer found that between six months and 12 months after the start of endocrine therapy, self-reported sleep quality with the PSQI went from poor (a score of 6-10) to very poor (a score of ≥ 10) (p=0.03).² A third study found that breast cancer patients receiving cancer treatment tended to report worse sleep (p<0.06) and experience longer sleep latency (p<0.10) than those not receiving treatment.³ They also found that sleep disturbance was correlated with reported deficits in quality of life including decreased ability to perform daily tasks and feelings of low energy.³ These studies demonstrate that women experience sleep disturbance both before the start of treatment and throughout the course of treatment.

A few studies have demonstrated that sleep disturbance can extend beyond the completion of cancer treatment and can persist for years. One survey found that women can experience it an average of 4.2 years after completion of treatment.⁴ A cross-sectional study investigated sleep-wake disturbance in BCS who were a mean of 5.6 years after completion of cancer treatment and age-matched them to women without breast cancer.⁵ Sleep disturbance was found to be more common and more severe in the BCS. Mean global PSQI scores were significantly different between groups (p<0.01), and the PSQI sub-categories of sleep quality, sleep latency, sleep duration, number of disturbances, and daytime dysfunction were all found to be significantly worse (p<0.05 for all variables) in women with breast cancer.⁵ A strength of this study was that it included a sample of

African American BCS, adding to the diversity and generalizability of results.

Limitations include the fact that the percentage of women on endocrine therapy in the sample was low, so it may not be representative of all BCS. Further, there could be a source of selection bias as women were recruited to a “quality of life study” and this may attract women who are already seeking improvement in their sleep disturbance.⁵

2.2.2 Interventions for Sleep Disturbance in Breast Cancer Survivors

Treatment for sleep disturbance in BCS is primarily focused on the use of either pharmaceutical interventions or CBT-I. The choice of medication is usually from one of the following classes: non-benzodiazepine hypnotics, benzodiazepines, or sedative antidepressants.⁶ All three classes have shown to be beneficial for sleep in cancer patients; however, they each contain a side effect profile and the first two classes have habit-forming and addiction potential, respectively.⁶ Additional pharmaceutical treatments include melatonin, some types of antipsychotic medications, anticonvulsants, and valerian root.⁶ These medications have proven beneficial for sleep disturbance for BCS in the short term, but they are not meant to be used for chronic insomnia. Additionally, side effects can further complicate comorbidities.⁶

CBT-I is a form of psychotherapy that uses the techniques of stimulus control behaviors and sleep restriction to help a patient learn how to better sleep.⁷ It is the gold-standard treatment for insomnia as recommended by the American Academy of Sleep Medicine.⁷ It has shown to be effective for insomnia in cancer survivors and, unlike medications, has effects that last after cessation of treatment.⁶ Though benefits exist, successful treatment with CBT-I is often dependent on access to clinicians, insurance coverage of sessions, and a patient’s willingness to attend sessions.^{7,8} Often clinicians lack

knowledge of effective treatment options for insomnia like CBT-I and there is a shortage of providers with adequate training in the intervention.⁸ Yet, sleep disturbance continues to be a major concern for BCS with many reporting their symptoms going untreated.⁹ There is a need to offer more treatment options for sleep disturbance in this population.

After CBT-I, exercise is a primary non-pharmaceutical intervention recommended for sleep disturbance and multiple studies have demonstrated its benefits.⁶ A meta-analysis of 33 RCTs demonstrated that exercise had benefits on mental health, emotional and social well-being, and depression and anxiety in BCS.¹⁰ One study randomized postmenopausal BCS to either a 3-month exercise intervention or a control group and they found the intervention group to have significant improvements in PSQI-rated sleep duration ($p=0.03$).¹¹ This study had some limitations including small sample size, the inclusion of only women who had completed primary treatment, and only women with ductal carcinoma *in situ* or stage I-II breast cancer.¹¹ In a second study, a 3-month long exercise intervention based on physical activity recommendations by the American Cancer Society was found to significantly improve PSQI global sleep quality scores compared to a usual care intervention (mean between-group difference= -1.4; 95% CI=-2.1 to -0.7; $p<0.001$) in BCS.¹² The results remained significant at a 6-month follow up as well (mean between-group difference=-1.0; 95% CI=-1.7 to -0.1; $p=0.01$).¹² This study lacked generalizability as underrepresented racial and ethnic groups represented only a fraction of the study participants. However, a large sample size, strict randomization, and higher retention rates presented strengths that give the results more validity.¹²

2.2.3 The Benefits of Qigong

The benefits of Qigong extend to multiple aspects of health and well-being. This association has been studied in both the general population and in cancer patients. For the purpose of this literature review, we will include some studies that combined Tai Chi with Qigong or used gentler forms of Tai Chi. A review of the health benefits of Qigong and Tai Chi in the general population including healthy elderly individuals and those with chronic disease found benefits on the cardiorespiratory systems, physical function, balance and falls prevention, bone health, and patient-reported symptoms including quality of life, mood, and fatigue.¹³ One study investigated the effects of Qigong exercise in community-dwelling older adults with a mean age of 74.8 after a twice-weekly Qigong exercise session for eight weeks.¹⁴ Results showed statistically significant improvement in physical ability ($p < 0.001$), functional health ($p = 0.001$), balance ($p < 0.001$), functional reach ($p < 0.001$), depression ($p = 0.005$), and spiritual well-being ($p = 0.004$).¹⁴ The study also reported good adherence to the Qigong regimen with approximately 94% of participants performing Qigong at least once a week outside of sessions.¹⁴ Participants reported that the benefits they received from the practice gave them more incentive to continue with it. The study further demonstrated the physical benefits of Qigong to be comparable to that of aerobic exercise as there was a significant mean change in the six-minute walk test (6MWT). It should be noted that there was no control group in this study which brings forth a possible limitation of extension of these results and conclusions should be more conservative.¹⁴

In addition to Qigong being studied in the general population, it has also been studied in patients with various forms of cancer. One study compared Medical Qigong to

a usual care group in patients with breast, lung, prostate, and colorectal cancers.¹⁵ The Medical Qigong group had significant improvement in overall quality of life ($p < 0.001$), fatigue ($p < 0.001$), mood disturbance ($p = 0.021$), and inflammation as measured by C-reactive protein (CRP) ($p < 0.044$).¹⁶ It must be noted that this study did not explicitly define the usual care group making it difficult to interpret and apply the results of this study. Still, a similar study also reported that Medical Qigong improved inflammation and cognitive function.¹⁷ Finally, a third study on patients with advanced-stage non-small cell lung cancer and those with gastrointestinal cancer found that Medical Qigong appeared to have equivalent effects as standard endurance and strength training on anxiety, depression, and quality of life.¹⁸

Three studies have demonstrated the benefits of Qigong, or a combination of Qigong/Tai Chi, on sleep in patients with cancers other than breast cancer. In patients with non-Hodgkin's lymphoma undergoing chemotherapy, there was a statistically significant improvement in sleep quality over time from pre-test to post-test ($p < 0.001$) after 21 days of a Qigong intervention.¹⁹ When Qigong/Tai Chi was compared to exercise and a waitlist control in a population of prostate cancer patients during radiation therapy, sleep duration of participants in the Qigong/Tai Chi group was significantly longer than that of the exercise group ($p = 0.047$); there was also a trend for longer sleep duration in the Qigong/ Tai Chi group compared to the waitlist control group ($p = 0.07$).²⁰ However, the difference was no longer significant at the end of radiotherapy or at follow up time points. It must be noted that this study was limited by a small sample size.²⁰ Another study explored sleep disturbance in survivors of nasopharyngeal cancer by comparing a 6-month Qigong/Tai Chi intervention to a control group receiving no therapy.²¹ Sleep

disturbance, measured with the Medical Outcomes Study Sleep Scale (MOS), statistically decreased in the Qigong/Tai Chi group ($p < 0.006$) between mid-intervention and follow up, indicating that the results were durable.²¹ A limitation of this study was a lack of randomization of group allocation, presenting possible selection bias, as well as a high total attrition rate, though an intention-to-treat analysis was used.²¹

