SLEEP DISTURBANCE IN INDIVIDUALS DIAGNOSED WITH COLORECTAL CANCER: FACTORS ASSOCIATED WITH SLEEP DISTURBANCE AND CHANGES IN SLEEP DISTURBANCE

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A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Health Policy and Management in the Gillings School of Public Health.

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ABSTRACT

Theresa Marie Coles: Sleep Disturbance in Individuals Diagnosed with Colorectal Cancer: Factors Associated with Sleep Disturbance and Changes in Sleep Disturbance
(Under the direction of Bryce Reeve)

This dissertation evaluates sleep disturbance in individuals with colorectal cancer (CRC), with the objectives of providing insight on the patient, disease and treatment characteristics associated with sleep disturbance (and change in sleep disturbance), investigating whether there is variation in these factors across levels of sleep disturbance severity (and change in sleep disturbance severity), and finally assessing the relationship between sleep disturbance (and change in sleep disturbance) and exercise (and change in exercise). We also investigated possible heterogeneity in the relationship between sleep disturbance and these factors. Data were obtained from the MY-Health study, a community-based observational study of adults diagnosed with cancer collected through four Surveillance, Epidemiology and End Results (SEER) cancer registries. Patient-Reported Outcomes Measurement Information System (PROMIS) measures were administered to patients to measure sleep, anxiety, depression, fatigue, pain interference, and social and physical functioning. Participants (n = 734) self-reported demographic information, comorbidities, treatment type, and dates of treatment. Data were collected at two time points after diagnosis: approximately 10 and 17 months after diagnosis. Regression mixture models (RMM) (to evaluate heterogeneity) and multiple regression models were used to evaluate the relationship between sleep disturbance and patient, disease, and treatment factors, as well as exercise. Overall, results of the RMM analyses provided evidence that the relationship between sleep disturbance and patient, disease, treatment characteristics, and exercise levels was consistent at every severity level of sleep disturbance. Factors yielding statistically significant relationships with sleep disturbance at approximately 10 months after CRC were 2 or more comorbid conditions, non-retirees, anxiety, pain interference, and fatigue. Change in anxiety and fatigue yielded statistically significant relationships with change in sleep disturbance. Coefficients were small; CRC patients should be screened for sleep disturbance throughout the cancer continuum. We found no relationship between exercise approximately

at or above American College of Sports Medicine guidelines and sleep disturbance at approximately 10 and 17 months after CRC diagnosis (or change increase in exercise and change in sleep disturbance). Exercise has clear health benefits and although this study does not provide evidence that exercise is associated with better sleep quality, CRC patients should continue to be encouraged to exercise.

To Dragos and Luciana

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CHAPTER 1. INTRODUCTION

This dissertation highlights sleep as an important but often overlooked aspect of health-related quality of life (HRQOL) in individuals diagnosed with colorectal cancer (CRC). The prevalence of insomnia in cancer patients undergoing chemotherapy is 43%,[1] between 30% and 87% of cancer patients are estimated to experience sleep disturbance.[2] The prevalence of sleep disturbance in CRC patients is unknown but a secondary data analysis from a randomized control trial estimated that at least half of individuals diagnosed with CRC experience decrements in sleep.[3] Although CRC is the third most common adult cancer diagnosed in the United States[4] with more than 1.1 million individuals currently living with the disease,[5] few studies examined sleep quality in the CRC population. HRQOL differs by cancer site[6] and individuals diagnosed with CRC manage unique consequences of CRC treatment such as bowel control and stomas along with more general aspects of cancer and cancer treatment such as fatigue, anxiety, pain, and nausea,[7,8] all of which have implications for sleep quality.

Consequences of sleep disturbance include decreased cognitive functioning[9] and fatigue,[10,11] and cancer patients attribute impaired daytime functioning, trouble keeping up at work and social activities, and mood disturbance to sleep disturbance.[12] Sleep disturbance is also a risk factor for infectious and cardiovascular diseases and depression[13] and is associated with loss in work productivity and work quality as well as an increased number of visits to health professionals.[14] With a 90% five-year survival rate for localized disease and 70% five-year survival rate for regional stages,[15] patients diagnosed with CRC can expect to live relatively healthy lives for some time. With much of life still ahead for many CRC survivors, sleep quality should be assessed because the consequences of poor sleep negatively impact HRQOL, reduce work productivity, and increase risk of developing other comorbidities. Yet sleep has rarely been included as an outcome in CRC research.

Individuals diagnosed with CRC may experience a range of sleep quality stretching from no sleep disturbance to severe insomnia (or another diagnosed sleep disorder). The etiology and severity of sleep disturbance may vary from patient to patient. For example, sleep disturbance may be caused by anxiety

related to cancer diagnosis for one person,[16-19] but another person may attribute sleep disturbance to physical symptoms such as pain or nausea,[20,21] and these factors may vary by *severity* of sleep disturbance. Chemotherapy, in particular, has been shown to negatively impact circadian rhythms[19,22] and is associated with sleep disturbance in other cancers; the relationship between sleep disturbance and chemotherapy may be time dependent, with patients experiencing worse sleep disturbance during or immediately following chemotherapy. The relationship between sleep disturbance and CRC treatment is unknown. By understanding patient-level factors associated with poorer or better quality sleep, researchers could provide new insight to clinicians on the patient, disease, and treatment characteristics associated with worse sleep disturbance or worsen*ing* sleep disturbance. Identifying patient-level factors associated with sleep disturbance may also provide insight in the design of future randomized studies to identify patients who would benefit most from an intervention for severe sleep disturbance.

Once sleep disturbance has been identified in individuals diagnosed with CRC, patients who would benefit from interventions to improve sleep quality are faced with a number of treatment options aimed mostly at treating clinically significant levels of insomnia or other diagnosed sleep disorders. Exercise improves sleep quality in healthy individuals[23] and is recommended by the American College of Sports Medicine in cancer patients because it improves physical function, HRQOL, and cancer-related fatigue.[24] Little research has explored the relationship between exercise and sleep in the CRC population, and assessing the relationship between exercise and sleep disturbance in CRC patients is important because exercise may provide a simple, safe, practical, low-cost option for managing sleep disturbance that can be tailored to each patient. Further, exercise may mitigate sleep disturbance that is meaningful to a patient but does not meet specifications to be diagnosed as a clinical sleep disorder.

This dissertation evaluates sleep disturbance in individuals with CRC, with the objectives of providing insight on the patient, disease, and treatment characteristics associated with sleep disturbance, investigating whether there is variation in these factors across levels of sleep disturbance severity and finally assessing the relationship between sleep disturbance and exercise.

To address these objectives, we conducted a secondary data analysis using a community-based dataset including adults diagnosed with stage I-III CRC. Data were collected at two time points: approximately 10 months after CRC diagnosis and again around 17 months after diagnosis, key time

points in the cancer continuum when most stage I-III CRC patients are transitioning (or have transitioned) off treatment. This dissertation includes two overarching research aims:

Aim 1: Evaluate the relationship between sleep disturbance and patient, disease, and treatment characteristics:

- Aim 1a: evaluate relationship between sleep disturbance and patient, disease, and treatment characteristics approximately 10 months after diagnosis;
- Aim 1b: evaluate relationship between change in sleep disturbance and patient, disease, and treatment characteristics from approximately 10 to approximately 17 months after diagnosis.

Primary hypothesis: Time since last chemotherapy treatment will be among the strongest factors associated with sleep disturbance outcomes.

Aim 2: Evaluate the relationship between sleep disturbance and exercise.

Primary hypotheses: Patients who were classified as moderately or highly active exercisers will report less sleep disturbance than patients who did not exercise. Patients who increased exercise activity groups from 10 to 17 months after diagnosis would experience a decline in sleep disturbance.

This dissertation is organized into seven chapters. Chapter 2 is a literature review, describing CRC treatment and known HRQOL challenges for individuals diagnosed with CRC, the conceptual model for this research, known factors associated with sleep disturbance and exercise, and previous research on sleep disturbance. Chapter 3 provides a description of the overall methods used in this dissertation, outlining the overall study design, variables of interest, analytic models, and power analyses. Chapters 4 through 6 describe the three studies driving this dissertation. Chapter 4 (manuscript 1) addresses Aim 1 in its entirety: identifying patient, disease, and treatment characteristics associated with of sleep disturbance (and change in sleep disturbance) in individuals diagnosed with stage I, II, or III CRC and whether there was variation in patient, disease, and treatment characteristics across levels of sleep disturbance severity (or magnitude of change in sleep disturbance). Chapter 5 (manuscript 2) focuses on the relationship between the amount of exercise and severity of sleep disturbance cross-sectionally at approximately 10 and about 17 months after CRC diagnosis. Chapter 6 (manuscript 3) further addresses Aim 2 by evaluating the relationship between change in sleep disturbance and change in exercise from

approximately 10 to 17 months after diagnosis. Chapter 7 summarizes dissertation results and discusses clinical and policy relevance and future research.

CHAPTER 2. LITERATURE REVIEW

2.1 Overview

Sleep disturbance was considered a core cancer symptom by the National Cancer Institute Steering Committee[25] and a Delphi consensus,[26] but research on sleep in cancer patients is minimal compared to other aspects of health-related quality of life (HRQOL), particularly in the colorectal cancer (CRC) population. Within the cancer population, sleep studies are most prominent in breast cancer. Sleep literature from the general population and other cancers are integrated in this literature review to supplement not-yet-developed information in the literature about the CRC population. This chapter presents background information on key topics related to CRC (e.g., risk factors, treatment, prognosis) and sleep in CRC patients (e.g., factors associated with sleep disturbance, relationship between sleep and exercise). Chapter 2 also presents the conceptual model that ties these research topics together.

2.2 Colorectal Cancer Summary

CRC is cancer that starts in the colon or rectum.[27] CRC is the third most common adult cancer in the United States[4] and more than 1.1 million people live with CRC,[5] approximately the population of Rhode Island.[28] About 135,430 new cases are expected to be diagnosed in 2017.[29]

2.2.1 Risk Factors

Risk factors for CRC include certain health conditions, lifestyle factors, and specific racial/ethnic backgrounds. Health conditions associated with higher risk of CRC include inflammatory bowel disease, family history of CRC or polyps, genetic syndromes such as familial adenomatous polyposis or Lynch syndrome, and type 2 diabetes.[30,31] Lifestyle factors associated with increased risk of CRC include lack of physical activity, diet low in fruits and vegetables, obesity, and alcohol and tobacco use.[30] Some racial and ethnic backgrounds put patients at greater risk for developing CRC. For example, for unknown reasons, African Americans have the highest CRC incidence and mortality rates in the United States.[31] Ashkenazi Jews have the highest CRC risk in the entire world, a status attributed to a specific gene.[31] Another possible risk factor for CRC is night shift work.[32]

2.2.2 Symptoms that Signal CRC Prior to Diagnosis

CRC usually develops from adenomatous polyps in the colon or rectum.[33] Symptoms of CRC are usually due to these polyps, such as blood in stool, abdominal pain, aches or cramps that do not go away, and unexplained weight loss.[34] Some patients do not experience any symptoms,[34] highlighting the importance of CRC screening.

2.2.3 Screening

Treatment works best when CRC is found early, therefore regular screenings for adults between the ages of 50 and 75 are recommended by the United States Preventive Services Task Force (USPSTF).[35] Screening may include high-sensitivity fecal occult blood testing (FOBT), sigmoidoscopy, and colonoscopy.[36] High-sensitivity FOBTs are noninvasive and are recommended once a year.[37] Individuals collect a small amount of stool for lab testing where the samples are tested for blood.[37] A sigmoidoscopy is recommended every five years.[38] During a sigmoidoscopy, a physician inserts a thin, flexible tube into the rectum to detect polyps or cancer inside the rectum and lower one-third of the colon.[37] Colonoscopy is recommended every ten years and is similar to sigmoidoscopy except that the physician is able to check for polyps and cancer inside the rectum and entire colon.[37] During this test, clinicians may remove any polyps and some cancers.[37]

The median age of CRC diagnosis is 68 years, and most CRC patients are diagnosed between ages 65 and 75.[5] CRC is more often diagnosed at later stages with only 40% of patients diagnosed with localized-stage disease.[39] Incident cases are almost evenly split between males (47%) and females (36%).[5] Incidence rates are highest in blacks and lowest in Asians/Pacific Islanders.[40]

2.2.4 Stages and Grades

CRC stages and grades guide clinicians on how to treat the cancer. CRC staging is based on the results of various tests such as physical exams, biopsies and imaging tests, and surgery.[41] The American Joint Committee on Cancer (AJCC) Tumor Node and Metastases (TNM) system is most often used to stage CRC.[41] Clinicians take these three factors into account when naming the stage. Specifically, they will look at how far the *tumor* has grown into the wall of the intestine or nearby organs, if the cancer has spread to nearby lymph *nodes*, and if the cancer has *metastasized* (spread) to other organs of the body.[41] If CRC spreads, it usually spreads to the liver or lungs.[41] The cancer is given an overall numeric stage,

which is then subdivided into stage groupings determined by the status of the tumor, lymph nodes, and metastases (e.g., T, N, and M). Patients with stage 0 cancer are at the earliest stage in which the cancer has not grown beyond the inner layer of the colon or rectum.[41] Stage I cancer is defined as cancer that has grown through the inner layers of the colon or rectum (e.g., mucosa) but has not spread to nearby lymph nodes or distant sites.[41] Stage II cancer includes cancer that has grown into the outermost layers of the colon or rectum and may have reached nearby tissues but has not reached lymph nodes or distant sites.[41] Stage III is defined as cancer that has spread to nearby lymph nodes and may have grown to other nearby tissues or organs.[41] Stage IV CRC includes cancer that has grown through the walls of the colon or rectum and may or may not have spread to nearby lymph nodes but has spread to at least one distant organ or distant lymph nodes.[41] CRC grades also guide clinicians in treatment and prognosis decisions. CRC grade is decided based on a visual assessment of the cancer under a microscope[41] and grades are assigned between 1 and 4. Grade 1 indicates that the cancer resembles normal colorectal tissue and grade 4 indicates that the cancer looks very abnormal.[41] Lower-grade cancers are expected to grow and spread more slowly than higher-grade cancers.[41]

2.2.5 Treatment

Treatment for CRC varies by stage and grade. Stage I CRC includes surgery (which may take place during a colonoscopy) to remove the polyp. If the grade is high or if cancer cells were located at the edges of the polyp, follow-up surgery may be indicated. If the cancer was not part of a polyp, patients undergo a partial colectomy to remove a section of the colon and nearby lymph nodes. Other than surgery, no additional treatment is indicated for stage 0 and I CRC.[42,43]

Treatment for stage II CRC includes surgery to remove the section of the colon or rectum afflicted by cancer and nearby lymph nodes.[42,43] If the colon cancer is deemed higher risk, oncologists may recommend chemotherapy as an adjuvant treatment (after surgery).[42] Chemotherapy options include 5-FU, leucovorin and capecitabine.[42,43] If there is uncertainty about the surgery removing all of the cancer, providers may recommend radiation therapy to destroy any remaining cancer cells.[42,43] Stage II rectal cancer is more aggressive and treatment includes chemotherapy, radiation, and surgery.[43] To begin, patients with stage II rectal cancer may undergo both chemotherapy and/or radiation therapy.[43] The second phase is typically surgery, followed by the third phase, chemo.[43]

Stage III colon cancer includes surgery to remove the section of colon with cancer as well as nearby lymph nodes[42] and surgery is almost always followed up with adjuvant chemotherapy using the FOLFOX (5-FU, leucovorin and oxaliplatin) or CapeOx (capecitabine and oxalipatin) regimens (other regimens may apply depending on personal characteristics).[42] As with Stage II colon cancer, radiation therapy may be advised if it were suspected that cancer cells were left behind during surgery.[42] The treatment for stage III rectal cancer usually includes chemotherapy, radiation, and surgery[43]. First, patients are administered chemotherapy and radiation (called chemoradiation) to shrink the cancer before surgery.[43] The surgery removes the rectal tumor and nearby lymph nodes (and sometimes includes pelvic exenteration if the cancer has reached nearby organs).[43] After surgery, patients undergo chemotherapy for approximately six months.[43]

Patients with stage IV CRC have cancer in distant organs and tissues, therefore surgery is indicated when cancer has spread to only a few areas.[42] The purpose of the surgery is to remove the affected colon, nearby lymph nodes, and other tissues where the cancer may have spread. The cancer is either pre-treated with chemotherapy before surgery (called neoadjuvant chemotherapy) or chemotherapy may be given after surgery (adjuvant therapy) (or both).[42] If metastases are too large to be removed via surgery, chemotherapy is the primary treatment. In this case, surgery may be needed for other reasons, such as unblocking the colon.[42] Chemotherapy regimens for stage IV colon and rectal cancer are extremely varied but may include FOLFOX, CapeOX, FOLFIRI (leucovorin, 5-FU, and irinotecan), and combinations that include a compound to target the growth of blood vessels (vascular endothelial growth factor (VEGF)) in tumors such as bevacizumab.[42,43] Patients with rectal cancer may undergo additional treatments before and after surgery that include radiation.[43] For example, patients with stage IV rectal cancer may undergo chemo and/or radiation before surgery, then undergo chemotherapy and/or radiation after surgery.[43]

To aid in healing after surgery, patients may have a colostomy to connect the colon to the outside of the abdomen. This procedure allows stool to pass through the opening in the abdomen and collect into an external pouch. Colostomies may be temporary or permanent, but most are temporary.

2.2.6 Prognosis

Patients diagnosed with localized disease have an overall 5-year survival rate of 90% and patients diagnosed with regional disease have a 70% survival rate.[15] Table 2.1 displays the five-year survival rate for colon and rectal cancers by stage as reported by the American Cancer Society.[44] These statistics are based on stage of diagnosis (not current stage). Survival rates are derived from CRC statistics between 2004 and 2010 when current treatments may not have been available.[44]

Table 2.1. Five-Year Survival Rate for Colon and Rectal Cancers

	Colon	**Rectal**
Stage I	92%	87%
Stage II	63-87%	49-80%
Stage III	53-89%	58-84%
Stage IV	11%	12%

Death rates in blacks (29.4 per 100,000 population) are more than double Asians/Pacific Islanders (13.1 per 100,000 population) and approximately 50% higher than non-Hispanic whites (19.2 per 100,000 population).[40]

2.3 Importance of Studying Sleep Disturbance in Individuals Diagnosed with CRC

The survival rate for a majority of CRC survivors is relatively high (see Table 2.1); patients will live for quite some time with the HRQOL impacts of the disease, diagnosis, and treatment. CRC patients experience worse health-related quality of life (HRQOL) than that of the healthy population.[6,45,46] CRC not only has HRQOL implications for patients but also for caregivers.[47,48] Thus, the impact of CRC on HRQOL in the United States is substantial.

The prevalence of sleep disturbance or insomnia in the cancer population is approximately three times higher than the general population,[49] and the prevalence of sleep disorders in CRC is not well-studied, [50] but one study showed that half of the study participants diagnosed with CRC likely experience decrements in sleep.[3]

Most cancer-related sleep research is focused on breast cancer patients. The experiences of CRC patients are different from breast cancer (notably, night sweats attributed to hormonal therapies in breast cancer are associated with sleep disturbance,[51] and ostomies[52] are associated with sleepiness);

CRC is diagnosed in men and women, and the type and location of surgery and treatment regimens are different. Therefore, the information derived from breast cancer studies can only inform CRC research, not supplement CRC research. The severity of impact on HRQOL and the type of HRQOL domains impacted by cancer differ by cancer type;[6] CRC patients should be studied independently to better understand their unique HRQOL experiences.

2.4 HRQOL in Individuals Diagnosed with Colorectal Cancer

Individuals diagnosed with CRC may experience a number of symptoms and HRQOL impacts due to cancer or cancer treatment, all of which may change over time given changes in treatment and health status. This dissertation investigates sleep disturbance as patients transition out of treatment and into the survivorship stage, 10 to 17 months post-diagnosis. The following section will summarize relevant published research. Generally, HRQOL improved over time but CRC survivors may experience persistent HRQOL decrements for five or more years after diagnosis.

2.4.1 General Impact of CRC on HRQOL

A population-based observational study compared the HRQOL of older Americans (>= 65 years) after CRC diagnosis with the HRQOL of the general U.S. population.[45] CRC patients who had been diagnosed within the previous six months reported the most dramatic declines in physical functioning, general health, mental health, social functioning and vitality compared to the general population.[45] These declines exceeded minimally important difference thresholds relevant for each scale. Vitality and general health continued to decline until 12 and 18 months post-diagnosis for CRC patients respectively, also exceeding the minimal important difference thresholds.[45]

In a German study it was found that one year after CRC diagnosis, insomnia and fatigue were the most prominent symptoms compared to nausea, pain, appetite loss, constipation and diarrhea, with over half reporting symptoms related to insomnia (e.g., trouble sleeping) and almost 80% reporting symptoms of fatigue (e.g., feeling tired, weak).[20] CRC patients reported worse emotional and social functioning compared to the general German population.[20]

A qualitative study including individuals with CRC within 18 months of diagnosis identified common HRQOL themes described by patients.[8] Half of the participants reported no psychological changes since before CRC diagnosis. Of the patients that reported psychological changes, patients were

primarily concerned about cancer recurrence and reported changes in depression and anxiety. Approximately half of the patients described worsened physical function caused by loss of strength and fatigue. Social functioning was a concern for some patients due to access to bathroom facilities. Patients reported fewer social interactions attributed to tiredness and friends treating them differently. CRC patients reported that the cancer affected sexual relationships. These findings were also echoed in another qualitative study assessing open-ended responses written by CRC patients at various survivorship stages (mostly under 3 years post-treatment).[53] Bowel/ostomy trouble, sexual function, fatigue, and nerve toxicity were among the most impacted areas of life for CRC patients. Neuropathy, fatigue, and trouble with bowel/ostomy decreased in difficulty over time.