Qigong has been studied regarding its effect on the health and well-being of women with breast cancer. One study conducted in Malaysia investigated quality of life with the FACT-B in BCS participating in either a Qigong exercise group, a standard exercise program group, or a usual care group.²² The Qigong group's mean FACT-B scores at the end of the 8-week intervention period were 7.1 units higher (95% CI=0.36-13.9) than the exercise group, and 6.7 units higher (95% CI=0.04-13.3) than the usual care group.²² Similarly, an RCT conducted in Thailand in 2015 investigated the effects of a Qigong/Tai Chi program on self-esteem, fatigue, cortisol, and quality of life in women with breast cancer.²³ Participants were assigned to either a 4-week Qigong program or exercise intervention. Outcome measures included self-esteem as measured by the Rosenberg Self-Esteem Scale (RSE), fatigue as measured by the Fatigue Symptom Inventory (FSI), quality of life as measured by the FACT-B, and stress measured with cortisol samples.²³ Mean scores across 12 weeks significantly changed only in the Qigong group ($p < 0.05$ for all four outcomes) and remained significant after controlling for baseline scores.²³

The generalizability of these studies is limited by the fact that both were performed in Asian countries and had small sample sizes.^{22,23} People in Asian countries are more familiar with the practice of Qigong compared to people living in the United

States, so prior knowledge of the practice and its benefits could have presented sources of information bias to participants in these studies.^{22,23} Nevertheless, findings from these studies as well as others have demonstrated Qigong to be a safe and beneficial CM treatment for BCS.²²⁻²⁴

2.2.4 Qigong as an Intervention for Sleep Disturbance in Female Breast Cancer Survivors

Four studies to date have investigated the use of Qigong as an intervention for sleep disturbance in BCS. The first was an RCT conducted in Shanghai, China in 2013 looking at the effect of Qigong practice on quality of life outcomes including depressive symptoms, fatigue, sleep disturbance, overall quality of life, and stress in women with breast cancer undergoing radiotherapy.²⁵ Women with stage 0-III breast cancer were randomized to a Qigong intervention or waitlist control. Women in the Qigong intervention attended five, 40-minute Qigong classes throughout a 5-6-week period and were given additional materials to encourage practice on their own on non-meeting days. All participants completed the Center for Epidemiologic Studies Depression Scale (CES-D) to assess depression, the Brief Fatigue Inventory (BFI) to assess fatigue, the PSQI to assess sleep disturbance, and the Functional Assessment of Cancer Therapy- General (FACT-G) to assess overall quality of life. Stress was measured by salivary cortisol. Data were collected at baseline (T1), during the middle of radiation therapy (T2), during the last week of radiation therapy (T3), and 1 month (T4) and 3 months (T5) after the completion of radiation therapy. To evaluate the effectiveness of the intervention, the group by time interaction was investigated and they compared least squared means for

each group at each time point while controlling for baseline levels of each outcome variable.²⁵

Multilevel modeling analysis revealed a significant main effect of depression scores decreasing over time ($F(4,367)=10.91, p=0.001$) indicating that depression scores decreased in the Qigong group but not in the waitlist control group.²⁵ There were no significant group differences for fatigue, sleep disturbance, overall quality of life, or cortisol rhythms. When baseline symptoms of depression were controlled for, there were statistically significantly lower depressive symptoms ($F(4,368)=3.98; p=0.004$), fatigue ($F(3,275)=4.25; p=0.01$), and overall quality of life scores ($F(3,275)=3.03; p=0.02$) in the Qigong group versus the waitlist control group.²⁵ Although the results of this study did not demonstrate the benefits of Qigong on sleep, it was demonstrated that Qigong can benefit quality of life in women with breast cancer undergoing radiotherapy, and that the benefits can potentially extend beyond treatment completion. Further, this study demonstrated Qigong to be a safe therapy for patients in active treatment and adherence was high, with 65% of participants adhering to at least 80% of the Qigong classes.²⁵

There were limitations to this study that could potentially explain the lack of effect of the intervention on sleep. First, there was no active control group.²⁵ It cannot be ruled out that the effects of the intervention were due to social support at classes, a scheduled routine, or the attention participants gave to the intervention, as opposed to the waitlist control group that had no guidance or regimen. The sample was limited to Chinese women in one site in Shanghai, China. Though women with prior practice of Qigong were excluded from the study, it cannot be ruled out that participants may have had prior knowledge of Qigong and its benefits with it being of Eastern medicine origin.

This brings forth a possible source of information bias on the part of the participants. Furthermore, this limited sample inhibits the generalizability of results to the whole of the breast cancer population. It is not clear whether all participants in the sample had completed or were undergoing chemotherapy or endocrine therapy.²⁵ Therefore, it is possible this sample experienced sleep disturbance to different degrees than a sample would have that had all undergone some form of chemotherapy. It must be recognized that breast cancer patients undergoing treatment have been found to be more likely to experience sleep disturbance than those not undergoing treatment, and treatment effects can extend beyond the completion of therapy.^{3,4} Finally, follow up at three months after completion of radiation therapy may not have been long enough to see the benefits of Qigong on sleep. Therefore, studies with longer follow up after completion of therapy are needed.

The second study to look at the association was a double-blinded RCT investigating the effects of a combined Qigong/Tai Chi Easy (QC/TCE) intervention on fatigue, depression, and sleep disturbance in BCS.²⁶ Their aim was to test the effect of the meditative movement component of QC/TCE so the physical activity component was kept constant by comparing the intervention to a placebo “sham Qigong” (SQG). The SQG intervention used similar moves as the QC/TCE intervention but removed the emphasis on breathing and meditation. The interventions were both one-hour-long sessions meeting twice per week for 12 weeks and participants were blinded and randomized to the interventions. Eighty-seven postmenopausal women diagnosed with stages 0-III breast cancer who were 6 months to 5 years past primary treatment including surgery, radiation, or chemotherapy and reporting clinically significant fatigue were

enrolled in the study. Outcomes of the study included fatigue as measured by the FSI, sleep disturbance as measured by the PSQI, and depression as measured by the Beck Depression Inventory (BDI); outcomes were measured at baseline, post-intervention, and at 3 months follow up. Hierarchical linear models were used to assess independent effects of the interventions and time, and a likelihood ratio test was used to assess the interaction between time and intervention.²⁶

There was a statistically significant decrease in fatigue in the QC/TCE group at both the post-intervention timepoint ($p=0.005$) and at the 3-month follow up time point ($p=0.024$).²⁶ There was also a statistically significant interaction between the interventions and time for fatigue ($p=0.0116$). There was no statistically significant interaction between the two groups across time for either depression ($p=0.94$) or sleep disturbance ($p=0.27$). However, in both the QC/TCE and SQG groups individually there were statistically significant decreases across time for both depression and sleep disturbance (both $p<0.05$). These results demonstrated that the QC/TCE group was superior to the SQG group for BCS experiencing fatigue over time. They also demonstrated that both the QC/TCE intervention and the SQG intervention improved participants' depression and sleep disturbance over time, independently.²⁶

A strength of this study is that the “placebo” design helped control for any differences between groups in terms of attention, focus, or social aspects of being in a class, which other studies have lacked.²⁶ It allowed the investigators to analyze the meditative and breathing component of Qigong practice independent of the physical movement component. There were a few limitations to this study with the first being the possibility that the intervention and control group were not different enough and thus

lacked a strong enough comparison to see the benefits of one over the other. Furthermore, intention-to-treat analysis was not utilized which could have biased results by not accounting for dropouts. In this study, the QC/TCE intervention was specifically designed to achieve effects for fatigue which could have altered the results with a lack of focus on the other two outcomes, depression and sleep disturbance. Despite the lack of significance of between-group interaction on sleep, it is apparent that low-intensity physical activity, in general, is beneficial for sleep disturbance as both interventions incorporated this and demonstrated effects over time.²⁶ There is a need for a comparison group matched for exertion, dose, and frequency to a Qigong group, but with still enough contrast to elucidate its benefits.