Five or more years post-diagnosis, individuals diagnosed with CRC generally reported similar HRQOL compared with population norms.[54] However, CRC survivors reported slightly worse physical functioning, depression, and anxiety than the general population.

2.4.2 Impact of Surgery on HRQOL

A recent study of CRC patients who underwent surgery described trajectories of recovery within the first 2 years after surgery.[55] Patients were administered a number of HRQOL outcome measures (e.g., Quality of Life in Adult Cancer Survivors (QLACS), EQ-5D, Personal Wellbeing Index) at 3, 9, 15, and 24 months after surgery. Results show a general improvement in HRQOL over 24 months after surgery.

Age may play an important role in functioning within a month after surgery with older patients (> 70 years) having worse HRQOL outcomes (e.g., physical, emotional, and social functioning) than younger patients.[56]

2.4.3 Impact of Colostomy on HRQOL

After surgery, some patients have colostomies to aid in recovery. A study comparing HRQOL between patients who had ostomies due to cancer versus non-cancer patients who had ostomies for other reasons found that cancer patients reported better HRQOL than non-cancer ostomy patients.[52] Overall, patients reported that ostomies influenced their lives by causing fatigue, sleeplessness, leakages, pain, decrements in physical functioning, and special travel, clothing, and diet considerations.[52] A German study compared HRQOL outcomes for CRC patients with and without stomas, and patients

with stomas reported worse social functioning, fatigue, nausea/vomiting, pain, insomnia, and appetite loss.[20]

2.4.4 Impact of Chemotherapy on HRQOL

Oxaliplatin is approved for first-line adjuvant chemotherapy treatment of stage III CRC and advanced CRC.[57] Despite its efficacy, it is associated with peripheral neuropathy,[57] which presents as weakness, numbness, or pain in the hands and feet and is attributed to nerve damage. In an observational study, 89% of individuals diagnosed with stage III or IV CRC undergoing oxaliplatin chemotherapy experienced at least one symptom of peripheral neuropathy.[58] Notably, patients who experienced worse peripheral neuropathy also experienced worse sleep disturbance.

Another study compared HRQOL for patients who underwent a curative resection (surgery) and adjuvant chemotherapy treatment of oral uracil/ftorafur (UFT) plus leucovorin (LV) versus curative resection alone for individuals diagnosed with stage II and III colon cancer.[59] Clinically significant differences were found between treatment groups with worse HRQOL in the adjuvant chemotherapy arm on role function, fatigue, dyspnea, and financial difficulties.[59]

An RCT followed CRC patients' HRQOL through adjuvant chemotherapy and up to 5 years after as measured by the EORTC QLQ-C30.[60] Patients were randomized to protracted venous infusion (PVI) 5-FU for 12 weeks or 5-FU and leucovorin (LV) for 6 months.[60] HRQOL trajectories were similar with patients in the 12-week PVI 5-FU arm recovering more quickly than the 6-month 5-FU + LV arm.[60] HRQOL worsened within two weeks of starting chemotherapy, but patients recovered to pre-chemotherapy HRQOL as they transitioned off of the chemotherapy regimen (week 12 and 24 depending on the study arm).[60] HRQOL continued to improve after chemotherapy ended and reached a plateau between 1 and 5 years post-chemotherapy.[60]

A recent study examined patients' symptoms and HRQOL up to 16 months after chemotherapy.[61] The study included individuals diagnosed with CRC, lung cancer, or lymphoma who underwent chemotherapy. The study found that symptom severity generally persisted 16 months after chemotherapy.[61] Descriptive statistics show that sleep, fatigue, and pain outcomes fluctuated after chemotherapy, but fatigue and pain generally improved while sleep outcomes worsened.[61]

2.4.5 Impact of Radiotherapy on HRQOL

Patients who underwent adjuvant radiotherapy for rectal cancer were assessed prior to radiation and 4-6 weeks after radiation. Fatigue and appetite loss significantly worsened by the end of radiotherapy compared to before, but patient functioning did not change significantly. HRQOL in general returned to pre-treatment levels 4-6 weeks after radiotherapy.

2.5 Conceptual Model

Figure 2.1 illustrates a conceptual framework proposed by Evans and Stoddart to model determinants of health.[62] This model, called the Health Field Model, was developed by the Program in Population Health of the Canadian Institute for Advanced Research (CIAR).[63] The CIAR consisted of an interdisciplinary group of researchers, communicators, and policymakers in Canada who wanted to understand implications for resource allocations in population health and who were concerned about health inequities.[63,64] Evans and Stoddart were among the first researchers to call for a more holistic perspective on determinants of health, including the social environment.[65] Although the Health Field Model was developed by individuals interested in Canadian health policy, the seminal paper titled "Producing Health, Consuming Health Care" is widely read. The model is relevant in the United States,[66,67] many diseases,[64] nursing,[68] and even the design of outdoor spaces to increase public activity levels[69] and environmental policy.[70]

The Health Field Model emphasizes three aspects of health, including disease status (e.g., CRC), health and functional capacity (e.g., sleep), and well-being (e.g., HRQOL), each of which could be considered an outcome in research studies. The differentiation of these aspects of health is an important feature of the Health Field Model because it illustrates that each of the three health outcomes are a result of dynamic relationships among the individual factors. The model will be applied to this dissertation to provide a framework for identifying factors associated sleep disturbance ("Health and Function" box), and to evaluate exercise as a possible behavior associated with less sleep disturbance ("Individual Response" box). CRC status is affected by health care (e.g., chemotherapy, surgery), social environment, physical environmental, genetic and individual behaviors/biology, and indirectly by well-being and prosperity/financial status. Factors influencing health and function such as sleep disturbance include the disease itself and individual behaviors/biology, as well as health care/treatment indirectly. All of these

aspects play a role in well-being. Health behaviors (e.g., exercise) are seen as intermediate factors that are influenced by social, physical, genetic, and financial factors and even general well-being. The health behavior of interest in this dissertation is exercise. Sleep disturbance fits within the “Health and Function” box, thus this dissertation focuses on this aspect of health as the outcome. The model depicts “Health and Function” affecting well-being, which includes HRQOL.

Figure 2.1. Health field model.

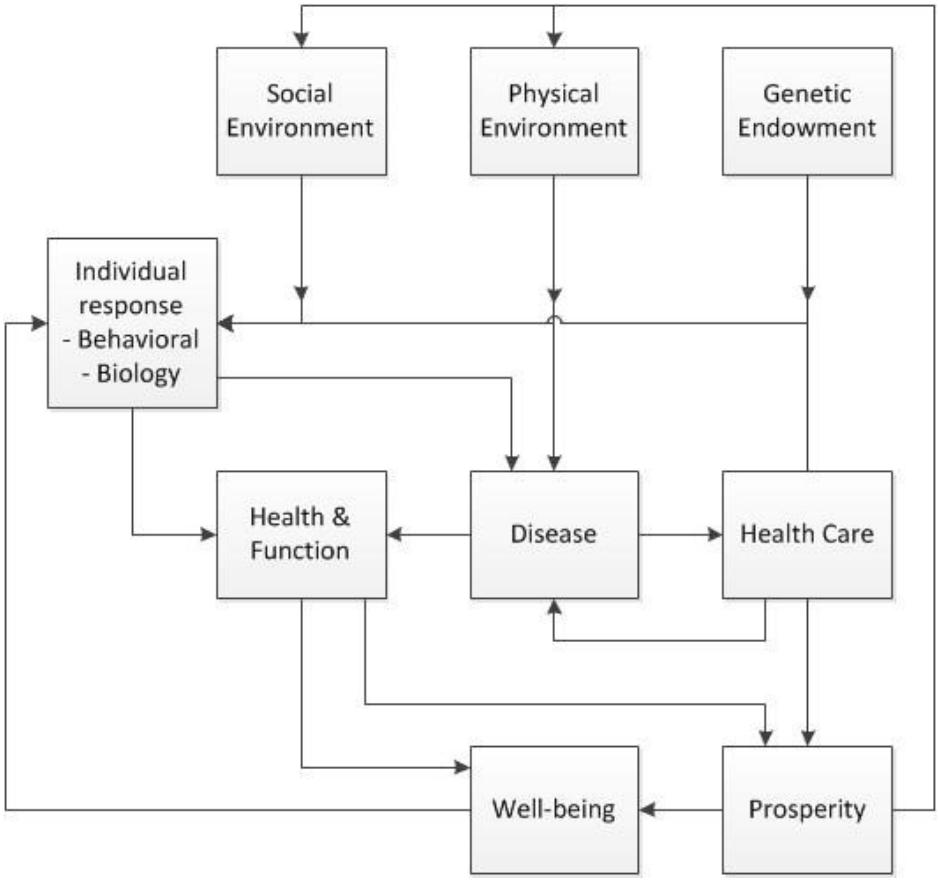

Figure redrawn from: Evans RG, Stoddart GL: Producing health, consuming health care. Soc Sci Med 31:1347-63, 1990[62]

2.6 Sleep

2.6.1 Sleep Physiology

The Bureau of Labor Statistics reports that Americans spend approximately one-third of time asleep.[71] Sleep physiology is complex and sleep patterns change over individuals' life span. This section provides a brief introduction to sleep physiology and adult sleep patterns.

There are two types of sleep: (1) non-rapid eye movement (NREM) and rapid eye-movement (REM). NREM includes four sleep stages, with each stage representing deeper sleep and NREM sleep makes up between 75% and 80% of total sleep time.[72] NREM and REM alternate cyclically during sleep episodes.[72] As individuals sleep, their REM time increases and dreaming most often occurs during REM sleep.[72]

Many physiological changes occur during NREM and REM sleep.[72] For example, brain activity decreases during NREM but increases in REM. Heart rate and blood pressure slow from wakefulness during NREM but then increase compared to NREM during REM. Sympathetic nerve activity increases during REM. Airway resistance increases during NREM and REM, and respiratory flow becomes increasingly faster and more erratic during REM. The cough reflex is suppressed during REM and NREM sleep. During REM, body temperature is not regulated (e.g., no shivering or sweating). Renal function changes cause more concentrated and reduced urine flow. Clearly, many body systems are affected during sleep, with many implications for individuals with sleep disorders.

As adults age, there are changes in how sleep is initiated and maintained, as well as the percentage of time spent in each stage of sleep. Generally, sleep efficiency, the ability to initiate and maintain sleep, decreases with age.[73] As adults age, they typically adopt earlier wake times and experience reduced sleep consolidation. Arousal during sleep increases with age. Specifically, night awakenings to go to the bathroom (nocturia) is a common experience among elderly and is associated with poorer sleep. Sleep complaints differ by gender with women expressing worse sleep problems than men.[73] There is some evidence of racial differences in sleep quality.[73]

2.6.2 Sleep Disorders

The International Classification of Sleep Disorders lists 59 sleep disorders[74] categorized into seven groups:

1. Insomnia (e.g., chronic short-term)
2. Sleep-related breathing disorders (e.g., obstructive sleep apnea, sleep-related hypoventilation disorders)
3. Central disorders of hypersomnolence (e.g., narcolepsy)
4. Circadian rhythm sleep-wake disorders (e.g., delayed sleep phase disorder, irregular sleep-wake rhythm disorder)
5. Parasomnias (e.g., sleep walking, sleep terrors)
6. Sleep-related movement disorders (e.g., restless legs syndrome, periodic limb movement disorder)
7. Other sleep disorders

Insomnia is defined as "persistent sleep difficulty despite adequate opportunity and circumstances for sleep, which is accompanied by daytime consequences that are attributable to the sleep disturbance."[75] Insomnia is often considered the primary sleep disorder associated with cancer.[11,76] The second category, sleep-related breathing disorders, is characterized by respiration problems during sleep due to obstruction or reduced/absent respiratory effort. Individuals who have sleep-related breathing disorders experience breathing cessation, reduced breathing and/or arousal from sleep due to airway resistance.[75] Sleep-related hypoventilation can be caused by obesity and medications that cause respiratory depression such as opioids, which are often administered to cancer patients for pain control.[75] The third category, central disorders of hypersomnolence, includes a range of sleep disorders that cannot be attributed to any other sleep disorder but cause daytime sleepiness.[75] Examples of these disorders include insufficient sleep syndrome and "Long sleeper" which are characterized by abnormally short or long episodes of sleep compared to age-defined norms. Hypersomnia (excessive sleepiness) can be caused by medical or neurologic disorders, drugs or substances, or psychiatric diagnoses.[75] Circadian rhythm sleep-wake disorders are caused by misalignments of individuals' circadian clocks. Irregular sleep-wake circadian rhythm sleep-wake disorder is caused by a lack of social schedule, physical activity, and daytime light synchronization and is often experienced by chronically ill individuals (including cancer patients).[75] Parasomnias include undesirable behaviors while sleeping such as nightmares, sleep terrors, or sleepwalking, none of which are necessarily associated with medications or other diseases.[75] Sleep-

related movement disorders include restless leg syndrome and bruxism (e.g., clenching/grinding of teeth during sleep).

2.6.3 Sleep Disturbance Defined

Cancer patients experience difficulty falling asleep, difficulty staying asleep, and nighttime awakenings.[76] Based on qualitative development with input from patients, clinicians, and stakeholders and subsequent quantitative evaluations of relevant sleep disturbance concepts, the Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance item bank and definition of sleep disturbance measured by these items was published.[77,78] The PROMIS Sleep Disturbance scale is the outcome variable in all aims of this dissertation, therefore the PROMIS definition of sleep disturbance applies to all aims of this dissertation:

> "The PROMIS Sleep Disturbance item bank assesses perceptions of sleep quality, sleep depth, and restoration associated with sleep; perceived difficulties and concerns with getting to sleep or staying asleep; and perceptions of the adequacy of and satisfaction with sleep. The PROMIS Sleep Disturbance Scale does not include symptoms of specific sleep disorders, nor does it provide subjective estimates of sleep quantities (e.g., the total amount of sleep, time to fall asleep, or amount of wakefulness during sleep)."[55]

2.7 Factors Associated with Sleep Quality

2.7.1 Factors in the General Population

In the general population, psychiatric conditions play an important role in sleep quality; depressive symptoms are associated with difficulties falling asleep but not with lower sleep efficiency or total sleep time and anxiety is associated with worse sleep quality.[73,79,80,81] Other health conditions impact the quality of sleep such as conditions associated with pain (e.g., chronic pain, arthritis, hip fracture, fibromyalgia, back pain), cardiovascular diseases (e.g., stroke, heart attack, angina), respiratory conditions (e.g., asthma, bronchitis), diabetes, and gastroesphageal reflux.[73] Retirement from work is associated with better sleep quality.[73] Physical functioning, such as mobility limitations, visual impairment, lack of exercise, alcohol use, and smoking[82] contribute to declines in sleep quality in adults.[73] Men experience more awakenings but women typically have more trouble falling asleep.[72] Being a parent is associated with worse sleep quality.[83,84] Employment status may play a role in sleep quality.[84] For example, patients who are employed may sleep less because of work anxiety. A sense of financial security also plays a role in sleep quality for individuals diagnosed with cancer.[85] Other demographic and

personal characteristics have been shown to be important predictors of insomnia in the general population, including lower education/socioeconomic status.[86]

Physiology. Patients' age and gender play important physiological roles in sleep quality.[72] Sleep efficiency declines with age[72] but the relationship between age and sleep is complicated.[73] For example, it is unclear if the physiological phenomenon of decreased sleep efficiency with age should be considered insomnia or merely accepted as part of normal aging by patients who are growing older.[73] Predictors of sleep disturbance may vary by age. Three key studies highlighted predictors of sleep disturbance in younger (age 17–24) and older (age 50 or older) populations. First, a study of sleep in older-adolescent/college students (age 17–24) found that poor sleep quality was associated with negative moods (e.g., anger, confusion, depression, fatigue, tension, stress) and illness.[87] Students reporting worse sleep consumed more alcohol per day than better sleepers and were more likely to use alcohol to induce sleep.[87] Tension and stress were the most salient predictors of sleep quality, and approximately 20% of students reported that stress interfered with sleep at least once a week.[87] Gender, alcohol, caffeine, exercise, and television/videogame exposure were not statistically significant predictors of sleep quality.[87] Second, in a recent review of risk factors for sleep disturbance in older adults, female gender, depressed mood, and physical illness were the most consistent risk factors for future sleep disturbance.[88] In this population, chronological age was not a consistent predictor of future sleep disturbance,[88] but this may be because the physiological changes due to age may have already taken place by age 50 or soon thereafter. Third, a population-based study examined the relationship between insomnia, psychological variables, and HRQOL variables in adults age 50 or older.[89] Researchers found that insomnia diagnoses and symptoms were predicted by previous insomnia episodes, depressive symptoms, and lower scores on the vitality and role physical (limitations in accomplishments/work due to physical health) subscales on the Short Form Health Survey (SF-12).[89]

2.7.2 Factors in Individuals Diagnosed with Cancer

Most studies that identify factors associated with sleep disturbance in cancer patients actually identify patient characteristics associated with *insomnia* or poor sleep using a cut point on the Pittsburgh Sleep Quality Index (PSQI) scale[90-92] instead of a continuous measure of sleep disturbance. In addition, although HRQOL differs by cancer site,[6] very few (if any) studies investigate factors related to sleep in the

CRC population specifically. Most studies assessing sleep disturbance have been in mixed-site advanced cancer and breast cancer populations. Of the relevant mixed-site cancer studies reviewed as part of this literature review, patients with CRC accounted for less than 22% of each sample.[91,93-95]

In the oncology literature, the independent variables entered into models to find factors associated with sleep disturbance vary from study to study, but depression,[90,92,93,95] anxiety,[94,95] and pain[94,95] were often statistically significant predictors of sleep disturbance or insomnia. Other factors include hopelessness,[93] post-traumatic stress disorder (due to cancer diagnosis),[93] physical health and functioning,[90,92,93] health behaviors (sleep behaviors),[90,91] patient characteristics (e.g., gender, age),[90-92] sedative use,[94] fatigue,[94] consuming more cigarettes,[92] and having undergone surgery.[91]

Although depression, anxiety, and pain are important factors associated with sleep disturbance in many studies, they are not always statistically significant in the models. Models varied widely from study to study depending on the cancer sites, stages, and window of time covered by the studies, as well as covariates entered in the models. For example, in a study that predicted sleep quality among head and neck cancer patients with any stage disease (stage 0-4) one year after diagnosis, depression, smoking, xerostomia[a] (dryness in mouth) and pain were predictors of sleep quality. Pain was highlighted as a strong predictor of worsened sleep, but pain is more prevalent among individuals diagnosed with head and neck cancer versus other cancers.[96] Another study including patients diagnosed with advanced lung, breast, gastrointestinal, urogenital (and other) cancers aimed to identify correlates of sleep quality.[93] All patients in the study were in palliative care, and statistically significant predictors of sleep quality (using multivariate methods) were the SF-12 mental and physical component scales and post-traumatic stress disorder (due to cancer diagnosis).[93]

In contradiction to the general population, in which older age is often associated with worse sleep, younger age is sometimes associated with higher risk for cancer-related insomnia.[2,21,97] The reason for this is unclear, but it is possible that the expectations for better health among younger patients might be a factor.[2] Also, younger patients often undergo more aggressive treatment regimens leading to worse HRQOL overall.[2]

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[a] Xerostomia, a side effect of radiation, may negatively impact individuals' sleep because patients may be more apt to wake up during the night due to discomfort, thereby drinking liquids during the night, and consequently causing more awakenings to use the bathroom.

Treatment-related factors may impact patients emotionally and physically (either directly or because of side effects). For example, medications commonly administered to patients diagnosed with cancer such as opioids, antiemetic medications, and corticosteroids are associated with sleep disruption.[98] Symptoms associated with cancer treatment such as dyspnea, gastrointestinal symptoms (e.g., chemotherapy-induced nausea), and pain are associated with sleep impairment.[21] Studies that reviewed the effect of cancer treatment on sleep disturbance found that chemotherapy was particularly detrimental to sleep.[21,99] Most studies that assessed the relationship between treatment trajectories and sleep or HRQOL were in breast cancer; other studies assessed a mixture of patients diagnosed with different types of cancer. One study including patients diagnosed with a variety of cancers, pointed to a decline in HRQOL severity within one year after diagnosis.[100] Two other studies assessing the longitudinal relationship between sleep and fatigue in breast cancer patients undergoing chemotherapy found that sleep quality was poor prior to chemotherapy but there was little change in sleep quality during chemotherapy.[16,17] Another study in breast cancer found persistent sleep problems before and after surgery for breast cancer.[101] HRQOL (including sleep) was assessed as part of a randomized trial of chemotherapy in ovarian cancer patients.[18] The study authors found an immediate deterioration in sleep and other aspects of HRQOL around the first cycle of chemotherapy and then a statistically significant improvement in sleep and other aspects of HRQOL throughout chemotherapy.[18] The trajectory of sleep disturbance throughout and after treatment for patients with CRC is unknown.