The third study was a single-arm pilot study investigating the benefits of Qigong exercise on sleep disturbance, fatigue, and quality of life in BCS.⁹ Participants included eight women diagnosed with stages I-III breast cancer and an average of 46.4 months from completion of primary cancer treatment including surgery, radiation therapy, or chemotherapy and all with a concern for sleep disturbance or fatigue. The subjects underwent two Qigong training sessions and then one group session per week for six weeks. In addition, they were instructed to complete exercises at home twice per day every day. Participants completed assessments at baseline and after the six-week intervention including the PSQI for sleep, the Multidimensional Fatigue Inventory (MFI-20) for fatigue, and the MOS short-form 36 (SF-36) for quality of life. A multivariate analysis of variance (MANOVA) was performed to look for differences in means between the outcomes. A MANOVA was also used to analyze significance in each of the seven subcategories of the PSQI and the eight subcategories of SF-36.⁹

There was a significant improvement in global PSQI scores ($p < 0.01$); the mean score went from 10.3 (SD 3.6) at baseline to 5.4 (SD 2.3) at the end of the study.⁹ There was also a significant improvement in the two PSQI subscales of sleep quality and daytime dysfunction ($p < 0.007$) with the rest of the subscales demonstrating non-significance. There were also significant changes in MFI-20 ($p < 0.01$) and SF-36 ($p < 0.01$) scores indicating improvements in both fatigue and quality of life in the population by the end of the intervention. The “role limitations due to physical health” subcategory of the SF-36 was significant ($p < 0.006$) but all other subcategories were not significant.⁹

This study demonstrated that Qigong exercise can improve sleep and quality of life in BCS experiencing sleep difficulties.⁹ It also found a correlation between sleep disturbance and fatigue as both improved after the intervention. Limitations of the study include the fact that the study was a pilot feasibility trial without a control group, the sample size was small, and study participants were not blinded to the intervention.⁹ Based on the limitations across these studies, there remains a need for an active control comparison group to fully investigate the effectiveness of Qigong.

The final study explored whether Tai Chi Chih (TCC), a slower and more gentle form of Tai Chi, was noninferior to CBT-I in BCS with diagnosed insomnia.⁷ Study participants included ninety female BCS who fulfilled criteria for insomnia in the Diagnostic and Statistical Manual Fourth Edition (DSM-IV) and the International Classification of Sleep Disorders, and who reported sleep difficulties greater than or equal to three times per week for greater than three months, and had completed treatment at least six months prior to the start of the study. Participants were randomly assigned to either TCC or CBT-I. The TCC intervention participated in one, 2-hour long group

session per week for three months that focused on movement meditation with an emphasis on control over physical function. The CBT-I intervention followed the same time, frequency, and length as the TCC intervention and was also delivered in a group format. Both groups participated in assessments at baseline, 2 months, 3 months, 6 months, and 15 months after the start of intervention. One assessment was the PSQI to measure insomnia treatment response, with the primary outcome being treatment response at month 15; behavior outcomes were also assessed using the FSI for fatigue, the Epworth Sleepiness Scale for sleepiness, and the Inventory of Depressive Symptoms for clinician-rated depressive symptoms. Participants also completed daily diaries using the Pittsburg Sleep Diary. Method of analysis was noninferiority using an F statistic from linear mixed models for the primary outcome, and Fisher's exact test for secondary outcomes.⁷

Results demonstrated noninferiority of TCC to CBT-I at the primary outcome endpoint of month 15 ($p=0.02$), as well as at month 3 ($p=0.02$), and month 6 ($p<0.01$).⁷ Mean PSQI scores at month 15 were less than the threshold for clinical sleep disturbance in both groups, demonstrating overall treatment effects ($p<0.001$). There were non-significant between-group differences ($p>0.4$) in total sleep time and wake after sleep onset from sleep diary data. For secondary outcomes, there were improvements in both groups on fatigue severity, daytime sleepiness, and depression ($p<0.001$), but between-group differences in the three categories were non-significant ($p>0.5$).⁷

This study demonstrated TCC to be noninferior to CBT-I on BCS with clinical insomnia.⁷ The benefits were found to persist after one year of follow up in both groups. Treatment exposure in the two groups were matched on time, frequency, and length.

Participants were blinded to the treatment protocol which helped to reduce information bias. The sample was somewhat limited with the majority of women being white and well-educated, limiting the generalizability of results. Another limitation to this trial was low adherence to TCC practice outside of sessions; yet because the two interventions were exposure matched, this did not appear to affect noninferiority results.⁷ Although TCC and Qigong differ, results from this study can be extended to the use of Qigong in our study as the foundation of both TCC and Qigong is that of meditative movement with a gentler foundation than that of traditional Tai Chi.

2.3 REVIEW OF RELEVANT METHODOLOGY

The following section is a review of methodology that is relevant to the proposed study. A more detailed explanation of the proposed study methods is discussed in Chapter 3.

2.3.1 Study Design

The proposed study will be a two-arm, single-blinded RCT examining the benefits of a biweekly Qigong class compared to a biweekly light exercise class for 12 weeks on sleep disturbance and quality of life in female BCS. The study will recruit from two hospitals in the Yale New Haven Health system in New Haven, CT as well as private oncology practices and support groups. The study will be conducted at community centers in the New Haven, CT area.

The choice of an RCT as the study design stems from a lack of previously conducted RCTs comparing Qigong with an active control with the primary outcome of sleep disturbance in BCS. As discussed previously, only three studies have utilized an RCT design to investigate Qigong or Qigong/Tai Chi on sleep in breast cancer patients or

survivors.^{7,25,26} These studies lacked generalizability with small sample sizes and limited, non-representative populations. Additionally, one study compared Qigong to a “sham Qigong” that potentially did not offer enough contrast as a control to the Qigong intervention itself.²⁶ No previous study directly compared Qigong to dose- and frequency-matched active exercise. A pilot pre-, post-intervention single-arm study showed benefits of Qigong on sleep in BCS; however, the single-arm nature of this study without a comparison group limited validity of results.⁹ Despite this lack of robust RCTs, other CM studies have utilized the RCT design including those comparing Qigong to exercise on patients with prostate cancer and non-Hodgkin lymphoma, as well as a study comparing Iyengar yoga to regimented exercise in female breast cancer patients.^{19,20,27} These studies allowed for the elimination of possible bias and confounders within the sample population by randomizing participants and standardizing a comparison group.^{19,20,27} For these reasons our study will follow the same design.

The proposed study will recruit participants from multiple sites to improve upon the small sample sizes and limited variation in populations of previous studies. We hope to extend the generalizability of our results and recruit a representative and larger sample population by recruiting from multiple sites. Recruitment in the proposed study is based on a study in which participants were recruited via two hospital state tumor registries in Connecticut with supplementation of referrals from both providers and self-referrals.²⁸ We will also recruit from Sisters’ Journey, a support group for African American women with breast cancer or a history of breast cancer in New Haven, CT. We hope to increase the heterogeneity of our sample population and the generalizability of results by including this site in our recruitment process.