2.8 Sleep and Symptom Clusters

Cancer patients experience a number of symptoms attributed to the disease or treatment. Until the early 2000s, most cancer symptom research focused on individual symptoms.[102] Although this research was important in understanding the precursors and effects of singular symptoms, cancer patients rarely report only one symptom[103] and symptoms may affect each other. Consequently, treating one symptom may have effects on other symptoms and functions. The term “symptom cluster” was introduced by Dodd and colleagues in 2001 to describe multiple co-occurring symptoms that may or may not have a common cause.[104] Ferrans posited that the relationship between symptoms and functional outcomes is not unidirectional.[105] Although sleep has been identified as a core cancer symptom [25 26] that has complicated relationships with other symptoms and functional outcomes,[9] many studies do not

include sleep in symptom cluster research. Few (if any) studies investigate symptom clusters specifically in CRC. Nonetheless, there is some evidence that sleep, depression, anxiety, and fatigue are related and comprise a symptom cluster in other cancers. For example, a prospective longitudinal evaluation of the symptom cluster of sleep, fatigue, depression, anxiety, and cognitive impairment in women with breast cancer undergoing chemotherapy found that the composition of the symptom cluster was supported with similar patterns of severity and changes over time.[106] Another study in breast cancer supported a similar cluster of depression, fatigue, and sleep disturbance.[107] A descriptive study of patients diagnosed with lung cancer who had undergone surgery within the previous week found that almost 77% of patients reported co-occurrence of pain, fatigue, sleep disturbance, and distress.[108] A small (n = 120) descriptive study with elderly patients diagnosed with colorectal, lung, head/neck, breast, gynecological, prostate, or esophageal cancer at any disease stage found that pain, fatigue, insomnia, and mood disturbance were very prevalent in elderly patients who were receiving chemotherapy or radiotherapy.[81]

2.9 Consequences of Disturbed Sleep

The importance of sleep is well-documented in the literature; sleep disturbance is associated with worse health, increased mortality, decreased cognitive functioning,[9] fatigue,[10,11] reduced immune response, and reduced HRQOL.[9,109,110] Sleep disturbance is also a risk factor for progression of CRC,[3] infectious diseases, cardiovascular diseases, and depression.[13] Further, cancer patients described impaired daytime functioning, trouble keeping up at work and with social activities, and mood disturbance as a result of sleep disturbance.[12] Thus, sleep disturbance has serious implications for overall HRQOL.

Sleep disturbance is also associated with increased healthcare resource use (e.g., visits to health professionals) and decreased work productivity and work quality in chronically ill patients.[14] The economic impact of fatigue in the workplace due to insomnia or insufficient sleep syndrome was estimated to be $13.2 million annually in a study published in 2010 based on the general U.S. population of working adults.[111]

2.10 Treatments for Sleep Disturbance

Cancer patients and clinicians are faced with two options for treating sleep disturbance: pharmacotherapies and cognitive behavioral therapy. Pharmacologic treatment options (e.g., benzodiazepine-receptor agonists, antidepressants, melatonin agonists) are associated with adverse

daytime side effects such as sedation or dizziness. Despite recommendations that pharmacotherapies should only be administered for 4 to 6 weeks,[21] cancer patients may be treated for sleep disturbance with these medications long beyond this period.

Cognitive behavioral therapy (CBT) is recommended by the American Academy of Sleep Medicine as a first-line therapy for patients with insomnia. CBT includes relaxation therapy, sleep hygiene, and cognitive therapy. Unfortunately, a lack of providers with CBT expertise and patient adherence issues are considerable barriers to sleep treatment efficacy.[9]

Of these treatment options, neither are directly associated with additional health benefits, but another potential treatment with accumulating evidence of its effectiveness is exercise. Exercise improves aerobic fitness[112] and other aspects of quality of life such as anxiety, pain, and fatigue, all of which are associated sleep disturbance.[113-115] Exercise has been evaluated as a treatment for sleep disturbance in the healthy U.S. population[23,116] and a number of RCTs and observational studies have investigated exercise as a possible treatment for sleep disturbance in cancer patients.[113,117-121] Exercise is generally accessible and a low-cost alternative treatment for sleep disturbance.

2.11 Exercise

2.11.1 Measuring Exercise

Exercise intensity is measured in various ways, including subjective and objective measurements.

Objective measures of activity.

Wearable devices such as accelerometers, pedometers, heart-rate monitors, and armbands are objective measures of physical activity.[122] Devices are more expensive than subjective measures of activity and require specialized software and hardware, but they are associated with many benefits.[122] Devices are generally easy to use and they can capture large amounts of data on duration of physical activity and time spent participating in different intensities of exercise.[122] Depending on the type of activity researchers are interested in measuring, some devices are better than others. For example, some accelerometers cannot differentiate body position (e.g., standing, sitting, lying down),[123] pedometers are accurate measures of running or walking but cannot measure other activities such as swimming.[122]

Exercise training is associated with improvements in cardiorespiratory fitness.[124] The gold standard measurement of cardiorespiratory fitness is the maximal or peak oxygen consumption

(VO_{2peak}).[125,126] VO_{2peak} has also been used to categorize training intensity in cancer patients.[124] To measure VO_{2peak}, cardiopulmonary exercise testing involves measuring patient metabolic data via expiratory gas analysis. After a brief warmup, patients' workload is increased incrementally throughout the test until patients feel overly fatigued (volitional fatigue), achieve a set respiratory exchange ratio (RPE) (e.g., 1.10[126]) or patients become limited by symptoms. For example, if patients experience chest pain, dizziness, or nausea, the test would stop. Heart rate, RPE and VO_2 are measured regularly throughout the test. VO_{2peak} is calculated using an average of the highest values during the last minute of the test.[126] Clearly, VO_{2peak} measurements require significant resources and measuring cardiorespiratory fitness to track exercise intensity is not feasible in many studies.

Subjective measures of activity.

Self-reported physical activity questionnaires are patient-reported and based on individuals' perceived exercise intensity, recall of activity duration, and frequency of exercise. Self-reported questionnaires are the most common mode of exercise assessment because they are easy and efficient to use and they are a low-cost alternative to objective measures.[122] Disadvantages of self-reported exercise include recall and social desirability bias.[122] Examples of self-reported questionnaires on physical activity commonly used in research to include the past-week Modifiable Activity Questionnaire (MAQ[127]), Recent Physical Activity Questionnaire (RPAQ[128]), and the 7-day Physical Activity Recall (PAR[129]).

Self-report activity diaries/logs are a specific type of self-reported questionnaire in which study participants record their physical activity in real time.[122] Diaries are more burdensome for patients but are associated with less recall bias. Bouchard's Physical Activity Record (BAR) is an example of a physical activity diary in which study participants record their physical activity every 15 minutes for three days.[130] The BAR is a highly reliable (intraclass correlation = 0.96) measure of energy expenditure over the three-day administration period.[130]

Another type of physical activity measurement is direct observation. Observers monitor and record study participants' activity.[122] This type of physical activity measurement is applicable when participants can be monitored in contained spaces (e.g., hospital room) or when participants have difficulty recalling their activities (e.g., young children, adults with cognitive deficits).[122] Direct observation

may only be cost-prohibitive when working with study participants who are unable to complete self-report questionnaires.

Exercise recommendations for cancer patients.

In 1995, the Centers for Disease Control and Prevention and the American College of Sports Medicine recommended that every U.S. adult should accumulate 30 minutes or more of moderate-intensity physical activity on most, preferably all, days of the week.[57] Other entities have provided cancer-specific recommendations. For example, the American College of Sports Medicine (ACSM) recommends 150 minutes of moderate-intensity exercise per week or 75 minutes of vigorous exercise per week.[15] Researchers from the American Cancer Society went further to say "some activity is better than none and exceeding the guidelines is likely to provide additional health benefits."[58]

The ACSM advises that cancer patients should be assessed for peripheral neuropathies, musculoskeletal morbidities, and cardiovascular disease.[24] Cardiac toxicity due to cancer treatments may go undetected.[24] Specific to CRC, the ACSM recommends that patients should establish consistent and proactive infection prevention for ostomies if they plan to participate in exercise more vigorous than walking.[24] Infection risk is higher for patients undergoing chemotherapy or radiation due to compromised immune function.[24] CRC patients with ostomies should also seek physician permission prior to participating in contact sports or weight training due to risk of hernia.[24]

Exercise defined.

The terms physical activity and exercise are often used interchangeably but there is an important difference in definitions. Physical activity is "any bodily movement produced by skeletal muscles that requires energy expenditure."[131] Exercise is physical activity that is "planned, structured and repetitive to improve physical fitness."[131]

Exercise measurement in this dissertation.

The MY-Health study included three patient-reported items intended to measure the number of times patients engaged in different intensities of exercise per week:

1. Now think about vigorous activities you did in your free time that take hard physical effort, such as aerobics, running, soccer, fast bicycling, or fast swimming. Do not include walking. In the past 7 days, how many times did you do vigorous activities?

2. Now think about the activities that take moderate physical effort that you did in your free time during the last 7 days. Moderate physical activities make you breathe somewhat harder than normal, such as bicycling, dancing, swimming and gardening. Do not include walking. In the past 7 days, how many times did you do moderate activities?
3. Now think about walking that you did in your free time during the last 7 days, such as walking for fun, relaxation, exercise or walking the dog. Please do not include walking for transportation. In the past 7 days, how many times did you walk during your free time?

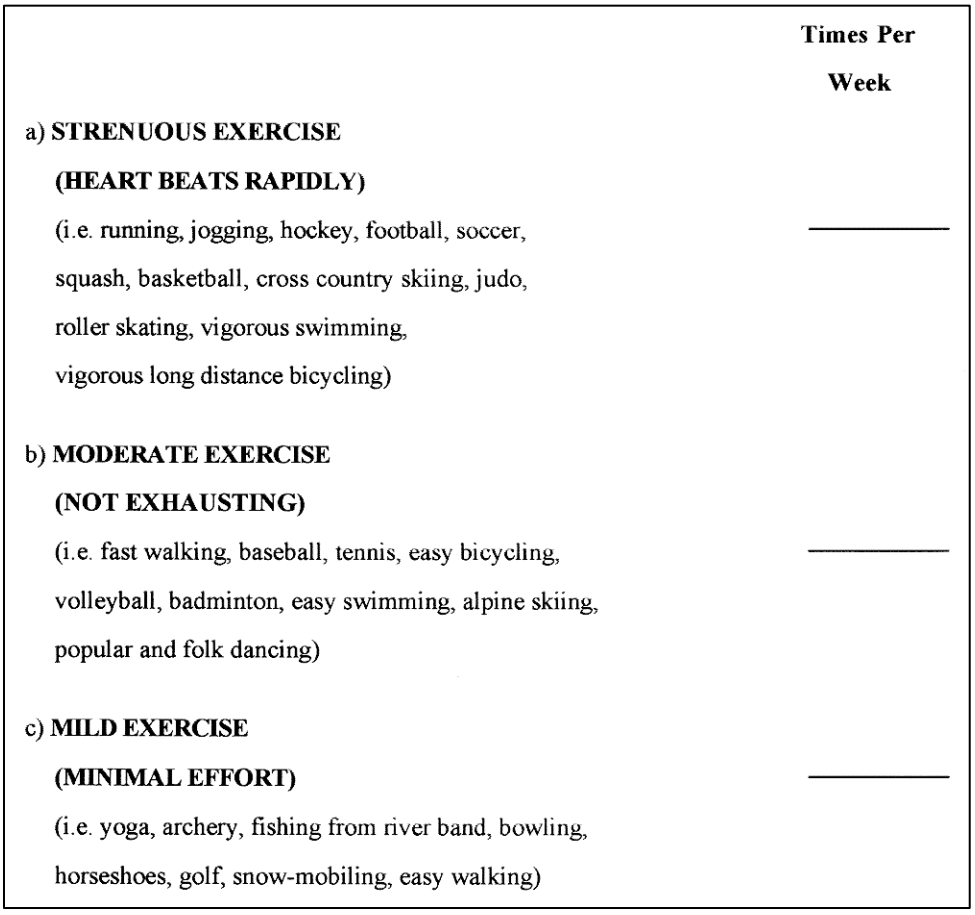
   Response choices for the three exercise items were:

   - None
   - Once
   - 2 to 4 times
   - 5 to 7 times
   - 8 to 10 times
   - 11 times or more

Four exercise groups were derived to characterize patients' level of activity (see Chapter 3 Methods for additional details on derivation).

The exercise questions administered in the MY-Health study are not part of a psychometrically evaluated scale, however the questions are very similar to those found in other psychometrically evaluated scales such as the Godin Leisure-Time Physical Activity Questionnaire[132] (relevant items pictured in Figure 2). The Godin Leisure-Time Physical Activity Questionnaire is often used in oncologic settings,[133,134] and validity studies support its use in ranking healthy adults into exercise categories of "active" and "insufficiently active."[135]

Figure 2.2. Portion of the Godin Leisure-Time Physical Activity questionnaire.



	Times Per Week
a) **STRENUOUS EXERCISE** **(HEART BEATS RAPIDLY)** (i.e. running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)	_____
b) **MODERATE EXERCISE** **(NOT EXHAUSTING)** (i.e. fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	_____
c) **MILD EXERCISE** **(MINIMAL EFFORT)** (i.e. yoga, archery, fishing from river band, bowling, horseshoes, golf, snow-mobiling, easy walking)	_____

2.11.2 Relationship Between Exercise and Sleep

Within the cancer population, exercise has been associated with many benefits including improved fitness,[112,136,137] quality of life,[136] physical function,[136] and reduced fatigue,[115] anxiety,[121,138] and depression.[138] Given the strong associations between sleep and HRQOL, it is plausible that exercise may also improve sleep, but not many exercise studies assess sleep as an outcome in the cancer literature. For example, a study of patients with stage II-III CRC found a statistically significant association between fitness and HRQOL and depression.[139] Had this study included sleep disturbance as an outcome, exercise may have also been a significant driver for improved sleep.

Two studies that looked at change in sleep over time showed no significant effect of exercise on change in sleep disturbance, but both studies were in breast cancer.[140,141] A meta-analysis conducted as part of a Cochrane review found a significant effect of exercise on sleep outcomes 3 months after the exercise interventions began compared to control arms. There was no statistically significant difference at time points longer than 3 months. Of the studies investigating sleep in the Cochrane review, none focused specifically on patients diagnosed with CRC.[121] Another recent RCT in breast cancer found that physical activity may prevent worsening of sleep disturbance.[142]

Three studies investigated the association between sleep and exercise with a focus on CRC patients, including two observational studies[120,119] and one RCT.[117] Of these studies, the RCT showed the most promising results indicating that exercise may improve sleep but all patients were diagnosed with stage IV disease. Cheville and colleagues enrolled 66 patients diagnosed with stage IV colorectal *or* lung cancer and followed patients over the course of 8 weeks. They assessed a home-based exercise intervention in which patients exercised four or more days a week. The intervention resulted in a statistically significant improvement in sleep for the patients who participated in the exercise intervention versus those who were randomized to the usual care arm.[117] The two observational studies did not find a relationship between sleep and exercise, but both were small—119 adult participants[119] and 45 adult participants[120]—and neither were powered to detect differences in sleep outcomes. The larger observational study conducted by Cho and colleagues incorporated a self-reported questionnaire to measure exercise.[119] The exercise questions were not part of a validated scale but were developed specifically for the study. Items measured frequency, intensity, and duration of exercise. The smaller observational study conducted by Lin and colleagues employed an opt-in exercise protocol such that participants were placed in a supervised exercise group or a usual care group based on their preference.[120] The supervised exercise group participated in moderate-intensity aerobic and resistance exercise for 12 weeks. Exercise intensity, duration, and frequency was not measured for the usual care group.

CHAPTER 3. METHODS

3.1 Methods Overview

The analyses conducted as part of this dissertation used data from a large community-based observational study that included over 5000 individuals diagnosed with cancer. These data were subset to colorectal (CRC) patients only to address research questions specific to this dissertation. The timing of data collection was of particular importance in developing research objectives and hypotheses. Thus, the parent study is described first (Section 3.2), then Section 3.3 outlines research objectives and hypotheses. Section 3.4 picks up with detailed information on the analysis dataset used in this dissertation. Analytic methods and power analyses are described in Section 3.5.

3.2 MY-Health Study

Data for this dissertation were obtained from a community-based study of over 5000 individuals diagnosed with cancer. Designed to evaluate the psychometric properties of Patient-Reported Outcomes Measurement Information System (PROMIS) measures in a diverse population of cancer patients, Georgetown University's Measuring Your Health study (MY-Health) recruited adults diagnosed with one of seven cancers (e.g., breast, prostate, colorectal, non-small cell lung, non-Hodgkin lymphoma, uterine, or cervical cancer) through four Surveillance, Epidemiology and End Results (SEER) cancer registries in the United States (California (two registries), Louisiana, and New Jersey) between 2011 and 2013.[143] Individuals aged 21 years and older and diagnosed within the previous 6–13 months were invited to participate in the MY-Health study via mail. Participants completed questionnaires using mail-in hard copy questionnaires at two time points:

(1) Approximately 10 months after diagnosis (mean = 9.73, range = 6-30 months)

(2) Approximately 17 months after diagnosis (mean = 17.42, range = 11-36 months)

For brevity, the first data collection will be referred to as the Month 10 data collection and the second data collection will be referred to as the Month 17 data collection.

Race/ethnic minorities and younger patients were oversampled. Questionnaires were available in English, Spanish, and Mandarin. Most data were collected via self-reported questionnaires, but some medical information (e.g., cancer site, age at diagnosis, cancer stage) were collected via SEER. Additional details on the study design, procedures, and measures administered in the study were previously published.[143]

3.3 Research Objectives and Hypotheses

As noted in Chapter 1 (Introduction), this dissertation included two aims with the purpose of splitting the largest aim, Aim 2, into two manuscripts. Because the dissertation includes three manuscripts, for clarity, research objectives and hypotheses will be referred to by manuscript number instead of by aim.

Research objectives and hypotheses:

3.3.1 MANUSCRIPT 1

Research objective 1a: Investigate whether there was variation in patient, disease, and treatment characteristics across levels of sleep disturbance severity at Month 10.

- Hypothesis 1a: Associations between factors (e.g., patient, disease, and treatment characteristics) and sleep disturbance differ by *severity* of sleep disturbance.

Research objective 1b: Evaluate the relationship between sleep disturbance and patient, disease, and treatment characteristics with the goal of identifying correlates of sleep disturbance at Month 10.

- Hypothesis 1b: Patients who were currently undergoing chemotherapy during the time of data collection or those who had more recently undergone chemotherapy would report worse sleep disturbance than patients who never had chemotherapy.

Research objective 1c: Investigate whether there was variation in patient, disease, and treatment characteristics across the magnitude of change in sleep disturbance severity from Month 10 to Month 17.

- Hypothesis 1c: Associations between sleep disturbance and patient-level factors (e.g., patient, disease, and treatment characteristics) vary by magnitude of change in sleep disturbance.

Exploratory research objective 1d: Evaluate the relationship between change in sleep disturbance (Month 10 to Month 17) and patient, disease, and treatment characteristics with the goal of identifying correlates of change in sleep disturbance.

3.3.2 MANUSCRIPT 2

Research objective 2a: Investigate whether the relationship between exercise and sleep disturbance differed by *severity* of sleep disturbance at Month 10 and at Month 17.

- Hypothesis 2a: The relationship between exercise and sleep disturbance differs by *severity* of sleep disturbance.

Research objective 2b: Evaluate the relationship between exercise and sleep disturbance at Month 10.

- Hypothesis 2b: Patients who were categorized as moderately or highly active at Month 10 would experience less sleep disturbance than patients who did not exercise.

Research objective 2c: Evaluate the relationship between exercise and sleep disturbance at Month 17.

- Hypothesis 2c: Patients who were categorized as moderately or highly active at Month 17 would experience less sleep disturbance than patients who did not exercise.

3.3.3 MANUSCRIPT 3

Research objective 3a: Investigate whether the relationship between change in sleep disturbance and change exercise differed by *magnitude of change* in sleep disturbance from Month 10 to Month 17.

- Hypothesis 3a: The relationship between change in sleep disturbance and change in exercise activity differs by magnitude of change in sleep disturbance.

Research objective 3b: Evaluate the relationship between change in sleep and change in exercise from Month 10 to Month 17.

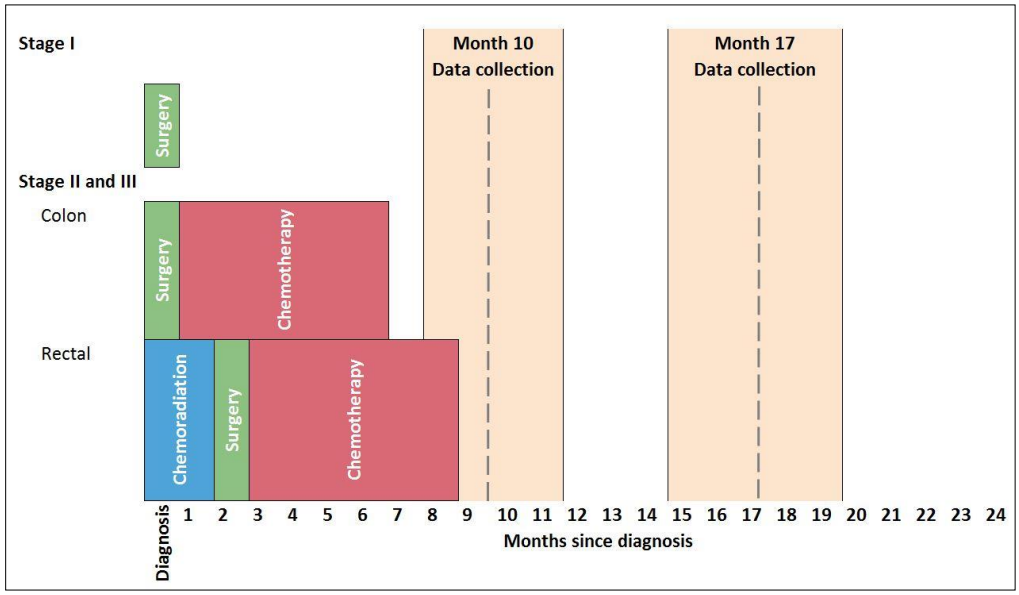
- Hypothesis 3b: Patients who increase exercise activity from 10 months to 17 months after diagnosis would experience a decline in sleep disturbance.

3.4 Analysis Dataset

Of the MY-Health sample, 734 individuals had been diagnosed with stage I, II, or III CRC and participated in the Month 10 data collection. Approximately 54% of these patients participated in the follow-up assessment at Month 17 (n = 400).

Figure 3.1 illustrates the MY-Health data collection time points and how they correspond to patients' diagnosis and general CRC treatment patterns. Time since diagnosis runs along the x-axis in months, starting with CRC diagnosis on the far left side. The mean time since diagnosis at the first data collection was 9.7 months for the CRC sample [denoted by the first dotted vertical line] (SD = 1.6, median = 9.5, min = 5.5, max = 21.3). The follow-up data collection occurred approximately 17.3 months after diagnosis for the CRC sample [denoted by the second dotted vertical line] (SD = 2.0, median = 17.0, min = 12.8, max = 26.4). The tan bars indicate approximately one standard deviation above and below the mean number of months since diagnosis when patients participated in the MY-Health survey. Typical treatment trajectories are shown by CRC stage (green, blue, and pink bars). The main takeaway from Figure 3.1 is that most CRC patients were likely transitioning off CRC treatment around the Month 10 data collection.

Figure 3.1. MY-Health study data collection for individuals diagnosed with CRC and typical CRC treatment timeframe.



3.4.1 Dependent Variables

Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance items were administered to patients at Month 10 and Month 17 data collections. PROMIS Sleep Disturbance measures concepts such as trouble staying asleep, not getting enough sleep, restlessness, feeling refreshed after sleep, and difficulty falling sleep in "the past 7 days." Results of the full psychometric evaluations of the PROMIS Sleep Disturbance item bank[144] and short forms[145] were previously published. A custom 6-item short form was scored; the psychometric properties of the 6-item form were evaluated in individuals enrolled in the MY-Health study (Cronbach's $\alpha = 0.88 – 0.95$).[146] PROMIS Sleep Disturbance is a continuous variable scored on a t-score metric with a mean of 50 and standard deviation (SD) of 10 based on the referent population (mixture of clinical and the general U.S. population[147]), and higher scores indicate worse sleep disturbance. Change in sleep disturbance was calculated by subtracting PROMIS Sleep disturbance scores at 10 months from scores at 17 months after CRC diagnosis. Positive change is indicative of worsening sleep.

3.4.2 Independent Variables

Factors associated with sleep disturbance.

The MY-Health dataset contained information on patient, disease, and treatment factors associated with sleep disturbance. There is a known link between cancer treatment and sleep disturbance, and some literature suggests that there is a relationship between time since treatment and sleep disturbance,[16-18,100,101] though the trajectory of sleep disturbance throughout and after treatment for adults with CRC is unknown. Cancer treatment type (e.g., surgery.[91] chemotherapy,[21,99] radiation) and most recent date of treatment were self-reported. (Few CRC patients [Month 10: n = 13, 17.9%, Month 17: n = 63, 8.6%] reported undergoing radiation, therefore radiation was not included in the analyses.) Categorical variables were derived to capture current/recent treatment compared to no treatment or less-recent treatment at Month 10 and Month 17. Categories were based on relevant physical recovery periods post-treatment and data availability. Time since chemotherapy was coded using four categories (i.e., currently receiving chemotherapy, chemotherapy 1–2 months ago, chemotherapy more than 2 months ago, never received chemotherapy [reference category]). Time since surgery was coded using three categories (i.e., surgery occurred within 0–4 months, surgery occurred more than 4 months ago,

never received surgery [reference category]). Comorbid conditions[73] were self-reported at Month 10 and included in the models as a derived variable with three categories (i.e., no comorbid diseases [reference category], 1 comorbid disease, 2 or more comorbid diseases). In addition to PROMIS Sleep Disturbance, other PROMIS domains were included in the models as independent variables to assess aspects of health-related quality of life known to be associated with sleep disturbance.[73,79 80 81,90,92-95,148,149] Anxiety (11 items), Depression (10 items), Fatigue (14 items), and Pain Interference (11 items). These PROMIS measures were normed to the general U.S. population[147] and higher scores indicate worse anxiety, fatigue, and pain interference respectively. PROMIS measures were administered at Month 10 and Month 17, therefore, change scores for PROMIS Anxiety, Depression, Fatigue, and Pain Interference were calculated (Month 17 – Month 10) and included in analyses modeling change in PROMIS Sleep Disturbance (negative change indicates improvement). Nausea severity was measured using a 5-point nausea[21] item from the FACT-G Physical Well-Being (PWB) subscale[150] with a recall period of the "past 7 days" and response choices ranging from 0 = "not at all" to 4 = "very much." Although the nausea item has not been psychometrically evaluated as a single measure of nausea, the entire FACT-G PWB scale, which has been evaluated extensively in cancer patients, covers concepts that overlap with PROMIS measures such as pain and fatigue. Therefore, only the nausea item was included in the models as a continuous variable and change in nausea from Month 10 to Month 17 was included in analyses modeling change in sleep disturbance (negative change indicates improvement). Other characteristics known to be associated with different levels of sleep disturbance were included in the models such as age at diagnosis,[2,21,97] sex,[72] time since diagnosis,[93] employment status (collected at Month 10 only),[84] and an indicator for living with children under 18 (collected at Month 10 only)[83,84] were included in the models. Age and race were also included in the model to account for the over-sampling of younger and minority persons from SEER registries. Race, employment status, and the living-with-child(ren) indicator were self-reported, and age at diagnosis, sex, and diagnosis date were obtained via SEER registry data.

Exercise.

The MY-Health study included three exercise-related survey items covering patient-perceived exercise intensity and patient-reported frequency of exercise in the previous 7 days:

1. “Now think about vigorous activities you did in your free time that take hard physical effort, such as aerobics, running, soccer, fast bicycling, or fast swimming. Do not include walking. In the past 7 days, how many times did you do vigorous activities?”
2. “Now think about activities that take moderate physical effort that you did in your free time during the last 7 days. Moderate physical activities make you breathe somewhat harder than normal, such as bicycling, dancing, swimming, and gardening. Do not include walking. In the past 7 days, how many times did you do moderate activities?”
3. “Now think about walking that you did in your free time during the last 7 days, such as walking for fun, relaxation, exercise or walking the dog. Please do not include walking for transportation. In the past 7 days, how many times did you walk during your free time?”

   Response choices for all three exercise questions were:

   - None
   - Once
   - 2 to 4 times
   - 5 to 7 times
   - 8 to 10 times
   - 11 times or more

Exercise items were administered at Month 10 and Month 17 data collection, capturing patients’ exercise routines during each slice of time during their treatment trajectory. Information on duration of exercise was not collected, but a recent Cochrane Review investigating the effect of exercise interventions on HRQOL reported that exercise sessions ranged from 20 to more than 90 minutes for cancer patients,[121] and another study reviewed a number of exercise interventions that included sessions where most were between 20 and 30 minutes in length.[151] It was assumed that one exercise session was approximately 20–30 minutes, meaning that patients would need to exercise at least 5 to 6 times at moderate intensity in the past 7 days to achieve the minimum American College of Sports Medicine (ACSM) guideline.[24]

We obtained guidance and feedback from two exercise physiologists on classifying patients into exercise categories based on their responses to the exercise items. A series of in-person meetings and phone and email communications were conducted from May 2016 through June 2016.[152] Patients' exercise was categorized into one of four activity levels:

1. **Not active**: This "not active" group includes patients who reported no vigorous, moderate, or walking activities in the past 7 days or only one vigorous, moderate, or walking activity in the past 7 days.

Rationale: One day of exercise per week is not associated with significant physiological changes, therefore patients who exercised 0 or 1 day a week were included in this group.

2. **Slightly active**: The slightly active group is composed of two groups of patients:
    a. patients who walked 2–4 times in the past 7 days but did not participate in any other activities in the past 7 days (e.g., no moderate or vigorous activities)
    b. patients who participated in 2 exercise activities at any intensity in the past 7 days total (i.e., patients who chose the "once" in the past 7 days response to two exercise items)

Rationale: This level of exercise per week is beneficial to adults diagnosed with CRC but not as physiologically beneficial as 3 or more activities, therefore this group is separated from moderately active individuals.

3. **Moderately active**: The moderately active category is characterized by three groups of patients:
    a. patients walked 5 or more days in the past 7 days and did not participate in any other moderate or vigorous activity
    b. patients who walked at least 2–4 times in the past 7 days in addition to at least one day of moderate or vigorous activity.
    c. patients who exercised at moderate or vigorous levels at least 2 times in the past 7 days but could not have exercised more than 4 times in the past 7 days based on *the minimum days reported in each response choice* (regardless of walking). For example, patients were categorized as having participated in the moderately active if they participated in 2–

4 moderate and 2–4 walking days (and no vigorous days) because their minimum number of days exercising would be 4.

Rationale: Patients who meet the moderately active threshold may have met the minimum ACSM guideline for 150 minutes of moderate-intensity exercise per week, but only if they were exercising closer to the maximum number of days provided in each response choice. In other words, patients would have had to exercise closer to 4 times in the past week when they responded "2-4 times a week."

4. **Highly active**: The highly active category was defined as at least 5 days of moderate or vigorous activity in the past 7 days (regardless of the number of walking days). Days of activity were defined by the *minimum* number of days that each patient could have exercised based on the response choice. For example, patients were categorized as highly active if they participated in 5–7 vigorous and 2–4 moderate days of activity because their minimum number of days exercising would be 7.

Rationale: Patients who meet the highly active threshold likely met the minimum ACSM guideline for 150 minutes of moderate-intensity exercise per week.

Exercise level was set to missing when responses to 2 or more exercise items were missing.

Patients classified in the "not active" or "slightly active" groups likely did not meet the minimum ACSM guideline of 150 minutes of moderate-intensity exercise per week or 75 minutes of vigorous exercise per week,[15] but patients in the "moderately active" or "highly active" groups likely met or exceeded the ACSM guideline. Exercise level was entered in the cross-sectional models as an indicator variable with "not active" as the reference category.

Change in exercise (Month 17 – Month 10) summarizes the change in exercise categories from 10 to 17 months after CRC diagnosis. Change in exercise was entered in the model as a categorical variable with five categories: (1) less active by 2 or 3 exercise categories, (2) less active by 1 exercise category, (3) no change in exercise activity, (4) more active by 1 exercise category, and (5) more active by 2 or 3 exercise categories. A second six-category change-in-exercise variable was derived for sensitivity analyses and provided more detail on patients who did not change exercise activity but were still active: (1) less active by 2 or 3 exercise categories, (2) less active by 1 exercise category, (3) no change in exercise activity—persistently not active or slightly active [reference category], (4) no change in

exercise activity—persistent moderately or highly active, (5) more active by 1 exercise category, and (6) more active by 2 or 3 exercise categories.

Factors associated with participation in exercise.

MY-Health variables also collected information on determinants of exercise participation (treatment selection). Exercise participation is partially determined by patients' ability to perform activities,[153-155] thus patients' PROMIS Physical Function scores were included as a covariate (higher scores indicate better physical functioning).[156] Social support is associated with participation in exercise and was measured using PROMIS Ability to Participate in Social Roles and Activities.[153-155,157] Both PROMIS measures, PROMIS Physical Function and PROMIS Ability to Participate in Social Roles and Activities, were collected at Month 10 and Month 17, therefore change scores were also calculated for models addressing change in sleep disturbance (Month 17 – Month 10: positive change indicates improvement). Higher weight is associated with less exercise, therefore body mass index (BMI) was derived from patient-reported weight and height (collected at Month 10 only).[72] Other factors already included in the model that are associated with participation in exercise and affect sleep include increased age, parenthood, sex, and race.[153-155]

3.5 Analytic Methods

Descriptive statistics were calculated and tabulated to describe the patient sample and distributions of variables included in analyses for each manuscript. The analytic method used to evaluate heterogeneity in the relationship between sleep disturbance (or change in sleep disturbance) and patient, disease, and treatment factors or exercise was regression mixture models (RMMs).[158,159]

3.5.1 Rationale for RMMs.

Previous research on the relationship between exercise and sleep in CRC shows mixed results. The most compelling study, a randomized trial including Stage IV lung and CRC patients, showed a decrease in sleep disturbance with exercise.[117] A host of other studies (including observational and randomized studies) showed no effect or mixed results when assessing the relationship between exercise and sleep in CRC and other populations.[119-121,160] In these studies, the effect of exercise on sleep disturbance could be lost in the average effects for the exercisers. RMMs provide an opportunity to identify subgroups of patients for which the relationship between exercise and sleep disturbance may

vary. An extreme but illustrative example is a case in which for one group of patients, exercise has a negative relationship with sleep disturbance (better sleep), but for another group, exercise has a positive relationship with sleep disturbance (worse sleep). The average of these groups is 0. This result is misleading, suggesting that there is no relationship between exercise and sleep disturbance for the exercise group when, in fact, for a subgroup of patients, exercise *is* associated with better-quality sleep. RMMs are particularly useful in identifying these types of subgroups of patients, or in other words, the *heterogeneity* in the relationship between exercise and sleep disturbance.

3.5.2 RMM Estimation

RMMs are special cases of finite mixture models, which model weighted combinations of different distributions. With RMMs, the component membership to each distribution is unobservable (a latent variable) and discrete. These distributions are called *classes*. Each patient in the dataset is associated with a probability of being in each class. Regression coefficients vary by class. The base equation for the cross-sectional mixture models was:

$$Sleep\ Disturbance_{(i)} = \beta_{0(C)} + \beta_{1(C)}Anxiety_{(i)} + \beta_{2(C)}Pain_{(i)} + \beta_{3(C)}Fatigue_{(i)} + \cdots + \epsilon_{(c)}$$

where β signifies the regression coefficients for each variable in the model, the subscript *C* indicates the coefficient for that class, *i* is the value for an individual *i,* and ϵ represents error in the model. Variables discussed in Section 3.4.2 were added in the ellipses depending on the research objective. For example, for Manuscript 2, in addition to other patient, disease, and treatment characteristics, exercise was added to the model with other variables accounting for participation in exercise. The RMM equation for models evaluating change in sleep disturbance included change in sleep disturbance from Month 10 to Month 17 data collection as the outcome variable and change in HRQOL factors (e.g., anxiety, pain, fatigue) as well as change in other factors that were collected at Month 10 and Month 17. Patient and cancer characteristics that were only captured at Month 10 were included in the change models at Month 10 (e.g., age, parent status). CRC treatment information was captured at Month 10 and Month 17, so the most recent treatment information was included in the change models (Month 17). Change models included PROMIS Sleep Disturbance at Month 10 as a covariate to account for starting sleep disturbance scores.[161]

RMMs were estimated using Dual Quasi-Newton optimization.[162] Models ranging from 1 to 4 classes were evaluated. Four classes were chosen as the maximum because anything beyond that would likely stretch the available sample size too far to obtain meaningful and interpretable estimates. For simplicity, the probability distribution for each component was set to a normal (Gaussian) distribution, and the link function was the Identity function. Class size was allowed to vary depending on the best model fit. The final models (e.g., choice of number of classes) were chosen based on fit (e.g., smallest Bayesian Information Criterion Index (BIC)) and interpretability. RMMs are preferable to multiple regression for assessing heterogeneity in patient, disease, and treatment characteristics related to sleep disturbance because multiple regression assumes a single association pattern apply to the whole study population. If only one class of sleep disturbance was found, then multiple regression (which assumes one common class of sleep disturbance and one common linear relationship between each x-variable and sleep disturbance) was used to model factors associated with sleep disturbance.

If RMM results point to more than one class, it would be concluded that the relationship between sleep disturbance and other patient-level factors (i.e., demographics, disease characteristics, treatment characteristics, exercise) was different for *subgroups* of patients. These subgroups are akin to interaction terms in a regression model, except that with RMMs, we can identify subgroups of patients with unobserved/unmeasured (latent) variables.

Relationships between candidate independent variables were evaluated for collinearity by calculating bivariate correlations and variance inflation factor (VIF) within multiple regression models. VIF values greater than 10 were considered a symptom of multicollinearity. Residuals were evaluated between candidate independent variables and PROMIS Sleep Disturbance to determine if higher-order terms needed to be included in the models.

Logistic regression was used to identify factors associated with patient attrition or incomplete surveys. The logistic regression models included patient characteristics collected at Month 10 that were related to sleep disturbance and potentially associated with survey compliance: sex, race, employment status, survey language, time between most recent chemotherapy and survey completion (Manuscript 1 only), level of exercise activity (Manuscripts 2 and 3 only), PROMIS Sleep Disturbance, and PROMIS Physical Functioning.

3.5.3 Analysis Conventions

Regression coefficients were reviewed to describe the relationship between sleep disturbance and covariates in the models. Complete case analyses were conducted for all models. An alpha of 0.05 or less was chosen as the criterion for statistical significance of the covariates in the RMMs. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). More specifically, we used a SAS procedure called PROC FMM to fit RMMs.[163]

3.5.4 RMM Starting Values

RMMs' Dual Quasi-Newton optimization[162] requires initial model parameter values that give the model a place to start optimization, called starting values. SAS PROC FMM supplies starting values for each class, but RMM results can be sensitive to starting values,[164] therefore a user-defined set of starting values were tested to evaluate the impact SAS PROC FMMs starting values on the number of classes chosen in each manuscript. A SAS macro was developed to generate starting values for all primary models. The generated starting values were tested and model fit results were tabulated. SAS starting values were derived and evaluated in 5 steps:

First, median sleep disturbance was calculated using PROMIS Sleep Disturbance (depending on the model's dependent variable, PROMIS Sleep Disturbance at Month 10, Month 17, or change from Month 10 to Month 17 was used). The analysis sample was divided into two subgroups: patients who scored below the median on PROMIS Sleep Disturbance and patients who scored greater than or equal to the median on PROMIS Sleep Disturbance.

The second step was to run a set of multiple regression models, one model for patients who scored below the median on PROMIS Sleep Disturbance and a second model for patients who scored at or above the median on PROMIS Sleep Disturbance. Coefficients were stored for use in Step 3. For example, age was an independent variable entered into all models and two coefficients on age were calculated—one for the patients who scored below the median on PROMIS Sleep Disturbance and one for patients who scored at or above the median on PROMIS Sleep Disturbance.

In Step 3, each regression coefficient estimate calculated in Step 2 was then randomized using a normal distribution and a standard deviation of 10 times the standard error of the coefficient. Step 3 was reiterated 100 times to calculate 100 sets of coefficient values.

In Step 4, two regression mixture models were calculated. First, a regression mixture model with one class (in other words, a multiple regression model) was calculated. Second, the randomized coefficient values from Step 3 were used as starting values in a regression mixture model with two classes. The regression mixture model with two classes was recalculated 100 times, with each set of coefficient values calculated in Step 3. Every time a regression ran, BIC was recorded.

In Step 5, BIC for all 100 iterations of the two-class RMMs were compared against the BIC for the one-class model. Models with BIC values less than the one-class model were tabulated and reviewed for interpretability.

The steps above describe the process for testing starting values for two classes, but this process could be expanded to test more than two classes.

Results of RMM starting value analysis.

Manuscript 1.

Month 10 model. Six out of 100 two-class solutions yielded lower BIC values than the one-class (multiple regression) solution, but the mixing probabilities were very small with the smaller classes composed of less than 8% of the sample, implying that the smallest classes contained outliers (Table 3.1).

Change model. For the change model, 10 out of 100 two-class solutions yielded lower BIC values than the one-class (multiple regression) solution. The mixing probabilities were also very small, with the smallest class composed of less than 11% of the sample (Table 3.1). The model parameters for all 10 of these two-class solutions were uninterpretable.