2.3.2 Selection Criteria

A complete list of inclusion and exclusion criteria can be found in Chapter 3. Selection criteria are based on previous studies of similar populations.^{9,26} Participants will be considered for our study if they are at least 18 years old, have been diagnosed with stages 0-III breast cancer, are six months to five years past completion of primary treatment for breast cancer (surgery, radiation, chemotherapy, or endocrine therapy), and show no evidence of cancer recurrence. Unlike previous studies that have either not required an insomnia diagnosis or strictly required an insomnia diagnosis for enrollment, we will enroll participants who score greater than a five on Global Sleep Quality on the PSQI. This is the threshold between which self-reported good and poor sleepers are distinguished.²⁹ Assessments will be administered upon enrollment with baseline assessment data. We will exclude women who have a diagnosis of a concurrent medical condition likely to influence short-term survival, a history of a major psychiatric illness requiring hospitalization including severe sleep-wake disorders, and current alcohol or drug dependence.³⁰ Exclusion of these factors will help preclude the possibility of results being attributed to other conditions rather than our intervention. The current use of sleep medication will not be part of the exclusion criteria. There is a sub-score on the PSQI that accounts for sleep-medication use, and randomization to intervention should account for any baseline differences between groups.

We will exclude women who have prior experience with Qigong and/or Tai Chi. This choice is consistent with one study that excluded women who had previous experience with Qigong or Tai Chi, but only within the past year.²⁵ This was especially important in the study as these practices are extremely well known in China where the

study was conducted. Another referenced study excluded those who had practiced Qigong or Tai Chi within the past year, as well as patients with physical disabilities including an inability to walk unassisted, chronic pain while walking, or difficulty walking for 20 mins.²⁰ We will follow suit regarding physical ability as both of our treatment groups require baseline abilities in order to perform the movements.

2.3.3 Potential Confounding Variables

Confounding variables can threaten the validity of the results of a study. Like previous studies, variables to be considered in this study include age, race, comorbidities, cancer stage, cancer treatment, treatment with endocrine therapy, time since diagnosis, menopausal state, baseline sleep quality, body mass index (BMI), and baseline level of physical activity.^{12,26} These are consistent with previous studies that have looked at Qigong or exercise on sleep in BCS.^{12,26} We will explore some of these variables in this review.

Studies are mixed regarding what age range experiences the most sleep disturbance in BCS. One reported that younger women may have a worse disease burden than their elder counterparts considering they will more likely be dealing with concurrent career and childcare concerns.⁴ They also reported an association between younger age and both increased disease severity and increased sleep disturbance.⁴ However, other studies have demonstrated that sleep disturbance may be worse for women who are post-menopausal and of older age.³¹ Age is also associated with different physical abilities.³² For these reasons, age will be controlled for in our study. We will include all women greater than age 18 in our study who meet the other inclusion criteria, and we will control for age differences with randomization to intervention.

Menopausal state, whether pre- or post-menopausal, endocrine symptoms, and treatment with endocrine therapy can all affect sleep disturbance in BCS.³³ Sleep disturbance is common in menopausal women independent of whether they are a BCS or a healthy woman.³³ Treatment with endocrine therapy can affect sleep disturbance as well as physical ability.³⁴ Aromatase inhibitors (AI), a type of endocrine therapy, have been associated with both insomnia and arthralgias.³⁴ In this study we will control for baseline menopausal symptoms by administering the Functional Assessment of Cancer Therapy-Endocrine Symptoms (FACT-ES) at baseline to control for differences between groups. To control for differences in menopausal status and treatment with endocrine therapy we will use self-report at enrollment.

Body mass index (BMI) and baseline physical activity are other possible confounders to be considered in our study. High BMI and obesity are prevalent in BCS and predictive of worse overall survival than normal BMI.^{31,35} Additionally, obesity is associated with sleep conditions such as sleep apnea and increased daytime sleepiness.³¹ Breast cancer treatment has been found to cause decreased physical activity both during and after treatment which can further contribute to sleep difficulties.⁵ Again, randomization of our sample to each intervention will attempt to control for differences in our population in regards to these factors. We will administer the International Physical Activity Questionnaire (IPAQ) at baseline to further account for any differences between groups.

2.3.4 Randomization and Blinding Technique

Randomization of participants to intervention will be based on two studies that investigated CM interventions on sleep in cancer survivors.^{7,36} Both of these RCTs used a

computerized random number generator and a 1:1 allocation to the intervention and control groups. Randomization in this way allowed for baseline characteristics to be controlled for and reduced the possibility of bias from confounding variables. The proposed study will follow the same guidelines for the allocation process.

Blinding of the proposed study will follow suit with a study that used a partial blinding protocol in which participants were blind to the hypothesis as well as the content of the other treatment group.⁷ Due to the nature of the intervention, participants cannot be blinded to their specific interventions. However, this method of partial blinding should allow for reduced information bias. In accordance with the same study, investigators and outcome assessors will be blinded to subject allocation at baseline and at assessment points thus creating a single-blinded trial.⁷

2.3.5 Intervention

The Qigong intervention will follow the framework used by three studies.^{14,20,37} The outcomes for our study will be based on the Layers Model created by Yang et al., and the framework of our intervention will follow this study in combination with another study that also based their intervention on the Layers Model.^{14,37} The first study created a Qigong exercise regimen comprised of seven movements; a sequence that was short and easy to remember but incorporated a wide range of motion for the entire body.³⁷ Their study centered on the need for the intervention to be accessible to nearly any level of physical ability and experience.³⁷ The second study employed a “Health Qigong” program based on gentle bodily movements, breathing exercises, and meditation taught and led by a Qigong practitioner and conducted in groups of 10-15 people to traditional

music.¹⁴ Unlike the first study whose intervention was three times per week for 24 weeks, we will follow suit with a third study in implementing a 12-week-long, biweekly intervention.²⁰ This will attempt to ensure participant adherence to the intervention and to avoid loss to follow up.

Instructors for the intervention will be trained under the accreditation standard guidelines for Tai Chi and Qigong by the Medical Tai Chi and Qigong Association (MTQA).³⁸ The guidelines were developed by health professionals, integrative medicine academics, Tai Chi and Qigong master instructors, and public safety officers from countries including USA, China, Canada, Korea, and several countries in Europe.³⁸

The light exercise comparison group will be based on the light exercise program that a referenced study implemented who compared Qigong to light exercise on sleep in survivors of prostate cancer.²⁰ Their light exercise program was led by an exercise physiologist and consisted of light resistance training and stretching, with the level of exertion and movement matching that of their Qigong intervention. As these researchers did, we will implement an active control in our study with light exercise matched on dose, frequency, and length to our Qigong intervention.

2.3.6 Primary and Secondary Outcome Measures

The Layers model is to be used as the basis for the outcomes in our study. It was developed by Yang et al. when they investigated the subjective experiences of Qigong/Tai Chi in older adults after a six-month intervention using semi-structured interviews.³⁷ The model is based on the idea that Qigong/Tai Chi affects participants in five overlapping dimensions: physical, mental, emotional, social, and spiritual. As

participants go deeper and longer into their practice, they transition from experiencing benefits in a single dimension (Layer 1) to experiencing complex integration of four and/or five dimensions (Layer 4).³⁷ Limitations of the study include small sample size, a purposeful selection process, and subjective data as results, bringing about considerations for both selection bias and information bias.³⁷ Still, the Layers Models presents a strong foundation to investigate our outcomes in this study. On this basis, our outcomes will be sleep disturbance as measured by the PSQI, objective sleep parameters as measured by a Fitbit Alta HR, and quality of life in the four other dimensions as measured by the FACT-B and the FACIT-sp.