Table 3.1. Manuscript 1 Starting Value Results

Model	BIC	Iteration	Mixing Probability for Smallest Class	Variance Estimate for Smallest Class	Standard Error for Variance of Smallest Class
Month 10					
	257.3	58	0.0647	0.0014	0.0003
	286.0	71	0.0650	0.0030	0.0007
	4301.7	53	0.0534	0.0014	0.0004
	4317.4	8	0.0665	0.0069	0.0022
	4330.9	52	0.0482	0.0015	0.0004
	4331.2	65	0.0703	0.0122	0.0032
	4344.4	One-class model (multiple regression)	-		
Change					
	2378.0	92	0.0658	0.0000	0.0000
	2394.4	2	0.0633	0.0003	0.0001
	2406.2	76	0.0548	0.0000	0.0000
	2410.7	37	0.0629	0.0003	0.0001
	2447.1	51	0.0878	0.0091	0.0024
	2448.9	84	0.0593	0.0005	0.0002
	2455.7	41	0.0721	0.0031	0.0009
	2468.1	55	0.0662	0.0077	0.0024
	2474.4	73	0.1071	0.0021	0.0009
	2482.3	96	0.0194	0.0000	0.0000
	2490.6	One-class model (multiple regression)	-		

Manuscript 2.

Month 10 model. Only 2 out of 100 two-class solutions yielded lower BIC values than the one-class (multiple regression) solution. The mixing probabilities for the smallest class were very small, suggesting that the smallest classes were picking up on outliers instead of modeling two interpretable classes of sleep disturbance (Table 3.2).

Month 17 model. Five of the 100 two-class models yielded better fit statistics than the one-class model (Table 3.2). Most of the smallest classes were over 10% of the sample, about 30–40 patients. On review of the model results for these solutions, parameter estimates were almost all statistically significant, suggesting that the smallest classes were composed of outliers.

Table 3.2. Manuscript 2 Starting Value Results

Model	BIC	Iteration	Mixing Probability for Smallest Class	Variance Estimate for Smallest Class	Standard Error for Variance of Smallest Class
Month 10					
	145.5	28	0.0565	0.0003	0.0001
	180.9	75	0.0170	0.0000	0.0000
	188.6	One-class model (multiple regression)	-		
Month 17					
	589.6	55	0.0421	0.0000	0.0000
	592.4	56	0.1362	0.0062	0.0014
	607.2	48	0.1024	0.0053	0.0015
	612.6	52	0.1120	0.0127	0.0032
	617.3	86	0.1220	0.0156	0.0035
	643.6	One-class model (multiple regression)	-		

Manuscript 3.

Eleven out of 100 two-class solutions yielded lower BIC values than the one-class (multiple regression) solution. Most of the mixing probabilities for the smallest class were less than 10% of the sample, a suggested cut-off for the size of the smallest class.[165] The coefficients on the smallest classes that represented more than 10% of the sample were all statistically significant, suggesting that the smallest classes were picking up on outliers instead of modeling two interpretable classes of sleep disturbance (Table 3.3).

Table 3.3. Manuscript 3 Starting Value Results

BIC	Iteration	Mixing Probability for Smallest Class	Variance Estimate for Smallest Class	Standard Error for Variance of Smallest Class
2272.5	65	0.0940	0.0001	0.0000
2283.9	69	0.0886	0.0000	0.0000
2308.2	42	0.1022	0.0003	0.0001
2309.0	7	0.1121	0.0020	0.0005
2323.5	78	0.1036	0.0008	0.0002
2325.4	34	0.1120	0.0010	0.0002
2333.4	92	0.0962	0.0007	0.0002
2333.5	19	0.0402	0.0000	0.0000
2349.3	33	0.1063	0.0026	0.0006
2363.5	37	0.1305	0.0153	0.0036
2403.6	4	0.0287	0.0000	0.0000
2424.2	One-class model (multiple regression)	-		

Conclusions—RMM starting value analysis.

The results of the starting value assessment show that even though two-class models were sometimes better fitting models than the one-class models, the two-class models were uninterpretable. The results of the RMM starting value evaluation provide evidence that the one-class solutions in Manuscripts 1, 2, and 3 were not driven by PROC FMM's built-in starting value algorithm.

3.5.5 Power

Two types of power analyses were conducted. First, we assessed power to detect two classes using RMMs. Second, we assessed power to detect a relationship between exercise and sleep disturbance (Manuscript 2), or a change in exercise and change in sleep disturbance (Manuscript 3).

Power to detect two classes.

A power analysis was conducted to ensure that the MY-Health sample was sufficiently large enough to detect two classes if two classes were present. The ability to detect two classes is a prerequisite of detecting more than two classes, thus power analyses for RMMs focused on detection of two classes.

Simulation methods.

Power to detect two classes was evaluated and confirmed using simulations based on MY-Health study data, which provided the covariance structure among the independent variables. A simulated covariance structure is based on hypothesized relationships that may not guarantee a good approximation of the actual relationships. By using the MY-Health study data as a starting point, actual relationships among variables were incorporated into the power analyses.

Sub-samples were randomly drawn from the study dataset to simulate 1000 datasets (replications) for each of the parameter modifications in the simulation: overall sample size, numeric differences between coefficients in each latent class, variance of the error term used to simulate sleep disturbance scores and proportion of sample within each class. Table 3.4 presents the characteristics modified to create simulations for cross-sectional (severity of sleep disturbance) or change analyses (change in sleep disturbance), and includes justification for the characteristics tested.

Regression coefficients (relationships between sleep disturbance and other independent variables in the model) were identified in published literature[93,91] and used to provide estimates of the

relationship between sleep disturbance and independent variables in the model. Regression coefficients from the literature were converted to quantify the relationship between a 100-point sleep disturbance scale and other independent variables.

A simulated sleep disturbance variable was calculated by applying regression coefficients identified in the literature to a regression equation using data for independent variables from the MY-Health study. To simulate two classes of sleep disturbance that were closer or further apart, two regression equations were calculated by splitting the sample into two subsamples and calculating two regression equations modeling the simulated sleep disturbance variable. The first equation included regression coefficients that were smaller than the regression coefficients found in the literature. The second equation included regression coefficients that were larger than the regression coefficients from the literature. The "distance" between regression coefficients (and classes) was varied allowing the classes to be closer or further apart.

The resulting simulated sleep disturbance data were modeled using SAS PROC FMM[163] to evaluate the number of times PROC FMM would identify two classes when two classes were indeed present. Fit statistics and the number of classes associated with the smallest Bayesian Information Criterion Index (BIC) were tabulated for each replication.

Table 3.4. Simulation Parameters

	Cross-sectional analyses (Manuscript 1 and 2)		Change analyses (Manuscript 1 and 3)	
Characteristic	**Values tested**	**Justification**	**Values tested**	**Justification**
Sample size	360, 600, 700	Approximate sample sizes yielded from models	200, 300, 380	Same justification as cross-sectional analyses
Numeric difference between coefficients in each latent class	0.05, 0.1, 0.15, 0.3	A well-accepted rule of thumb for identifying minimally important group differences from the patient perspective on a PRO measure is the half standard deviation[166]. At Month 10, the half standard deviation of PROMIS Sleep Disturbance was approximately 5 points. In order for classes to be meaningfully different, it was anticipated that the classes should be separated by the half standard deviation at the minimum. ▪ A distance of .05 resulted in a difference of approximately 3 points on the simulated sleep disturbance scores, less than the half standard deviation cutoff. ▪ A distance of .1 yields a difference of approximately 6 points, which is close to the half standard deviation cutoff. ▪ A distance of .15 yields a difference of around 9 points between classes. ▪ A distance of .3 yields a difference of approximately 17.5 points between classes.	3, 5, 6, 9	Regression coefficients identified in the literature for change analyses were generally larger than the cross-sectional regression coefficients, therefore the distance between coefficients was increased. ▪ Distance = 0.6, 0.9, 1.5 and 3, Mean difference between classes < 3 ▪ Distance = 5, Difference between classes ≈ 5 ▪ Distance = 6, Difference between classes ≈ 6 ▪ Distance = 9, Difference between classes ≈ 9.6
Size of the error term in the regression equation used to calculate the simulated sleep disturbance scores	RMSE = 1, 3, 4, 5, 8	Using sample data, a simple linear regression regressing PROMIS Sleep Disturbance on three independent variables provided an upper bound for the size of the error term in the final models (which will likely result in a better fit). The RMSE in the simple model was 8, therefore all the error term sizes were 8 and smaller.	RMSE = 1, 3, 4, 5, 7	Using sample data, a simple linear regression regressing PROMIS Sleep Disturbance on three independent variables provided an upper bound for the size of the error term in the final models (which will likely result in a better fit). The RMSE in the simple model was 7, therefore all the error term sizes were 7 and smaller.
Group size for healthy sample	80%, 70%, 50%	A recent systematic review found that the prevalence of sleep disorders in the cancer population can't be ascertained because studies do not measure sleep disturbance in a standard way[50], therefore a wide range of class sizes was tested differentiating poorer sleepers from better sleepers.	80%, 70%, 50%	Same as cross-sectional analyses.

Simulation results for cross-sectional models.

Figure 3.2 illustrates simulation results for the Month 10 cross-sectional models when the sample size was 360, 600, or 700 and the latent classes comprised 50% of the sample each. The y-axis shows the percent of simulated cases in which two classes were identified (power) and the x-axis displays numeric difference between coefficients in each class divided by error. The x-axis ranges from 0.006 to 0.050, with small numbers indicating smaller distance-to-error ratios (smaller distance between coefficients in each class and more error) and larger numbers representing larger distance-to-error ratios (larger distance between coefficients in each class and less error). For example, an x-axis value of 0.006 corresponds to a distance between class coefficients of 0.05 and an error term of 8 for simulated sleep disturbance. On the other end of the scale, an x-axis value of 0.05 corresponds to a distance between coefficients in classes of 0.15 and an error term of 3 or a distance of 0.05 and an error term of 1. One circle represents the results of 1000 simulated replications drawn from the MY-Health study dataset all with the same simulation parameters applied. The color of the circles represents the sample size.

Ideally, RMMs would be able to detect the two simulated latent classes in all circumstances, but the dynamic relationships between each characteristic (e.g., sample size, error term size, distance between classes) made it easier or harder for the model to identify two classes when two classes exist. Circles closer to the top of the figure represent simulations in which two classes were detected more often than one class. Circles close to the bottom of the figure represent simulations in which only one class was detected more often. At a distance between coefficients of 0.15 or above, which was equivalent to approximately 9 points on the simulated sleep disturbance scale and considered a meaningful difference, two classes were detected regardless of the other characteristics permeated in the simulation (x-axis values ≥ .038). If the distance between coefficients in each class was small and error was large (smaller x-axis values), then the RMMs were not able to identify two classes (bottom left corner of the figures). The proportion of the sample within each class had very little effect on power. Additional values on the x-axis were tested above 0.05 to 0.30 (distance = .3, error = 1), but after 0.050, regardless of the permutations of the simulation characteristics, power was always 100%. Results were almost identical for different class sizes with the largest class comprised of 70% of the sample (Figure 3.3), and 80% of the sample

(Figure 3.4). Based on the characteristics discussed above, the cross-sectional models should be sufficiently powered to detect two classes.

Figure 3.2. Simulation results for cross-sectional models (proportion of patients in class with healthier sleepers = 50% of sample, proportion of patients in class with poorer sleepers = 50% of sample).

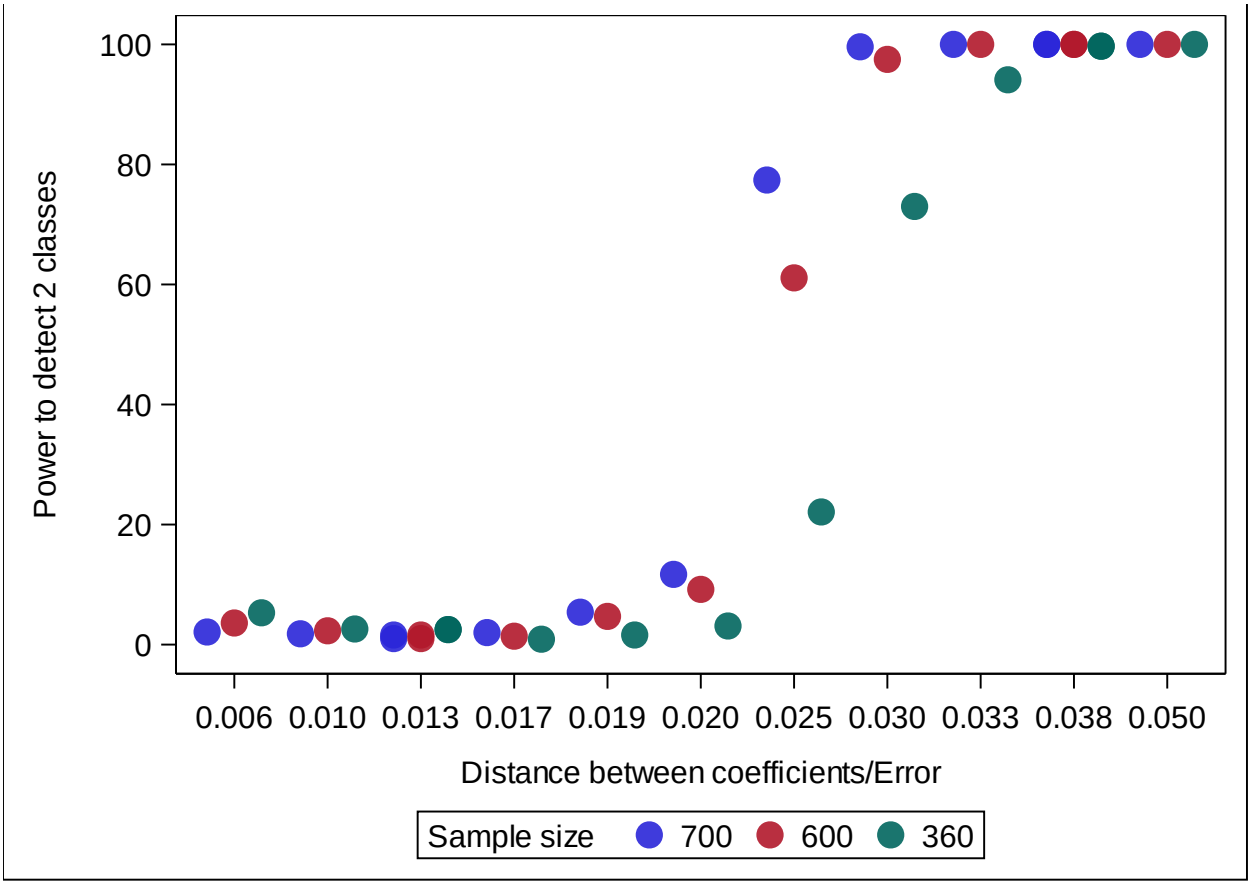


Figure 3.3. Simulation results for cross-sectional models (proportion of patients in class with healthier sleepers = 70% of sample, proportion of patients in class with poorer sleepers = 30% of sample).

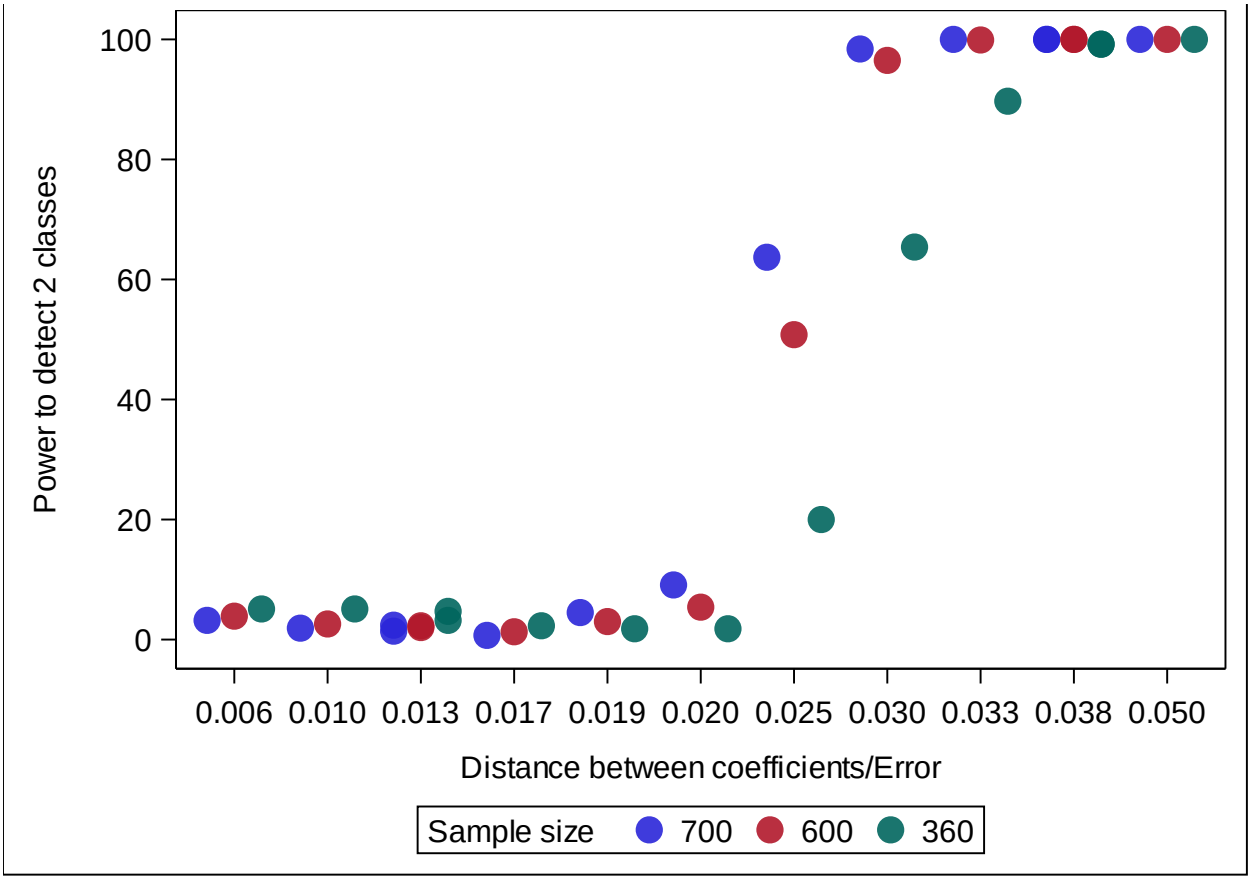
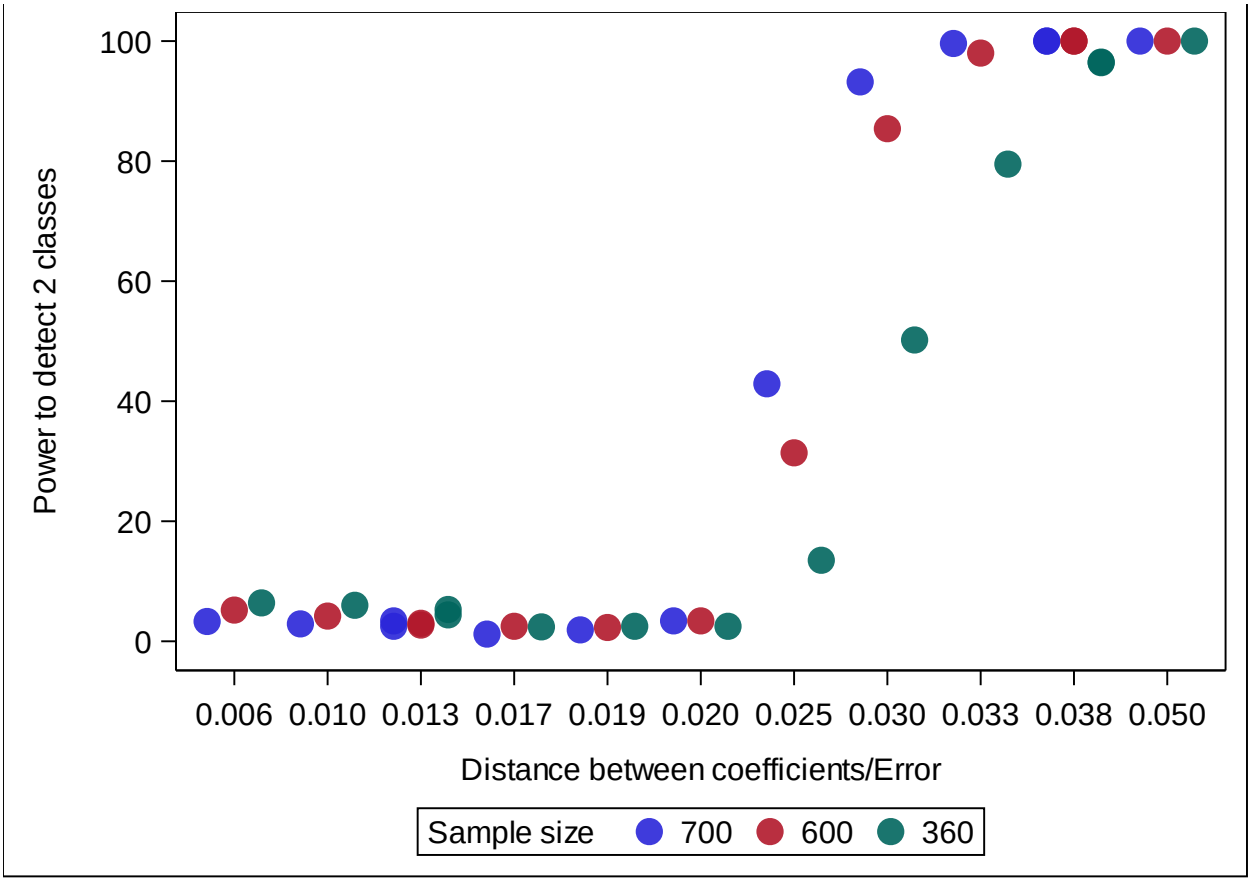


Figure 3.4. Simulation results for cross-sectional models (proportion of patients in class with healthier sleepers = 80% of sample, proportion of patients in class with poorer sleepers = 20% of sample).