The primary outcome of this study is subjective sleep disturbance as measured by the PSQI. The PSQI is a 19-item self-report questionnaire that assesses sleep quality and quantity.²⁹ The *Global Sleep Quality* scale is an overall sleep quality score that uses the 19 items to assess global sleep quality with higher scores indicating worse sleep quality.²⁹ It has a reliability coefficient, or Cronbach's alpha, of 0.83 in the general population.²⁹ There is evidence supporting the internal consistency of the PSQI in cancer patients. Data from two studies on the *Global Sleep Quality* scale from the PSQI in cancer patients yielded Cronbach's alphas of 0.81 and 0.77, demonstrating this tool as reliable in the assessment of sleep in cancer patients.²⁹ A score of greater than 5 on *Global Sleep Quality* distinguishes between good and poor sleepers and has a diagnostic sensitivity of 89.6% and specificity of 86.5%.²⁹ The questionnaire also yields 7 component subscales: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction.²⁹

One secondary outcome will be objective measures of sleep patterns recorded by a Fitbit Alta HR. Adding an objective measure of sleep will help reduce sources of response bias from the self-report PSQI. Polysomnography (PSG) is the gold standard objective measurement for the diagnosis of sleep disorders but there remain a few disadvantages.³⁹ The environment in which it is conducted can be uncomfortable, anxiety-provoking, and can interfere with sleep.³⁹ It is also expensive, requires trained technicians, and formal sleep facilities, yet less than 50% of sleep studies in recent years have been conducted in formal sleep facilities.³⁹ Wristband actigraphy is another objective measure of sleep widely used in sleep studies that senses accelerated motion.³⁹ However, this technology is also expensive with watches and software ranging from \$1225 to \$1850 a piece.⁴⁰ It has been found to overestimate sleep time and has a low sensitivity for detecting wake after sleep onset time (WASO).³⁹ Instead, this study will measure objective sleep patterns using the Fitbit Alta HR, a wearable wrist device that can measure both daytime activity and sleep.³⁹ It is easy to use, already widely used by many consumers, and inexpensive at about \$100 per device.⁴⁰

The Fitbit Alta HR uses body movement, heart rate, and heart rate variability (HRV) to assess multiple parameters of sleep.³⁹ In this study, the primary outcomes to be observed by use of the Fitbit will be total sleep time (TST) measured in minutes, sleep efficiency (SE) measured as a percentage, wake after sleep onset (WASO) measured in minutes, and sleep onset latency (SOL) measured in minutes; these outcomes correlate most with the subscales of the PSQI. The Fitbit Alta HR is a newer-generation Fitbit model and in a systemic review was found to better estimate TST, SE, and WASO than early-generation models.³⁹ In comparison to PSG, there was a lack of statistically

significant difference in values of WASO ($p=0.92$), TST ($p=0.29$), and SE ($p=0.19$), as well as only small differences in SOL (0.03).³⁹ The Fitbit Alta HR was also found to have higher sensitivity (0.95-0.96) and specificity (0.58-0.69) in detecting sleep epochs than earlier-model Fitbits and actigraphy.³⁹

Other secondary outcomes in this study will be the four other dimensions of quality of life affected by Qigong: mental, emotional, social, and spiritual. We will assess these using the FACT-B and the FACIT-Sp. The FACT-B is a 44-item self-rated questionnaire that is composed of the FACT-G plus a 9-item subscale specific to quality of life in those with breast cancer.⁴¹ The FACT-G component of the FACT-B is a multidimensional tool with five subscales including Physical Well-Being (PWB), Emotional Well-Being (EWB), Social Well-Being (SWB), Functional Well-Being (FWB), and Relationship with Doctor (RWD).⁴¹ The reliability coefficient for the FACT-G subscales are noted to be >0.80 , but only around 0.63 for the breast cancer subscale, the FACT-B.⁴¹ However, it has been noted that the breast cancer subscale has expected correlations with other measures of quality of life in this population and may be low due to items being specific to breast cancer patients.⁴¹ The FACIT-Sp is a 12-item subscale of the FACT-G and is used to assess spirituality specifically for those with chronic and/or life-threatening illnesses.⁴² It has a Cronbach's alpha reliability coefficient 0.87.⁴²

2.3.7 Sample Size and Statistical Significance

Previous data from studies using both Qigong and exercise and the PSQI will be used to calculate sample size for this study. One study found a mean change of 1.3 points (SD 3.2) on the PSQI at 3 months after an aerobic and strength-based intervention in BCS, an intervention close to that of the comparison group in our

proposed study.¹¹ Two other studies found similar mean changes at 1.4 units and 1.49 units; however, one study had a more frequent and vigorous exercise regimen than our proposed study, and the other was in endometrial cancer survivors, respectively.^{12,43} For these reasons, 1.3 was chosen as this study's expected mean change for the comparison group. A study found a mean change of 4.9 (SD 3.6) difference in the PSQI after a 12-week Qigong intervention and this study most closely follows the same length, intervention type, and study population as our proposed study.⁴⁴ Taking these studies into account we aim to detect an effect size of 3.6 units on the PSQI with a standard deviation of 3.6. Analysis of previous clinical trials using Qigong has demonstrated dropout rates between 2-10%; we will conservatively use 10% as an estimate of dropout rate in our study.^{25,26} Statistical analysis will follow that of a study that used a multiple time by interaction model.²⁶ Considering multiple comparisons, an alpha of 0.01 with a Bonferroni adjustment for multiple comparisons between groups will be used with 90% power. Accounting for a 10% dropout rate, a sample size of 36 participants per group, or 72 participants total will need to be recruited for the proposed study (Appendix C).

2.4 CONCLUSION

This literature review presents studies demonstrating the problem of sleep disturbance in BCS and its impact on quality of life. There is evidence supporting different avenues for both pharmacological and non-pharmacological treatment, though the literature reports that women are seeking more forms of CM treatment for their sleep disturbance. Qigong is one CM option that has been tested as a means for treating sleep disturbance in BCS and has demonstrated improvements, yet few robust studies exist

demonstrating its efficacy. Studies have lacked generalizability with small sample sizes and restricted sample population characteristics. They have also lacked active controls with an exercise comparison matched for dose, frequency, and duration of treatment. We propose a single-blinded RCT comparing the effects of Medical Qigong to light exercise on sleep disturbance in female BCS who are within six months to five years past completion of primary treatment for breast cancer. Adding to the literature of this treatment modality will inform patients on effective means of quality of life improvement and increase the knowledge base of medical providers when counseling patients.

2.5 REFERENCES

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CHAPTER 3: STUDY METHODOLOGY

3.1 STUDY DESIGN

The study design will be a two-arm, single-blinded RCT.

3.2 STUDY POPULATION AND SAMPLING

Participants will be sampled on a non-random, consecutive basis via convenience sampling from multiple sites including the Tumor Registry from Yale New Haven Hospital York Street Campus and Yale New Haven Hospital Saint Raphael Campus in New Haven, Connecticut. Participants will also be recruited from Sisters' Journey support group, breast and survivorship clinics, and private oncology practices, all in New Haven, CT, if meeting the study criteria.

See Table 1 for a complete list of inclusion and exclusion criteria. At baseline, participants will complete the PSQI and only those scoring above a 5 on *Global Sleep Quality*, indicating the presence of sleep disturbance, will be included in the study. Subjects will also complete the FACT-B, the FACIT-Sp, the FACT-ES, and the IPAQ at baseline. There will be a baseline characteristics enrollment survey completed upon enrollment.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Female age \geq 18 years old Clinical diagnosis of breast cancer stages 0-III 6 months to 5 years past completion of primary cancer treatment (surgery,	Diagnosis of a concurrent medical condition likely to influence short-term survival History of a major psychiatric illness requiring hospitalization including severe sleep-wake disorders

radiation, chemotherapy, or endocrine therapy)	Current alcohol or drug dependence
No evidence of cancer recurrence	Practice of Qigong or Tai Chi within the last year
Ability to read and write in English	Physical disabilities including an inability to walk unassisted, chronic pain while walking, or difficulty walking for 20 mins
Physically capable of participating in exercise	
A score of >5 in <i>Global Sleep Quality</i> on the PSQI	

3.3 SUBJECT PROTECTION AND CONFIDENTIALITY

The clinical site will be IRB approved under the Yale Human Investigations Committee (HIC). All research staff will undergo Health Insurance Portability and Accessibility Act (HIPAA) training before the start of the study. Any protected health information (PHI) will only be accessed by HIPAA-trained research staff and only accessed through university-approved secure electronic health records (EHR) on encrypted devices. A partial waiver of authorization under HIPAA will be requested to access the Tumor Registry PHI. Each participant will be provided with the details of the study as well as risks, benefits, and statements of confidentiality. They will be given an opportunity to read and ask questions regarding the most updated IRB approved Authorization and Consent form (Appendix A), and will be asked to give written, signed consent.

3.4 RECRUITMENT

The primary recruitment process will include the use of the hospital Tumor Registry from Yale New Haven Hospital York Street Campus and Yale New Haven Hospital Saint Raphael Campus which will generate a list of eligible subjects. We will

use passive physician consent for this recruitment strategy. The provider of each subject will be contacted via a letter from the primary investigator. The provider will be asked to identify any patients who should not be approached for the study. If providers do not identify patients not to contact within two weeks, the research staff will contact subjects from the Tumor Registry list to determine interest in participation. Additional recruitment will involve the distribution of flyers to the Sister's Journey support group, breast and survivorship clinics, and Yale Cancer Center Community Care practices.

Interested participants will be evaluated by research staff for eligibility. Research staff will provide information about the study including risks and benefits and schedule an appointment for informed consent and baseline assessments. Recruitment and enrollment into the study will take place over nine months on an ongoing basis.

3.5 STUDY VARIABLES AND MEASURES

Qigong Intervention: The Qigong intervention will consist of two, 60-minute group sessions per week for 12 weeks. Participants will be encouraged to practice at home outside of sessions using materials provided. Groups will consist of 12 people and will take place at various community centers in New Haven, CT led by accredited Qigong instructors. The intervention will be based on seven movements: "Preparatory Form", "Lazy About Tying Coat", "Fist Under Elbow", "Step Back and Whirl Arms on Both Sides", "Part Horse's Mane", "Wave Hands Through Clouds", and "Close".¹ Sample Qigong movements can be viewed in Figure 1. The length of meditations during class will increase throughout the 12 weeks to build experience with the practice and attempt to reap the most benefits. Each session will include a 5-minute warm up, 40 minutes of

Qigong exercise, and 5 minutes of relaxation at the end. A 10-minute break will be provided mid-way through the 40-minute exercise session.

Figure 1. Sample Qigong Movements



Chang PS, Knobf MT, Oh B, Funk M. Physical and psychological effects of Qigong exercise in community-dwelling older adults: An exploratory study. *Geriatr Nurs.* 2018;39(1):88-94.

Active Control: The light exercise program will consist of group exercise classes matched for the time of the Qigong intervention: two, 60-minute sessions per week for 12 weeks. Participants will be given materials and encouraged to practice their exercises at home on off days. The program will be implemented in groups of 12 and will be led by a trained exercise physiologist. Exercises will focus on light resistance training and stretching with a mild aerobic component matching the level of exertion and movement expected in the Qigong group. Stretching exercises will align with the targeted muscle groups of that day's training. The light exercise group will also be conducted at community centers in New Haven, CT, but at different locations than the Qigong group

as to not allow the two groups to have a chance of seeing the other intervention. The active control will have the opportunity to enroll in Qigong classes equivalent to our intervention at the conclusion of the study free of charge.

Adherence to Assigned Intervention: Adherence to the interventions will be ensured using documented attendance at each session as well as at assessment points. Instructors at each session will pass around an attendance sheet. Additionally, research staff will conduct random observations of sessions of each group to ensure intervention fidelity. Participants in both groups will be asked to log hours of exercise outside of group classes. Participants will be encouraged to discontinue their usual exercise routine during the study.

Primary and Secondary Outcomes: The primary outcome measure for this study is sleep disturbance as measured by the PSQI (Appendix B). A Fitbit Alta HR will measure objective sleep parameters including total sleep time (TST, min), sleep efficiency (SE, %), wake after sleep onset (WASO, min), and sleep onset latency (SOL, min). These objective outcomes will be considered secondary outcome measures. Fitbits will be given to participants at the onset of study free of charge and participants will wear them overnight the night before each assessment point. Other secondary outcomes include quality of life in the five remaining dimensions as presented in the Layers Model of Qigong—mental, emotional, social, and spiritual—and will be measured using the FACT-B and the FACIT-Sp.

Baseline Variables: At baseline participants will complete an enrollment survey which will ask patients about age, cancer stage at diagnosis, time since treatment, type of treatment, treatment with endocrine therapy, education level, income, menopausal status,

BMI, and insurance coverage. Baseline characteristics will also be gathered through the EHR if a participant is unsure of an answer. Participants will complete the PSQI, FACT-B, and FACIT-Sp at baseline; they will also complete the FACT-ES and the IPAQ to assess baseline endocrine symptoms and physical activity, respectively.

3.6 BLINDING OF INTERVENTION AND OUTCOME

Blinding of intervention: Due to the nature of the intervention it is not possible to blind participants or instructors to both groups. However, participants will be blinded to the hypothesis as well as to the alternative group for the duration of the study. Instructors will also be blinded to the hypothesis and will only be informed that the study is for improvement in lifestyle for BCS. Participants will be instructed not to discuss their intervention when undergoing assessments.

Blinding of Outcome: The study will follow a single-blinded approach where investigators and outcome assessors will be blinded to allocation at baseline and each assessment point.

3.7 ASSIGNMENT OF INTERVENTION

Upon enrollment, participants will complete baseline assessments and then be randomized to intervention. A computerized random number generator will randomize patients with 1:1 allocation to intervention or control. Investigators and other staff will be blind to allocation as each allocation will be concealed in a sequentially numbered, opaque, and sealed envelope. They will also not have access to participant data before allocation.

3.8 DATA COLLECTION

Subjects will complete the IPAQ and FACT-ES at baseline and all remaining questionnaires at baseline, at the end of the 12-week intervention, and again at 3 months and 6 months follow up. The 6-month follow up timepoint will allow researchers to assess the lasting effects of the Qigong intervention in our population. Participants will retrieve Fitbits at enrollment and wear them overnight at home the night before each assessment point. The next day upon questionnaire assessment participants will return Fitbits to research staff for data collection and receive them back before leaving. Research staff will be trained on each questionnaire and on Fitbit software, and will score each tool at every time point.

3.9 SAMPLE SIZE CALCULATION

A simple t-test calculator Power and Precision version 4.0 (Biostat Inc.) was used to look for a difference in means for an anticipated effect size of 3.6 units on the PSQI with a standard deviation of 3.6, though the actual test will be a fixed-effects model. A sample size of 32 participants per arm is needed to provide 90% power. To account for multiple comparisons, we are adjusting the alpha to 0.01 with a Bonferroni adjustment for multiple comparisons between groups and the effects of time interaction. The final sample size will account for an estimated 10% dropout rate and thus a total of 36 participants will be randomized to each arm for a total of 72 participants in the study (Appendix C).