Simulation results for change models.

The simulation results for change models are presented in Figure 3.5 through Figure 3.7. These figures are analogous to the cross-sectional simulation figures except that they present results of the change model simulations with a sample size of 200, 300, and 380. Change models should be sufficiently powered to detect two classes when error variance of the simulated sleep disturbance variable is relatively small (error < 4, x-axis ≥ 0.2), or when the distance between coefficients is at least 5 or larger (corresponding to a mean difference in sleep disturbance between classes of about 5 points, considered a meaningful difference based on the half-SD method, x-axis value > 0.7). Larger distance-to-error values were tested but left out of the x-axis because the power to detect two classes was 100 or very close to 100 for all permutations of the simulation characteristics beyond 0.214 (distance between coefficients = 1.5, error = 7).

Figure 3.5. Simulation results for change models (proportion of patients in class with healthier sleepers = 50% of sample, proportion of patients in class with poorer sleepers = 50% of sample)

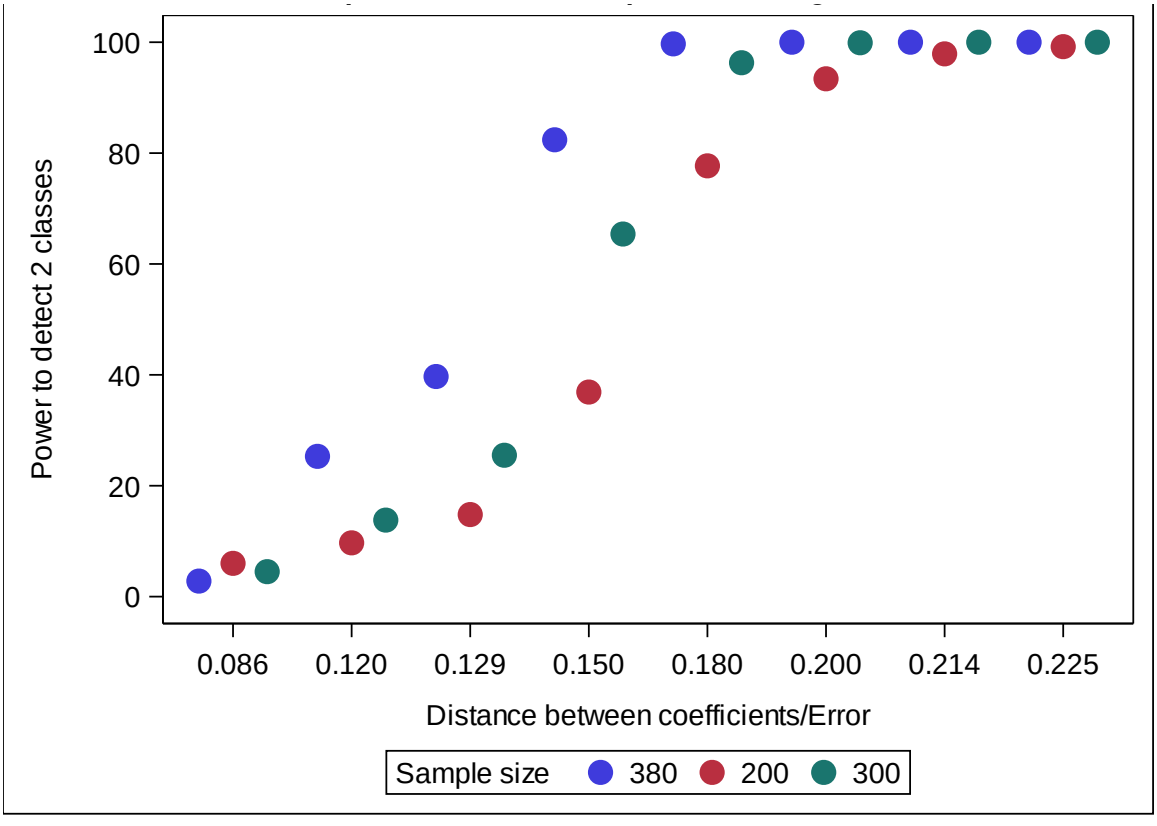


Figure 3.6. Simulation results for change models (proportion of patients in class with healthier sleepers = 70% of sample, proportion of patients in class with poorer sleepers = 30% of sample).

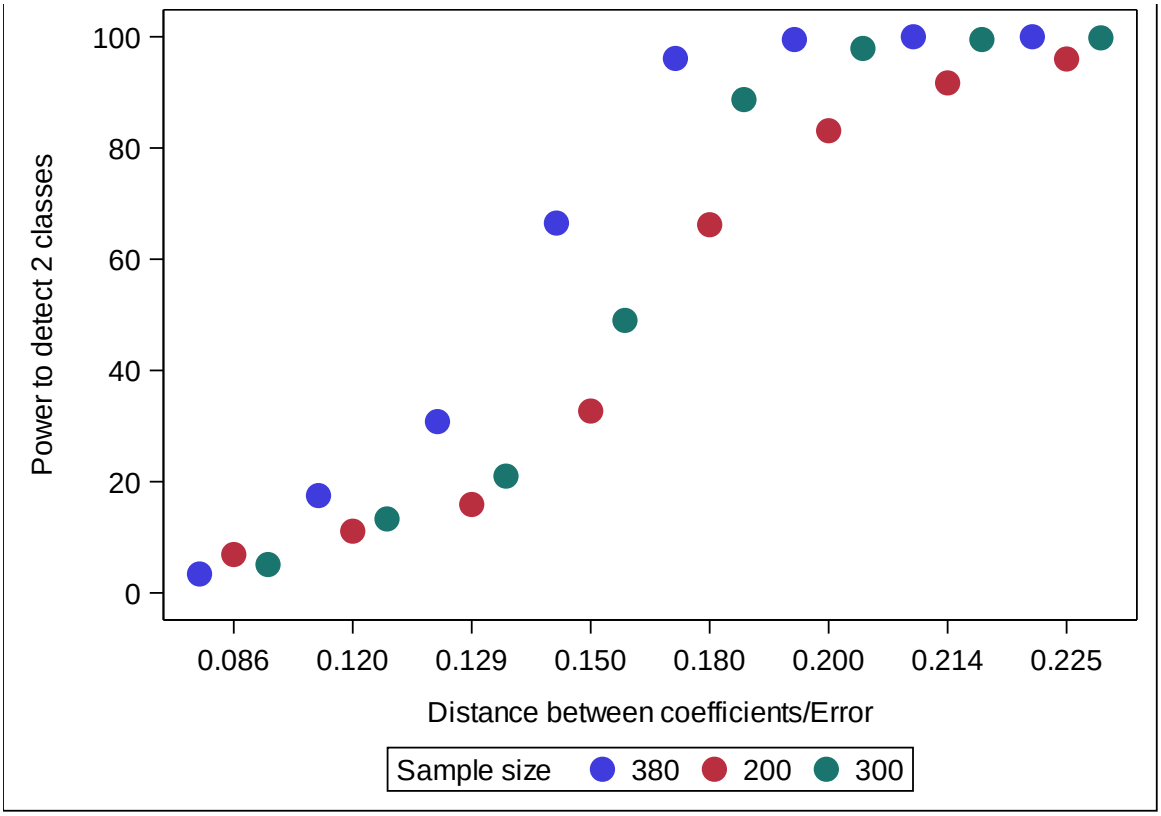
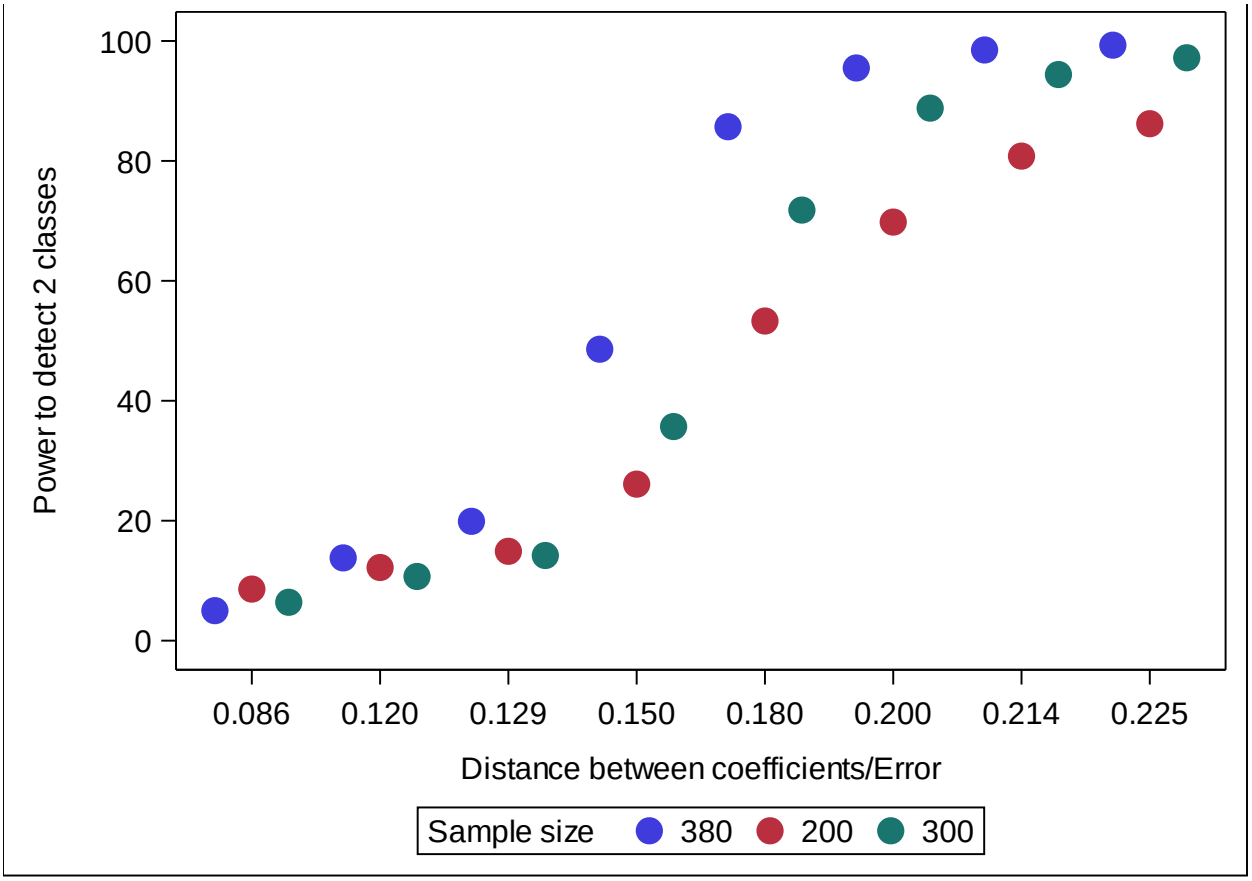


Figure 3.7. Simulation results for change models (proportion of patients in class with healthier sleepers = 80% of sample, proportion of patients in class with poorer sleepers = 20% of sample).



Power to detect exercise effect.

Background and methods.

Exercise was evaluated in Manuscripts 2 and 3, thus this section applies only to these manuscripts. Plausible effect sizes were abstracted from published randomized controlled trials investigating the effect of an exercise intervention on sleep disturbance in other populations. Partial correlations varied greatly across studies, therefore a wide range of plausible effect sizes were tested for the power analyses. One study included adults diagnosed with stage IV CRC and yielded a partial correlation of 0.64 for a home-based exercise intervention of four days or more sessions per week.[117] Two other studies included women diagnosed with stage I–III breast cancer and yielded partial correlations of 0.14[140] and 0.05.[141]

Because RMMs may yield multiple classes, each a portion of the total sample size for the model, power to detect exercise was evaluated by possible class size. Estimates for the prevalence of sleep

disorders in the cancer population vary;[50] latent class size was varied in the power analyses to test various possible outcomes. Depending on the number of classes that emerged from the mixture models and the size of each class, a wide range of sample sizes within each class were possible.

Exercise power results.

Figure 3.8 and Figure 3.9 show the power results for the hypotheses in Manuscripts 2 and 3 respectively. The x-axis displays plausible partial correlations and the y-axis shows power. The bar colors correspond to sample sizes.

As the partial correlations increased (relationship between sleep disturbance and exercise increase), the power to detect statistically significant exercise effects also increased. Based on available published literature, we would expect the partial correlation to fall between .05 and .6, an extremely wide range. Nonetheless, for the cross-sectional models (Figure 3.8), the power for all partial correlations except .05 is sufficient for class sample sizes of 220 or larger. Similarly, the power to detect an exercise effect in the change models was sufficient when the partial correlation was 0.40 or higher, when the partial correlation was 0.14 and the class sample size was 400, or when the partial correlation was 0.20 and the class sample size was 200 or larger (Figure 3.9). When partial correlations were above 0.20, the power to detect an exercise effect was 100%, thus the figures show x-axis values up to 0.20.

Figure 3.8. Power results for cross-sectional exercise models (Manuscript 2)

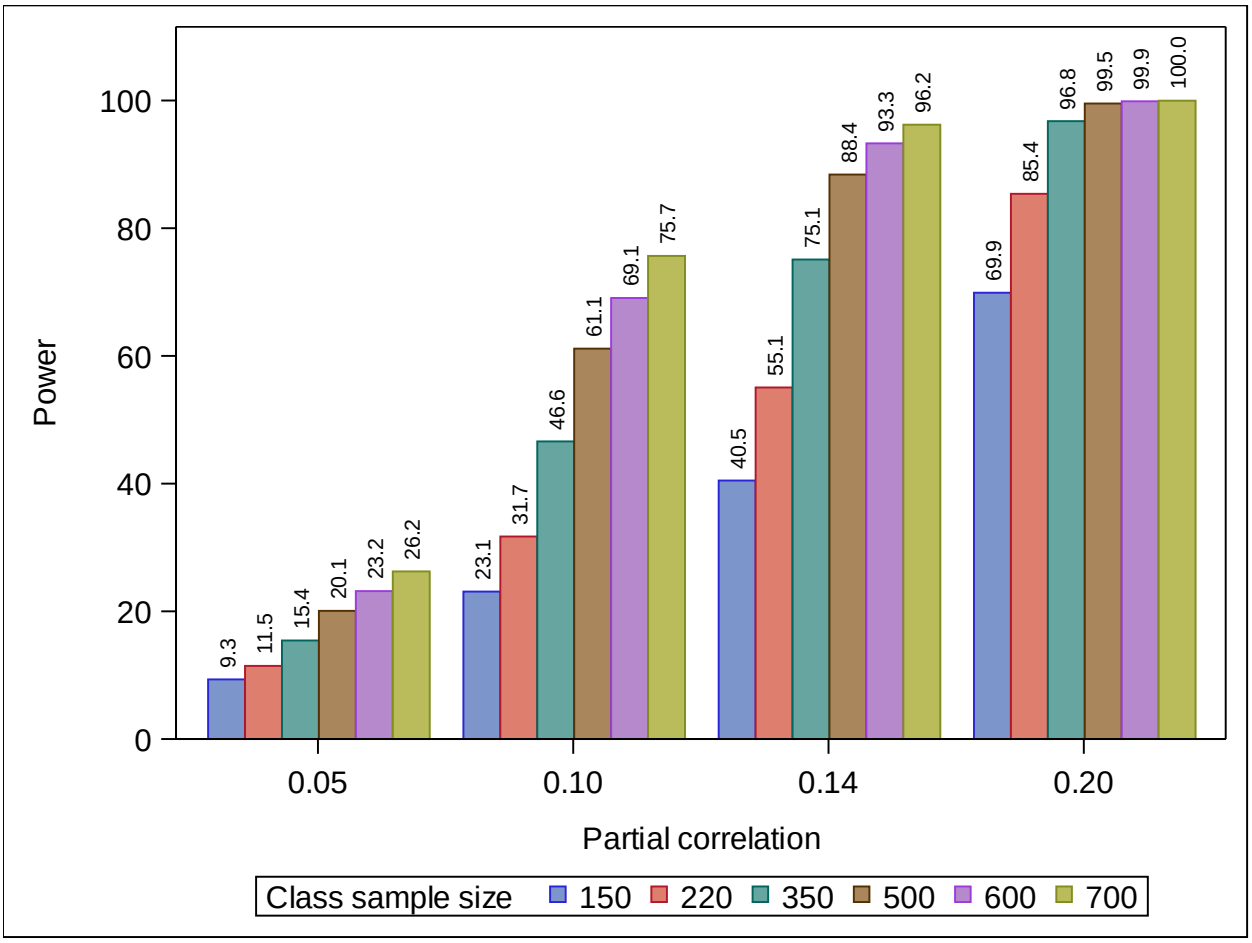
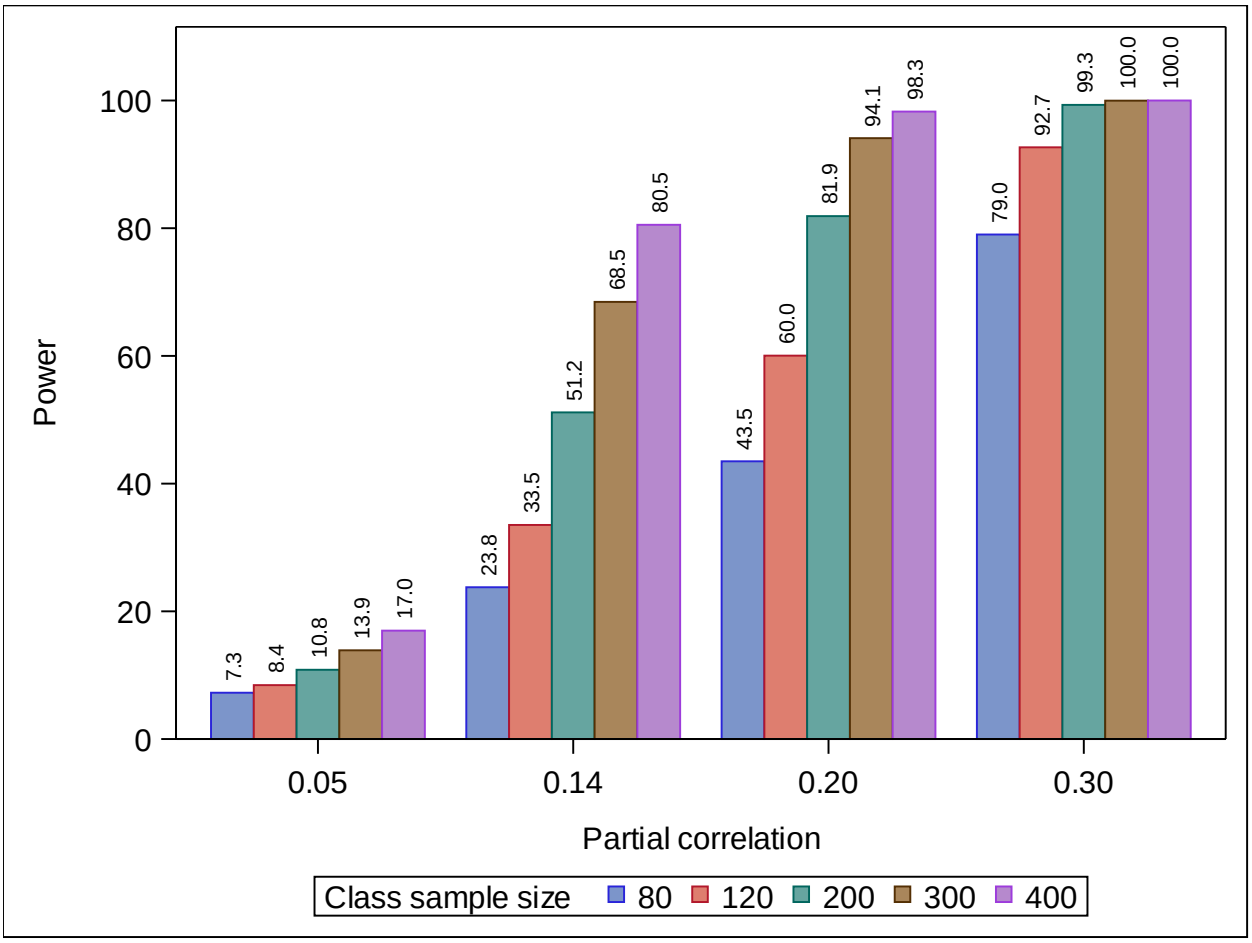


Figure 3.9. Power results for exercise change model (Manuscript 3)



CHAPTER 4. SLEEP QUALITY IN INDIVIDUALS DIAGNOSED WITH COLORECTAL CANCERS: FACTORS ASSOCIATED WITH SLEEP DISTURBANCE AS PATIENTS TRANSITION OFF TREATMENT (MANUSCRIPT 1)

4.1 Background

Colorectal cancer (CRC) is the third most common adult cancer,[4] with more than 1.1 million individuals currently living with the disease in the United States.[5] Of these patients, it is estimated that half experience decrements in sleep.[3] Consequences of sleep disturbance include decreased cognitive functioning[9] and fatigue.[10,11] Cancer patients have attributed sleep disturbance with impaired daytime functioning, trouble keeping up at work and with social activities, and mood disturbance.[12] Sleep disturbance is also a risk factor for infectious and cardiovascular diseases, and depression.[13] It is also shown to be associated with a loss in work productivity, work quality, and an increased number of visits to health professionals.[14]

Although sleep disturbance is prevalent in the cancer population (between 30% and 87%[2]), most individuals diagnosed with cancer do not discuss sleep difficulties with their clinicians.[167] Sleep has rarely been included as an outcome in CRC research. Given the lack of communication between patients and clinicians regarding sleep, clinicians could benefit from knowing which patients are at risk for worse sleep outcomes, and researchers would benefit from being able to target high-risk sleep populations for future intervention studies.