3.10 ANALYSIS

Descriptive statistics of baseline characteristics will be run. Continuous variables including age and time since cancer treatment completion will be reported as means and

standard deviations. A student t-test will be used to compare continuous variables at baseline. Relative frequencies will be used for categorical variables including income, race, insurance status, employment status, education level, cancer treatment type, menopausal state, and other chronic health conditions including diabetes, hypertension, hypo- or hyperthyroidism, and any autoimmune disorders. Comparisons between categorical variables will be conducted using a chi-square test.

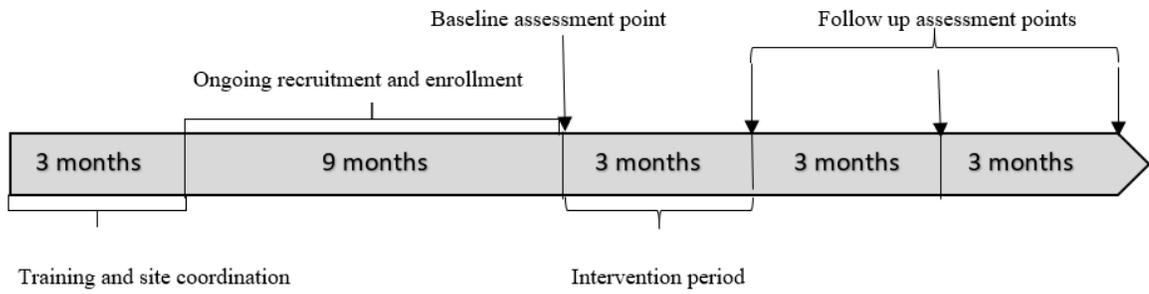
Outcome data will be analyzed using an intention-to-treat analysis. Baseline scores on the PSQI, FACT-B, FACIT-Sp, IPAQ, and FACT-ES will be compared between groups using a student t-test. Baseline data from the initial night sleeping with the Fitbit (i.e. TST, WASO, SOL all measured in minutes, and SE measured as a percentage) will also be compared between groups with a student t-test. The primary outcome of this study, mean change in sleep disturbance as measure by the PSQI, will be operationalized as a continuous variable. To determine the statistical significance of the effect of Qigong versus light exercise, we will use hierarchical linear mixed-effects models to assess the independent effects of the intervention group (either Qigong or light exercise) and time (baseline, post-intervention, 3-month follow up, and 6-month follow up) for the primary and secondary outcomes. The baseline measurement for each outcome variable will be the reference value for time, with fixed effects for post-intervention, 3-month follow up, and 6-month follow up. There will be three, time by intervention interaction terms since there will be three fixed effects for time (post-intervention, 3-month follow-up, a 6-month follow up).

3.11 TIMELINE AND RESOURCES

The timeline of the proposed study can be found in Figure 2. The proposed study will take place within two years. Training of research staff and coordination with intervention sites will take place over the first 3 months. Recruitment of participants for the study will take place over the next 9 months. The intervention will be 3 months. Follow up assessments will occur at the end of the intervention, at 3 months, and at 6 months after completion of the intervention. Data analysis and manuscript preparation will take place within 6 months of study completion.

The principal investigator (PI) for the study will be M. Tish Knobf, PhD, RN, FAAN and the co-principal investigator (co-PI) will be Elisabeth Mirenda, PA-SII. Research assistants and statisticians at Yale University will be recruited to help conduct the study and will be trained in the scoring of each assessment tool, as well as in the use and scoring of Fitbit software. Qigong instructors and exercise physiologists will be recruited from the region and compensated for their time. Before the start of the study and within the first 3 months, the PI and co-PI will approach community centers within the New Haven, CT area to request the use of facilities for the study. Participants will be provided with a Fitbit device at enrollment and will be asked to wear the device overnight the night before each assessment. Participants will be compensated with a \$20 Visa gift card at every assessment point and free parking at study sites. Participants will be given the opportunity to keep the Fitbit device at the end of the study if desired.

Figure 2. Timeline of Intervention



3.12 REFERENCES

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CHAPTER 4: CONCLUSION

4.1 ADVANTAGES AND DISADVANTAGES

This study will be the first to use an RCT design to compare the practice of Qigong to light exercise with a focus on improving sleep in BCS. Unlike previous studies that have lacked an active control group, our study will potentially gain insight into the unique properties of the practice of Qigong and its multidimensional effects by directly comparing it to an active exercise control.^{1,2} Through a randomized controlled design, we hope to gain insight into the benefits of Qigong by minimizing selection bias and potential bias from confounding variables. Unlike previously discussed studies that have been limited in sample size and single sites, we hope to extend the generalizability of our results by gaining a larger sample size and conducting the study at more than one research site.^{1,2} By recruiting patients from the Sisters' Journey support group we will create a more heterogeneous sample in order to further improve the generalizability of results. Finally, providing both a subjective and objective measure of sleep will allow researchers to gain a better understanding with more robust evidence as to the efficacy of our intervention on sleep.

There are some limitations to the proposed study that must be considered. First, the single-blinded design presents the possibility for participants to be biased in regards to their intervention placement. By blinding participants to the hypothesis and to the comparison group we will attempt to minimize adverse effects on results. There is a possibility that the length of the intervention of 12 weeks may not be long enough to provide lasting effects from the Qigong intervention and future studies may consider providing a longer outcome. However, this study is designed to prevent drop out and the

length of 12 weeks should help control for it. Our study recommends that women discontinue their normal exercise routine upon enrollment, yet it is not possible to completely limit women from partaking in other exercises outside of their assigned intervention. We will attempt to control for this potential limitation by running the IPAQ questionnaire on baseline physical activity.

By using a subjective measure of sleep quality in our population, there is an opportunity for participants to influence their responses by overestimating or underestimating aspects of their sleep habits. We will attempt to control for this form of response bias by initiating a concurrent objective measure of sleep with the Fitbit device. It must be noted that previous studies have demonstrated inconsistencies between subjective and objective measures of sleep.³ However, none of these studies utilized the Fitbit device as an objective measure and rather involved either PSG or actigraphy. In this study the Fitbit will only be worn at assessment points (four times throughout the study) for one night at a time, whereas the PSQI will ask for information regarding at least the previous 30 days of sleep. This could potentially provide inconsistencies between these two measures. The Fitbit has not been widely studied as an objective measure of sleep, especially in cancer populations as it is still a new device used for sleep. However, this study poses an opportunity to increase knowledge and data regarding the device and sleep. Finally, the Fitbit device is a user-dependent device; there will be those who are familiar and those who are unfamiliar with the device. The device also may not be user-friendly to older women who are less familiar with the technology. As with any study utilizing technology, these limitations must be considered when analyzing results.

4.2 CLINICAL AND PUBLIC HEALTH SIGNIFICANCE

Breast cancer diagnosis and treatment can adversely affect women's physical, psychological, emotional, social, and spiritual well-being and can last for years after diagnosis. With improved survival, providers will be treating increasingly more women with post-treatment side effects and comorbidities that affect quality of life, and women will be seeking treatment options for them. It is important that providers are equipped with evidence-based guidelines for symptom management. Insurance companies may be more inclined to pay for alternative treatment modalities when the literature is more robust regarding their efficacy. If the findings of this study improve sleep and quality of life in BCS, providers will have evidence for an alternative sleep and healthy lifestyle behavior to recommend. Qigong is accessible and easy to learn for all ages and abilities. Previous studies have compared Qigong to CBT-I and future studies should consider comparing Qigong to medical treatments and how it could be beneficial to implement lifestyle modalities before medicine.

4.3 REFERENCES

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APPENDICES

APPENDIX A: AUTHORIZATION AND CONSENT FORM

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE
YALE NEW HAVEN HOSPITAL

Study Title: Medical Qigong Versus Exercise on Sleep Disturbance and Quality of Life in Breast Cancer Survivors

Principal Investigator: M. Tish Knobf, PhD, RN, FAAN

Co-Investigator: Elisabeth Mirenda, PA-SII

Funding Source: Yale University School of Medicine Physician Associate Program

Invitation to Participate and Description of Project

You are invited to participate in a research study investigating sleep and other aspects of quality of life in breast cancer survivors using two different types of exercise-based interventions. You have been asked to participate because you have a history of a diagnosis of breast cancer and began treatment within the last year. Approximately 72 women with breast cancer will participate in this study.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of the research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits, and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you agree to participate in this study, you will be randomly assigned to one of two types of exercise classes in groups of 10-15 people. Random assignment is like flipping a coin with a 50/50 chance of one group or the other. You will be asked to attend an hour class twice per week for 12 weeks. You will also be encouraged to work on what you have learned in class at home on your days off. These classes will take place at community centers in the New Haven, CT area. Parking will be free of charge. You will be asked to log your exercise time outside of class. You will receive reminder calls or texts for sessions from a research assistant. Randomization will be done by a computer program and will not be based on any personal baseline information. During the course of the study you will be encouraged to discontinue your current exercise regimen.

At the start of the study, you will complete 5 questionnaires regarding your sleep habits and other aspects of your physical, emotional, and psychological well-being. You will also complete these questionnaires at the end of the 12-week exercise course, and at visits 3 and 6 months after the end of the course. You will be compensated for attendance to assessment visits in the form of a \$20 Visa gift card at each assessment point.

You will be asked to wear a Fitbit wristband device overnight on 4 different nights throughout the study. Fitbits will be worn the night before your assessment visit at the start of the study, after the 12-week intervention, and at the 3- and 6-month visits. They will be returned to research staff at your assessment visit. Information taken from Fitbits will include heart rate, respiratory rate, and sleep time. You will be allowed to keep the Fitbit at the end of the study if you desire.

You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate. Research results will not be returned to your doctor. If research results are published, your name and other personal information will not be given.

Risks and Inconveniences

We do not anticipate any major risks in participating in this study. Due to our intervention being based on basic exercise principles and a decrease in physical activity among women after breast cancer therapy, there is a potential risk for some side effects such as muscle aches or strained muscles. Though risks of negative outcomes are small, our interventions may make participants more aware of psychosocial factors in their lives and emotional distress. We can provide referrals to appropriate providers if needed.

There is a risk of breach of confidentiality about your health status and participation in this study, though this is unlikely to occur. All research staff will be thoroughly trained and certified in the privacy of research studies.

Benefits

Benefits of participation in this study may include improvements in mental, emotional, social, and spiritual health, improvements in sleep, and improvements in physical health. This study may also provide information on how to integrate complementary therapy, such as non-strenuous exercise, into daily lives.

Economic Consideration

Exercise classes will be provided free of charge. Parking at facilities will be free. You will be compensated at each assessment visit in the form of a \$20 Visa gift card. Upon completion of the study you will be gifted the Fitbit device if you desire to keep it.

Treatment Alternatives/ Alternatives

The alternative to participating in this study is to decline participation. If you do not wish to participate you will be provided the standard treatment for sleep-related issues at the discretion of your healthcare provider.

Confidentiality and Privacy

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or state law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Information will be kept confidential by using only identification numbers on study forms, storing signed forms in locked cabinets, and password protecting data stored on a computer. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific permission for this activity is obtained.

We understand that information about your health is personal, and we are committed to protecting the privacy of the information. If you decide to be in this study, the researcher will get information that identifies your personal health information. This may include information that might directly identify you, such as your name, birth date, or address. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you and your coded information, and this link will be kept secure and available only to the principal investigator or selected members of the research team. Any information that can identify you will remain confidential. The link to your personal information will be kept for 5 years, after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

The information about your health that will be collected in this study includes:

- Research study records
- Records about phone calls made as part of this research
- Records about your study visits

Information about you and your health which might identify you may be used by or given to:

Representatives from Yale University, the Yale Human Research Protection Program, and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.

By signing this form, you authorize the use and /or disclosure of the information described above for this research study. The purpose of the uses and disclosures you are

authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and those hospitals involved in this study are required to comply with HIPAA and to ensure the confidentiality of your information. You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies. This authorization to use and disclose your health information collected during your participation in this study will never expire.

Voluntary Participation and Withdrawal

Participation in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing from the Study

If you do become a subject of this study, you are free to stop and withdraw at any time during its course.

To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer wish to participate. This will cancel any future appointments. Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw or take away your permission to use and disclose your health information at any time. If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary, to ensure the integrity of the study and/or study oversight.

You do not give up any of your legal rights by signing this form.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you do not understand and to consider this research and the consent form carefully—as long as you feel is necessary—before you make a decision,

Authorization and Permission:

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purpose, the particulars of my involvement, and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use [and give out] information about me for the purpose described in this form. By refusing to give permission, I understand that I will not be able to be in this research study.

Name of Subject: _____

Signature: _____

Date: _____

Signature of Principal Investigator

Date

Or

Signature of Person Obtaining Consent

Date

If after you have signed this form you have any questions about your privacy rights, please contact the *Yale Privacy Officer at (203) 432-5919.*

If you have further questions about this project or if you have a research-related problem, you may contact the co-Principal Investigator, Elisabeth Mirenda. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the *Yale Human Investigation Committee at (203) 785-4688.*

APPENDIX B: SAMPLE PSQI

The Pittsburgh Sleep Quality Index (PSQI)

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

1. When have you usually gone to bed?
2. How long (in minutes) has it taken you to fall asleep each night?
3. When have you usually gotten up in the morning?
4. How many hours of actual sleep do you get at night? (This may be different than the number of hours you spend in bed)

Choose: Not during the past month (0), Less than once a week (1), Once or twice a week (2), Three or more times a week (3)

5. During the past month, how often have you had trouble sleeping because you...
 - a. Cannot get to sleep within 30 minutes
 - b. Wake up in the middle of the night or early morning
 - c. Have to get up to use the bathroom
 - d. Cannot breathe comfortably
 - e. Cough or snore loudly
 - f. Felt too cold
 - g. Felt too hot
 - h. Have bad dreams
 - i. Have pain
 - j. Other reason(s), please describe, including how often you have had trouble sleeping because of this reason(s):
6. During the past month, how often have you taken medicine (prescribed or “over the counter”) to help you sleep?
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?

Choose: Very good (0), Fairly good (1), Fairly bad (2), Very bad (3)

9. During the past month, how would you rate your sleep quality overall?

Component 1: #9 score _____

Component 2: #2 score (≤ 15 min=0; 16-30 min=1; 31-60 min=2, >60 min=3) + #5a score (If sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3) _____

Component 3: #4 Score ($>7=0$; 6-7=1; 5-6=2; $<5=3$) _____

Component 4: (total # of hours asleep)/ (total # of hours in bed) x 100;
>85%=0, 75%-84%=1, 65%-74%=2, <65%=3_____

Component 5: Sum of Scores #5b to #5j (0=0; 1-9=1; 10-18=2; 19-27=3) _____

Component 6: #6 score _____

Component 7: #7 score + #8 score (0=0; 1-2=1; 3-4=2; 5-6=3) _____

Add the seven component scores together. Global PSQI Score: _____

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APPENDIX C: SAMPLE SIZE CALCULATION

Group	Population Mean	Standard Deviation	N Per Group	Standard Error	99% Lower	99% Upper
Population 1	1.3	3.6	32			
Population 2	4.9	3.6	32			
Mean Difference	-3.6	3.6	64	0.90	-5.98	-1.22
Alpha= 0.010, Tails= 2				Power	91%	

Power and Precision Version 4.0 Biostat Inc., Englewood, NJ

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