Research on sleep disturbance in the general population is much more comprehensive than in the cancer literature. In the general population, comorbidities such as cardiovascular diseases (e.g., stroke, heart attack, angina), respiratory conditions (e.g., asthma, bronchitis), diabetes, and gastroesphageal reflux[73] affect sleep quality. Men experience more awakenings but women typically have more trouble falling asleep.[72] Being a parent is associated with worse sleep quality.[83,84] Retirement from work is associated with better sleep quality.[73] Less is known about correlates of sleep disturbance in the cancer population.

In cancer patients, depression,[90,92,93,95] anxiety,[94,95] and pain[94,95] were often associated with sleep disturbance, but these variables were not always statistically significant in published research. Other factors include physical health and functioning,[90,92,93] patient characteristics (e.g., gender, age),[90-92] sedative use,[94] fatigue,[94] cigarette use,[92] and having undergone surgery.[91] Cancer treatment–related factors may impact patients' emotional and physical health (either directly or because of side effects). For example, medications commonly administered to patients diagnosed with cancer such as opioids, antiemetic medications, and corticosteroids are associated with sleep disruption.[98] Symptoms associated with cancer treatment such as dyspnea, gastrointestinal symptoms, and pain are associated with sleep impairment.[21] There is a known link between cancer treatment and sleep disturbance, and some literature suggests that there is a relationship between time since treatment and sleep disturbance.[16-18,100,101] Two studies in breast cancer patients undergoing chemotherapy found that sleep quality was poor prior to chemotherapy but there was little change in sleep quality during chemotherapy.[16,17] Another study in breast cancer found persistent sleep problems before and after surgery for breast cancer.[101] HRQOL (including sleep) was assessed as part of a randomized trial of chemotherapy in ovarian cancer patients,[18] and researchers found an immediate deterioration in sleep and other aspects of HRQOL around the first cycle of chemotherapy and then a statistically-significant improvement in sleep and other aspects of HRQOL throughout chemotherapy.[18] The relationship between trajectories of sleep disturbance and CRC treatment over time is unknown.

Individuals diagnosed with CRC may experience a range of sleep quality stretching from no sleep disturbance to severe insomnia (or another diagnosed sleep disorder). The etiology and severity of sleep disturbance may vary from patient to patient. For example, sleep disturbance may be caused by anxiety related to cancer diagnosis for one person, but another person may attribute sleep disturbance to physical symptoms such as pain or nausea, and these factors may vary by *severity* of sleep disturbance. By understanding patient-level factors associated with poorer or better quality sleep, studies could provide new insight to clinicians on the patient, disease, and treatment characteristics associated with worse sleep disturbance or *worsening* sleep disturbance. Identifying patient-level factors associated with sleep disturbance may also provide insight in the design of future randomized studies designed to identify patients who would benefit most from an intervention for severe sleep disturbance.

The purpose of this study is to identify patient, disease, and treatment characteristics associated with of sleep disturbance (and change in sleep disturbance) in individuals diagnosed with stage I, II, or III CRC. Specifically, the first objective is to investigate whether there was variation in patient, disease, and treatment characteristics across levels of sleep disturbance severity. We test the hypothesis that associations between factors (e.g., patient, disease, and treatment characteristics) and sleep disturbance differ by *severity* of sleep disturbance. The second objective of this study is to identify correlates of sleep disturbance; we test the hypothesis that patients who were currently undergoing chemotherapy or those who had more recently undergone chemotherapy would report worse sleep disturbance than patients who never had chemotherapy. We go further by evaluating *change* in sleep disturbance after CRC diagnosis. The third objective is to investigate whether there was variation in patient, disease, and treatment characteristics across magnitude of change in sleep disturbance severity as patients transition off of CRC treatment with the hypothesis that associations between sleep disturbance and patient-level factors (e.g., patient, disease, and treatment characteristics) vary by magnitude of change in sleep disturbance. The final and fourth objective was exploratory: to identify correlates of change in sleep disturbance.

4.2 Methods

4.2.1 MY-Health Study Design

This secondary data analysis was conducted using data from Georgetown University's Measuring Your Health (MY-Health) study which included over 5000 patients who enrolled between 2010 and 2012.[143]. Potential study participants were identified from four SEER cancer registries located in California (2), Louisiana, and New Jersey. Individuals age 21–84 years diagnosed with one of seven cancers (CRC, prostate, non-small cell lung, non-Hodgkin lymphoma, female breast, uterine, or cervical) were invited to participate in the MY-Health study via mail. Mail-in hard copy questionnaires were administered to patients at two time points: Time 1 data collection occurred approximately 10 months after diagnosis and Time 2 data collection occurred 17 months after diagnosis on average. The MY-Health study oversampled black, Hispanic, and Asian cancer patients and patients under 50. Questionnaires were administered in three languages English, Spanish, and Mandarin (simple and traditional). Additional details on the study design and procedures are published.[143]

4.2.2 Participants

Patients who were identified as being diagnosed with stage I, II, or II CRC were included in the analyses for this study: Round 1 of data collection occurred at 10 months on average after diagnosis and included 734 patients (range: 5.5 to 21.3); 400 patients participated in Round 2, which was collected approximately 17 months after diagnosis on average (range: 12.8 to 26.4). Although the data collection windows were approximately 15 and 13 months wide respectively, for brevity, the first data collection will be called the Month 10 data collection and the second data collection will be referred to as the Month 17 data collection.

4.2.3 Measures

Dependent variable.

Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance items were administered to patients at 10 and 17 months after CRC diagnosis. PROMIS Sleep Disturbance includes a seven-day recall and measures concepts such as trouble staying asleep, not getting enough sleep, restlessness, feeling refreshed after sleep, and difficulty falling sleep. Results of the full psychometric evaluations of the PROMIS Sleep Disturbance item bank[144] and short forms[145] were previously published. A custom six-item short form was scored; the psychometric properties of the six-item form were evaluated in individuals enrolled in the MY-Health study (Cronbach's $\alpha = 0.88 – 0.95$).[146] PROMIS Sleep Disturbance is a continuous variable scored on a t-score metric with a mean of 50 and standard deviation (SD) of 10 based on the referent population (mixture of clinical and the general U.S. population[147]), and higher scores indicate worse sleep disturbance. Change in sleep disturbance was calculated by subtracting PROMIS Sleep disturbance scores at 10 months from scores at 17 months after CRC diagnosis. Positive change is indicative of worsening sleep. A recent study by Leung et al.[168] provided a cut point on PROMIS Sleep Disturbance indicative of clinically significant sleep disturbance (≥ 57, area under the curve = 0.92).

Independent variables.

The MY-Health dataset contains information on patient, disease, and treatment factors associated with sleep disturbance. Cancer treatment type (surgery,[91] chemotherapy,[21,99] radiation) and most recent date of treatment were self-reported. Categorical variables were derived to capture

current/recent treatment compared to no treatment or less-recent treatment. Categories were based on relevant physical recovery periods post-treatment and data availability. Time since chemotherapy was coded using four categories (i.e., currently receiving chemotherapy, chemotherapy 1–2 months ago, chemotherapy more than 2 months ago, never received chemotherapy [reference category]). Time since surgery was coded using three categories (i.e., surgery occurred within 0–4 months, surgery occurred more than 4 months ago, never received surgery [reference category]). Comorbid conditions[73] were self-reported and included in the models as a derived variable with three categories (i.e., no comorbid diseases [reference category], 1 comorbid disease, 2 or more comorbid diseases). Three PROMIS domains were included in the models as independent variables to assess aspects of health-related quality of life known to be associated with sleep disturbance.[73,79 80 81,90,92-95] Anxiety (11 items),[149] Fatigue (14 items),[148] and Pain Interference (11 items).[149] These PROMIS measures were normed to the general U.S. population[147] and higher scores indicate worse anxiety, fatigue, and pain respectively. Nausea severity was measured using a five-point nausea[21] item from the FACT-G Physical Well-Being (PWB) subscale[150] with a recall period of the "past 7 days" and response choices ranging from 0 = "not at all" to 4 = "very much." Although the nausea item has not been psychometrically evaluated as a single measure of nausea, the entire FACT-G PWB scale, which has been evaluated extensively in cancer patients, covers concepts that overlap with PROMIS measures such as Pain Interference and Fatigue. Therefore, only the nausea item was included in the models as a continuous variable. Other characteristics known to be associated with different levels of sleep disturbance were included in the models such as age at diagnosis,[2,21,97] sex,[72] time since diagnosis,[93] employment status,[84] and an indicator for living with children under 18[83,84] were included in the models. Age and race were also included in the model to account for the over-sampling of younger and minority persons from SEER registries. Race, employment status, and the living-with-child(ren) indicator were self-reported, and age at diagnosis, sex, and diagnosis date were obtained via SEER registry data.

4.2.4 Analyses

The overall purpose of this study is to identify patient, disease, and treatment characteristics associated with of sleep disturbance (and change in sleep disturbance) in individuals diagnosed with stage I, II, or III CRC. Analyses were divided into two sub-analyses by addressing cross-sectional

objectives in the first sub-analysis (objectives 1-2), and addressing change in sleep disturbance in the second sub-analysis (objectives 3-4). In the first sub-analysis incorporates data collected approximately 10 months after diagnosis. This time point is important in patients' cancer trajectories because it evaluates factors associated with sleep when patients are transitioning off of treatment. Although patients included in these analyses completed study questionnaires between 5 and 21 months after CRC diagnosis, the mean number of months since CRC diagnosis was 10 months. Therefore, for brevity, these analyses will be referred to as Month 10 analyses. The second analysis focuses on change in sleep disturbance from roughly 10 months after diagnosis to approximately 17 months after diagnosis (referred to as the Change analyses). This timeframe is important because it captures changes in patients' sleep disturbance and changes in other factors (e.g., anxiety, pain, fatigue) as patients transition off of treatment into a more stable recovery phase and survivorship.

Methods.

Descriptive statistics were tabulated. Relationships between candidate independent variables were evaluated for collinearity by calculating bivariate correlations and variance inflation factor (VIF) within multiple regression models. VIF values greater than 10 were considered a symptom of multicollinearity. The correlation coefficient between PROMIS Anxiety and PROMIS Depression was strong ($r = 0.87$) suggesting collinearity between scores. PROMIS Anxiety was included in the model and PROMIS Depression was excluded for simplicity (anxiety is associated with disturbed sleep, but depression is associated with both disturbed sleep and hypersomnia[169]). Residuals were evaluated between candidate independent variables and PROMIS Sleep Disturbance to determine if higher-order terms needed to be included in the models.

Regression mixture models (RMMs)[158,159] are special cases of finite mixture models, which model weighted combinations of different distributions. With RMMs, the component (class) membership to each distribution is unobservable (a latent variable). In this study, we employed RMMs to test if heterogeneity was present in the associations between sleep disturbance severity (and change in sleep disturbance) and other patient, disease, and treatment characteristics. Specifically, if patient, disease, and treatment factors varied by severity of sleep disturbance approximately 10 months after CRC diagnosis (objective 1) or from 10 to 17 months after CRC diagnosis (objective 3).

RMMs were estimated using Dual Quasi-Newton optimization.[162] Models ranging from one to four classes were evaluated. The final models (e.g., choice of number of classes) were chosen based on fit (smallest Bayesian Information Criterion Index (BIC) and Akaike information criterion (AIC)) and interpretability. RMMs are sensitive to starting values,[164] thus user-provided starting values were also tested to confirm the number of classes identified by SAS-generated starting values. If only one class of sleep disturbance was identified, then multiple regression (which assumes one common class of sleep disturbance) was used to model factors associated with sleep disturbance.

A logistic regression was used to identify factors associated with patient survey completion Month 10 (outcome = 1) versus participating in the Month 10 survey but not completing enough questions to be included in the analyses. The logistic regression model included patient characteristics at Month 10 that were related to sleep disturbance and potentially associated with survey compliance: sex, race, employment status, survey language, time between most recent chemotherapy and survey completion, PROMIS Sleep Disturbance, PROMIS Physical Functioning.

There was substantial patient attrition from the Month 10 survey data to the second survey data collection (approximately 17 months after CRC diagnosis); factors associated with patient persistence in survey participation from Month 10 data collection to the second data collection were evaluated using descriptive statistics and logistic regression to address participant drop-out in the Change model. Patients who participated in the first (approximately 10 months post-diagnosis) and second survey (approximately 17 months post-diagnosis) administrations (outcome = 1) were compared with patients who participated in the Month 10 but not the second data collection (approximately 7 months later) (outcome = 0) using logistic regression. The model included patient characteristics that were related to sleep disturbance and potentially associated with patient attrition: sex, race, employment status, survey language, time since most recent chemotherapy and Month 10 survey completion, PROMIS Sleep Disturbance, PROMIS Physical Functioning.

A sensitivity analysis was conducted to describe the impact of including anxiety in the models instead of depression. Anxiety was removed from the Month 10 and Change models, and depression was added. Model results were compared.

Power.

Power to detect multiple classes was evaluated and confirmed using simulations based on MY-Health study data, which provided information about the covariance structure among the independent variables. Sub-samples were randomly drawn from the study dataset to simulate 1000 datasets for each of the parameter modifications in the simulation: overall sample size, numeric differences between coefficients in each latent class, variance of the error term used to simulate sleep disturbance scores, and proportion of sample within each class. A well-accepted rule of thumb for identifying minimally important group differences on a PRO measure is the half standard deviation.[166,170] The half standard deviation of PROMIS Sleep Disturbance was approximately 5 points for the Month 10 analysis. For classes to be meaningfully different, we anticipated that the classes should be separated at a minimum by the threshold for minimal important difference. For the Month 10 analyses, based on a sample size of 600, a mean difference between sleep disturbance scores in each class approximately 6 points apart, equal-size classes (i.e., proportion of patients in class 1 = 50% and proportion of patients in class 2 = 50%) and an error term variance of 3 or less, the power to detect multiple classes was 100%. When the variance of the error term used to compute the simulated sleep disturbance scores increased to 4, 5, or 8 and all other parameters were the same, power reduced to 61.1%, 9.2%, and 1.6%, respectively. Power to detect multiple classes was above 95% for all circumstances when the mean difference between simulated sleep disturbance between classes differed by approximately 9 and 17 points and the variance of the error term used to simulate sleep disturbance scores was less than 8. The proportion of the sample designated to each class was modified in the simulations but the effect on power was negligible. Regarding the Change model, power to detect multiple classes was also evaluated for a sample size of 360. When the classes were of equal sizes, the mean difference between sleep disturbance scores in each class was over 5.4 points apart, and the variance of the error term used to simulate the sleep disturbance scores was 1 or greater, then power to detect multiple classes was approximately 100%. The proportion of the sample within each class had very little effect on power.

Analysis conventions.

Regression coefficients were reviewed to describe the relationship between sleep disturbance and covariates in the models. An alpha of 0.05 or less was chosen as the criterion for statistical

significance of the covariates in the RMMs. All categorical and ordinal variables (except for the nausea item which was entered as a continuous variable) were entered in the models as dummy variables. Analyses were performed using SAS software (SAS Institute Inc, Cary NC).

4.3 Results

The mean patient age at diagnosis was 62.3 years (SD = 12.3, range from 22 to 84 years), and just over half the sample was female (52.7%) (Table 4.1). Almost two thirds of the patients were diagnosed with at least one comorbid condition (61.2%). Most patients (82.5%) underwent surgery more than four months before the first round of data collection (approximately 10 months after diagnosis), and just over half of the sample had undergone chemotherapy by the first data collection (54.6%). Less than 20% of the patient sample at the first data collection received radiation (18.5%). The mean FACT-G Physical Well-being Nausea score was 0.6, between “Not at all” and “A little bit.”

The mean PROMIS Sleep Disturbance score was similar to the average scores observed in the referent population (i.e., patients who went to sleep clinics and healthy sleepers) at Month 10 data collection (mean = 50.6), with 25.0% of patients classified as likely experiencing clinically significant sleep disturbance per Leung’s cut point.

On average, there was little change in mean PROMIS Sleep Disturbance scores from approximately 10 to 17 months after CRC diagnosis, with a mean change of -0.1 (Table 4.2). Based on the distribution-based threshold of 5 points, 21% of the sample (n = 75) experienced potentially meaningful improvement in sleep disturbance, and 23% (n = 82) experienced worsening from Month 10 to Month 17 data collection [data not shown].

4.3.1 Regression Mixture Models

Model fit and heterogeneity.

To address objectives 1 and 3, RMMs were estimated to examine whether patient, disease or treatment factors varied by severity of sleep disturbance (objective 1) or by magnitude of change in sleep disturbance (objective 2). Models with one through four classes were estimated for the cross-sectional Month 10 model, and the Change model. Table 4.3 presents BIC statistics for both models based on SAS-generated starting values.

For the Month 10 model, the smallest BIC and AIC were associated with the one-class model, therefore a multiple regression was determined to be the most appropriate model for the Month 10 analyses. Regarding the Change model, BIC and AIC were lowest for the two-class model and the four-class Change model did not converge. The two-class model was uninterpretable with the smallest of the two classes composed of only 32 patients (out of 361). Regression coefficients for the smallest class were all statistically significant, suggesting that the smaller class modeled outliers instead of a meaningful group of patients. Therefore, a multiple regression was determined to be the most appropriate model for the Change model. Together, the model fit statistics provide evidence that there are no meaningful subgroups (i.e., latent classes) of patient, disease, and treatment characteristics associated with different levels of sleep disturbance severity (objective 1) or magnitude of change in sleep disturbance (objective 3).

Relationship between sleep disturbance and patient, disease, and treatment characteristics.

Month 10 model.

Table 4.4 presents the results of the Month 10 model. Although not statistically significant, model coefficients support the hypothesized direction of the relationship between sleep disturbance and current chemotherapy: Patients who were currently undergoing chemotherapy reported more sleep disturbance than patients who had never undergone chemotherapy, on average. Patients who underwent chemotherapy in the past appeared to report better sleep quality compared to patients who never had chemotherapy, but this relationship was not statistically significant.

Being diagnosed with two or more relevant comorbid conditions (compared to no comorbidities), retirement (compared to working full-time, part-time, or enrolled as a student), anxiety, fatigue, and pain were statistically significant factors in the model. Being diagnosed with two or more relevant comorbidities was associated with a PROMIS Sleep Disturbance score of 1.5 additional points (worse) on average compared to no comorbidities. Being retired was associated with better sleep quality compared to patients who were working (full-time, part-time, or enrolled as a student). Poorer anxiety, fatigue, or pain interference was associated with worse sleep disturbance, though the coefficients are small.

Change model.

Change in anxiety and fatigue and sleep disturbance at Month 10 were statistically significant in the Change model (Table 4.5). A 25-unit worsening change (increase) in anxiety was associated with a 3.4-point worsening in PROMIS Sleep Disturbance. The negative coefficient on PROMIS Sleep Disturbance at Month 10 indicates that poorer sleepers at Month 10 had greater improvement in sleep from Month 10 to Month 17 data collection.

Sensitivity analysis: Anxiety and depression.

Due to the collinearity between anxiety and depression, a sensitivity analysis was conducted to test depression in the model instead of anxiety for the Month 10 and Change models. The models including depression (instead of anxiety) yielded almost identical results to the primary models. The Month 10 RMM supported one class, and the multiple regression yielded statistically significant relationships between sleep disturbance and 2 or more comorbid conditions (B = 1.71), retirement (B = -2.7), depression (B = 0.22), fatigue (B = 0.29), and pain interference (B = 0.09) [data not shown]. The Change model fit statistics supported two classes, but the two-class solution was uninterpretable, likely modeling outliers. The Change model (using multiple regression) including depression instead of anxiety yielded a very similar result compared to the Change model including anxiety with statistically significant relationships between change in sleep disturbance and change in depression (B = 0.12), change in fatigue (B = 0.22), and sleep disturbance at month 10 (B = -0.20) [data not shown].

4.3.2 Missing Data and Patient Attrition

Due to missing data, 121 of the 734 CRC patients (stage I–III) included in the MY-Health study were removed from the RMM/multiple regression analyses leaving 613 participants in the Month 10 analysis sample. The 121 patients who were not included in the Month 10 analyses were compared with the 613 patients who were included in the analyses using descriptive statistics and logistic regression (Supplemental Table 1). No patient characteristics were statistically significantly in the logistic regression model, suggesting that patient compliance completing survey questions at Month 10 was not related to any particular patient-level factor (e.g., age, sex, employment).

Patient attrition and missing data were factors in the Change analysis sample size (n = 361), therefore patients who were included in the Change analysis were compared with the 373 patients who

participated in the Month 10 survey but were not included in the Change analysis (due to patient attrition in survey participation or missing data) (Supplemental Table 2). Retirement (OR = 1.6) was associated with continued participation in the survey from 10 to 17 months, and patients classified as “Other” or “multiple” races were more likely to not participate in the Month 17 data collection (OR = 0.63) [data not shown].

4.4 Discussion

In this large sample of CRC survivors surveyed approximately 10 and 17 months following diagnosis, we found the majority of patients to have similar severity of sleep disturbance as the PROMIS Sleep Disturbance referent population, which was based on less-healthy patients than in the general population including patients who went to sleep clinics.[171] Although some CRC patients experienced much more severe sleep disturbance than others, 10 Month RMM analyses identified only one class of sleep disturbance. These results are important because they provide evidence that the patient, disease, and treatment characteristics associated with sleep disturbance are consistent at every severity level of sleep disturbance. In other words, researchers and clinicians can consider the presence of 2 or more comorbid conditions, non-retirees, anxiety, pain interference, and fatigue as correlates of sleep disturbance in patients diagnosed with CRC regardless of how mild or severe sleep disturbance is for each patient. This knowledge is important in clinical practice; patients with severe anxiety, pain, or fatigue should also be assessed for sleep disturbance. Regarding the Change analyses, the variability in sleep change underscores the range of patients’ experiences with sleep disturbance from 10 to 17 months after diagnosis when they are transitioning off treatment. The RMM analyses did not identify patient, disease, or treatment characteristics that varied by magnitude of change in sleep disturbance, but the results show that poorer sleepers at Month 10 had greater improvement in sleep disturbance from Month 10 to Month 17 data collection. These results are important for future clinical trial research because they suggest that some patients will improve more than others based on the quality of their sleep disturbance at baseline; future clinical trial endpoints regarding change in sleep disturbance should take baseline sleep disturbance into account in analyses.

Based on previous research in other cancers showing that symptoms of cancer treatment are detrimental to sleep[21] and other evidence that the initiation of chemotherapy is associated with

deterioration of sleep quality in another cancer population,[2] we hypothesized that current or recent chemotherapy would be associated with worse sleep outcomes compared to no chemotherapy. The results of our analyses (non–statistically significant coefficients) did not support this hypothesis. It is possible that the factors driving sleep disturbance due to treatment are already included in the model, such as pain and fatigue. Also, failure to find an association between chemotherapy and sleep disturbance may well be because the worst symptoms had already passed by the time patients were surveyed approximately 10 months after diagnosis. Future research should address the temporal relationship between CRC treatment and sleep disturbance at different points in time during the treatment trajectory, especially right after diagnosis. By understanding the temporal relationship between sleep disturbance and patient, disease, and treatment characteristics, researchers could provide patients and clinicians with a clearer picture of what to expect with sleep disturbance immediately after diagnosis and thereafter, possibly pre-empting sleep disturbance issues due to treatment. For example, if future research shows that individuals diagnosed with CRC do indeed suffer from worse sleep disturbance due to chemotherapy initiation, clinicians could actively monitor patients' sleep disturbance over time and intervene if necessary, or refer higher-risk patients for sleep therapy.

Results of these analyses show a link between sleep disturbance and anxiety, depression, fatigue, and pain interference (Month 10 only), underscoring the concordance between sleep and other aspects of HRQOL. Addressing modifiable factors of HRQOL such as anxiety, depression, or fatigue (or both) may improve sleep disturbance. Likewise, addressing sleep disturbance may help improve symptoms of anxiety, depression, or fatigue. It should be noted that the coefficients were relatively small. These results are of particular importance because the correlates of sleep disturbance have yet to be investigated in a sample of individuals diagnosed with CRC as they transition off of treatment.

Retirement was associated with better sleep quality 10 months after diagnosis. The relationship between employment and sleep disturbance has been previously investigated in other populations,[73,84] but these results are key because few studies investigate employment as an important factor in sleep disturbance within the CRC population.

The results of this study should be considered in light of some limitations. Anxiety, depression, pain interference, fatigue, and sleep disturbance are known to be closely related and effects could be bi-

directional. For example, pain may cause sleep disturbance, but if sleep disturbance is severe, it could cause pain due to increased inflammation or inability of the body to heal with less sleep. Endogeneity limits the conclusions that can be drawn from regression analyses: regression coefficients represent *associations* between sleep disturbance and the independent variables. Therefore, independent variables are not necessarily predictors of sleep disturbance. Another limitation to this study was loss to follow-up from Month 10 to Month 17 data collection. Minorities were less likely to participate in the follow-up survey and retirees were more likely to participate in both study data collections. Finally, we do not have information on patients' sleep disturbance prior to CRC diagnosis; without this information, it is more difficult to extract the effect of CRC treatment on sleep disturbance. When patient attrition is not completely at random or missing at random, parameter estimates may be biased. Some patients may have already been experiencing poor sleep prior to CRC diagnosis; this omitted variable does not allow us draw conclusions about the relationship between the severity of sleep disturbance or changes in sleep disturbance strictly with CRC or treatment characteristics.

PROMIS Sleep Disturbance, the outcome variable in all models in this study, was developed with some of the most rigorous qualitative and quantitative psychometric methods available,[12,77,144,149] and the six-item scores were recently evaluated in the full MY-Health study cohort.[146] One strength of PROMIS measures is that results of any study can be compared back to the referent population. Lab-based sleep measures are considered the gold standard for sleep measurement, but they may not adequately characterize sleep disturbances at home or sleep disturbances over time.[13] The inclusion of PROMIS Sleep Disturbance in the MY-Health study allows researchers to gain a broader understanding of the patient-, disease-, and treatment-related factors associated with CRC than what would have been possible with lab-based measures.

As a community-based observational study, the MY-Health data provide information on experiences from a very diverse sample of patients who were evaluated during the course of usual care without controlled interventions. Understanding the severity of sleep disturbance in patients with CRC without controlled interventions and the factors associated with sleep disturbance are building blocks to developing controlled trials for treatment of sleep disturbance. This information can be used to design future randomized control trials aimed at mitigating sleep disturbance.

4.5 Conclusion

The results of this study confirm the relationships between sleep disturbance and other aspects of HRQOL (e.g., pain, anxiety, fatigue) that have been identified in other studies,[90-95] and now in a sample of adults diagnosed with CRC. The association between retirement (compared to employment/enrolled as a student) and sleep disturbance is a new finding in the cancer literature that points to the importance of patients' outside responsibilities as important factors in their symptom management. The results of this research are important because they confirm the relationship between well-established HRQOL factors associated with sleep disturbance in a CRC sample, all of which are modifiable. Strategies to reduce one factor may positively impact other aspects of HRQOL.

Table 4.1. Patient Characteristics at Month 10 Data Collection

Characteristic	*Month 10 (n = 613)*
Age at diagnosis	
Mean (SD), Median, Min - Max	62.3 (12.3), 64.0, 22-84
Sex	
Female	323 (52.7%)
Race	
Other or multiple	163 (26.6%)
White	335 (54.6%)
Black	115 (18.8%)
Employment status	
Work	237 (38.7%)
Retired	264 (43.1%)
Unemployed or disabled	112 (18.3%)
Living status	
Live with child(ren) under 18 years old	99 (16.2%)
Relevant comorbidities	
No comorbid conditions	238 (38.8%)
1 comorbid condition	163 (26.6%)
2 or more comorbid conditions	212 (34.6%)
Cancer stage	
Stage I	178 (29.0%)
Stage II	191 (31.2%)
Stage III	244 (39.8%)
Months between most recent chemotherapy and Month 10 data collection	
0 = never	278 (45.4%)
1 = current	128 (20.9%)
2 = 1-2 months	107 (17.5%)
3 = > 2 months	100 (16.3%)
Months between most recent surgery and Month 10 data collection	
0 = never	53 (8.6%)
1 = 0-4 months	54 (8.8%)
2 = more than 4 months	506 (82.5%)
Radiation	
Ever received radiation	112 (18.5%)
Months since diagnosis at Month 10 data collection	
Mean (SD), Median, Min – Max	9.7 (1.6), 9.5, 6-21
PROMIS Sleep Disturbance T-Score	
Mean (SD), Median, Min – Max	50.6 (9.8), 51.4, 30-75
Clinically-meaningful PROMIS Sleep Disturbance T-Score [172]	
≥ 57	153 (25.0)
PROMIS Anxiety T-Score	
Mean (SD), Median, Min – Max	49.5 (11.0), 49.6, 36-84
PROMIS Depression T-Score	
Mean (SD), Median, Min – Max	48.4 (10.7), 48.0, 36-81
PROMIS Fatigue T-Score	
Mean (SD), Median, Min - Max	52.2 (10.6), 51.8, 29-81
PROMIS Pain Interference T-Score	
Mean (SD), Median, Min - Max	53.1 (10.9), 54.9, 40-79
FACT-G Physical Well-being Nausea Item	
Mean (SD), Median, Min - Max	0.6 (1.0), 0.0, 0-4
Survey language	
English	552 (90.0%)
Spanish or Chinese	61 (10.0%)

FACT-G = Functional Assessment of Cancer Therapy-General, max = maximum; min = minimum; PROMIS = Patient-Reported Outcomes Measurement Information System, SD = standard deviation.

Note: Percent calculated out of non-missing responses.

Table 4.2. Descriptive Statistics for change in patient-reported outcome measures

Characteristic	*Change (Month 17 – Month 10) (n = 361)*
PROMIS Sleep Disturbance	
Mean (SD), Median, Min - Max	-0.1 (7.2), 0.0, -25-19
PROMIS Anxiety	
Mean (SD), Median, Min - Max	0.3 (9.0), 0.0, -28-28
PROMIS Depression	
Mean (SD), Median, Min - Max	0.5 (8.6), 0.0, -34-29
PROMIS Fatigue	
Mean (SD), Median, Min - Max	-1.8 (8.3), -1.2, -27-24
PROMIS Pain Interference	
Mean (SD), Median, Min - Max	-1.8 (9.1), 0.0, -38-25
FACT-G Physical Well-being Nausea Item	
Mean (SD), Median, Min - Max	-0.2 (0.9), 0.0, -4-3

FACT-G = Functional Assessment of Cancer Therapy-General, max = maximum; min = minimum; PROMIS = Patient-Reported Outcomes Measurement Information System, SD = standard deviation.

Table 4.3. RMM Model Fit Statistics

	Month 10 model		***Change model***	
Number of classes	***BIC***	***AIC***	***BIC***	***AIC***
1	4344.4	4251.6	2490.6	2405.0
2	4485.6	4295.6	2392.8	2217.8
3	4626.8	4339.6	2489.7	2225.2
4	4768.0	4383.6	Did not converge	Did not converge

BIC = Bayesian Information Criterion Index, AIC = Akaike Information Criterion

Table 4.4. Multiple Regression Results, Relationship Between Sleep Disturbance and Patient, Disease, and Treatment Characteristics Approximately 10 Months After Diagnosis (n = 613)

Effect	*Categories*	*Estimate*	*Standard Error*	*Z*	*P value*
Intercept		22.364	3.88	5.77	<.0001
Months between chemotherapy and Month 10 data collection	Current	0.050	0.92	0.05	0.9562
	1-2 months	-1.271	0.90	-1.42	0.1558
	> 2 months	-0.219	0.92	-0.24	0.8114
	Never	ref	-	-	-
Months between surgery and Month 10 data collection	0-4 months	0.090	1.52	0.06	0.9530
	More than 4 months	0.101	1.12	0.09	0.9276
	Never	ref	-	-	-
Race	Black	1.094	0.83	1.32	0.1880
	Other or multiple	-0.136	0.74	-0.18	0.8535
	White	ref	-	-	-
Number of relevant comorbidities (collected at Month 10 data collection)	1 comorbid condition	1.446	0.79	1.84	0.0659
	2 or more comorbid conditions	1.532	0.77	1.99	0.0461
	No comorbid conditions	ref	-	-	-
Sex (Collected via SEER)	Female	0.324	0.62	0.52	0.6028
	Male	ref	-	-	-
Live with child under 18 years old (collected at Month 10 data collection)	Checked	1.050	0.92	1.14	0.2525
	Unchecked	ref	-	-	-
Employment (collected at Month 10 data collection)	Retired	-2.488	0.87	-2.85	0.0044
	Unemployed or disabled	-0.628	0.93	-0.68	0.4974
	Working full time, part time or student	ref	-	-	-
Months between diagnosis and Month 10 data collection		-0.028	0.19	-0.15	0.8836
Age at diagnosis (years) (Collected via SEER)		-0.038	0.04	-1.02	0.3098
PROMIS Anxiety at Month 10 data collection		0.218	0.04	5.46	<.0001
PROMIS Fatigue at Month 10 data collection		0.287	0.05	6.16	<.0001
PROMIS Pain Interference at Month 10 data collection		0.093	0.04	2.39	0.0167
FACT-G Physical Well-being Nausea Item at Month 10 data collection		0.067	0.41	0.16	0.8706
Variance		56.226	3.21		

FACT-G = Functional Assessment of Cancer Therapy-General, PROMIS = Patient-Reported Outcomes Measurement Information System.

Table 4.5. Multiple Regression Results, Relationship Between Change in Sleep Disturbance and Change in Patient, Disease, and Treatment Factors from Approximately 10 to 17 Months After Diagnosis (n = 361)

Effect	*Categories*	*Estimate*	*Standard Error*	*Z*	*P value*
Intercept		10.385	4.91	2.11	0.0345
Months between chemotherapy and Month 17 data collection	Current	1.480	1.76	0.84	0.3994
	1-2 months	0.710	1.80	0.40	0.6928
	> 2 months	-0.064	0.75	-0.09	0.9321
	Never	ref	-	-	-
Months between surgery Month 17 data collection	0-4 months	-1.714	1.77	-0.97	0.3339
	More than 4 months	0.042	1.25	0.03	0.9729
	Never	ref	-	-	-
Race (Collected at Month 10)	Black	-0.192	0.92	-0.21	0.8341
	Other or multiple	-0.295	0.90	-0.33	0.7420
	White	ref	-	-	-
Number of relevant comorbidities (Collected at Month 10)	1 comorbid condition	1.591	0.88	1.82	0.0694
	2 or more comorbid conditions	-0.074	0.85	-0.09	0.9306
	No comorbid conditions	ref	-	-	-
Sex (Collected via SEER)	Female	-0.166	0.68	-0.24	0.8075
	Male	ref	-	-	-
Live with child under 18 years old (Collected at Month 10)	Checked	-0.729	1.11	-0.66	0.5121
	Unchecked	ref	-	-	-
Employment (Collected at Month 10)	Retired	-0.578	0.96	-0.60	0.5482
	Unemployed or disabled	-0.440	1.12	-0.39	0.6944
	Worked full time, part time or student	ref	-	-	-
Months between diagnosis and Month 17 data collection		0.091	0.17	0.53	0.5956
Age at diagnosis (years) (Collected via SEER)		-0.018	0.05	-0.38	0.7026
PROMIS Anxiety change (Month 17 – Month 10)		0.135	0.04	3.07	0.0021
PROMIS Fatigue change (Month 17 – Month 10)		0.203	0.05	4.17	<.0001
PROMIS Pain Interference change (Month 17 – Month 10)		-0.025	0.04	-0.62	0.5358
FACT-G Physical Well-being Nausea Item change (Month 17 – Month 10)		0.100	0.40	0.25	0.8049
PROMIS Sleep Disturbance at Month 10		-0.209	0.04	-5.59	<.0001
Variance		40.544	3.02	_	_

FACT-G = Functional Assessment of Cancer Therapy-General, PROMIS = Patient-Reported Outcomes Measurement Information System.

Supplemental Table 4.1. Descriptive Comparison of Patients not in the Month 10 Analysis Due to Missing Responses Compared to Patients Included in the Month 10 Analysis

Patient Characteristics Collected at Month 10	*Patients who participated in survey at Month 10 but not included in the Month 10 analyses due to missing responses (n = 121)*	*Month 10 analysis sample (n = 613)*
Age at diagnosis		
Mean (SD), Median, Min - Max	64.3 (11.1), 66.0, 36-84	62.3 (12.3), 64.0, 22-84
Sex		
Female	58 (47.9%)	323 (52.7%)
Race		
Other or multiple	29 (24.0%)	163 (26.6%)
White	58 (47.9%)	335 (54.6%)
Black	34 (28.1%)	115 (18.8%)
Employment status		
Work	37 (37.4%)	237 (38.7%)
Retired	51 (51.5%)	264 (43.1%)
Unemployed or disabled	11 (11.1%)	112 (18.3%)
Months between most recent chemotherapy and Month 10 data collection		
0 = never	44 (51.2%)	278 (45.4%)
1 = current	15 (17.4%)	128 (20.9%)
2 = 1-2 months	17 (19.8%)	107 (17.5%)
3 = > 2 months	10 (11.6%)	100 (16.3%)
PROMIS Sleep Disturbance		
Mean (SD), Median, Min - Max	50.3 (9.6), 52.2, 30-75	50.6 (9.8), 51.4, 30-75
Survey language		
English	109 (90.1%)	552 (90.0%)
Spanish or Chinese	12 (9.9%)	61 (10.0%)

Max = maximum; min = minimum; PROMIS = Patient-Reported Outcomes Measurement Information System, SD = standard deviation.
Note: Percent calculated out of non-missing responses.

Supplemental Table 4.2. Descriptive Comparison of Patients not Included in the Change Analysis Compared to Patients Included in the Change Analysis

Patient Characteristics Collected at Month 10	*Patients who participated in survey at Month 10 but not included in the Change analyses due to missing responses (n = 373)*	*Change analysis sample (n = 361)*
Age at diagnosis		
Mean (SD), Median, Min - Max	61.5 (12.9), 63.0, 22-84	63.7 (11.2), 65.0, 30-84
Sex		
Female	203 (54.4%)	178 (49.3%)
Race		
Other or multiple	120 (32.2%)	72 (19.9%)*
White	174 (46.6%)	219 (60.7%)
Black	79 (21.2%)	70 (19.4%)
Employment status		
Work	142 (40.5%)	132 (36.6%)
Retired	136 (38.7%)	179 (49.6%)*
Unemployed or disabled	73 (20.8%)	50 (13.9%)
Months between most recent chemotherapy and Month 10 data collection		
0 = never	162 (46.2%)	160 (46.0%)
1 = current	68 (19.4%)	75 (21.6%)
2 = 1-2 months	56 (16.0%)	68 (19.5%)
3 = > 2 months	65 (18.5%)	45 (12.9%)
PROMIS Sleep Disturbance		
Mean (SD), Median, Min - Max	51.5 (9.6), 52.6, 30-75	49.5 (9.8), 50.2, 30-75
Survey language		
English	327 (87.7%)	334 (92.5%)
Spanish or Chinese	46 (12.3%)	27 (7.5%)

Max = maximum; min = minimum; PROMIS = Patient-Reported Outcomes Measurement Information System, SD = standard deviation.
Note: Percent calculated out of non-missing responses.
*$p < 0.05$.

CHAPTER 5. RELATIONSHIP BETWEEN SLEEP AND EXERCISE IN A SAMPLE OF INDIVIDUALS DIAGNOSED WITH COLORECTAL CANCER (MANUSCRIPT 2)

5.1 Background

Colorectal cancer (CRC) is the third most common adult cancer,[4] with more than 1.1 million individuals currently living with the disease in the United States.[5] It is estimated that at least half of all individuals diagnosed with CRC experience decrements in sleep.[3] Consequences of sleep disturbance include decreased cognitive functioning[9] and fatigue.[10,11] Sleep disturbance is associated with financial implications as well, such as loss in work productivity and work quality and increased number of visits to health professionals.[14] Poor sleep is also linked to long-term implications such as being a risk factor for infectious diseases, cardiovascular diseases, and depression.[13]

Despite the substantial repercussions of sleep disturbance, few treatment options are available to help individuals with CRC who experience sleep disturbance improve their sleep. The two most widely used treatment options include cognitive behavioral therapy (CBT) and pharmacotherapies. CBT is recommended by the American Academy of Sleep Medicine as a first-line therapy for patients with insomnia. CBT for sleep disturbance includes relaxation therapy, sleep hygiene, and cognitive therapy. Unfortunately, there are an inadequate number of providers trained in CBT for sleep disturbance, and patient adherence issues pose considerable barriers to the adequacy of sleep treatment.[9] Pharmacologic treatments (e.g., benzodiazepine-receptor agonists, antidepressants, melatonin agonists) are associated with adverse daytime side effects such as sedation or dizziness. Further, cancer patients may experience disturbed sleep for a substantially longer duration than the 4 to 6 weeks for which pharmacologic sleep aids are recommended.[20,21].

Neither CBT nor pharmacologic treatments are directly associated with additional health benefits. However, exercise is an alternative treatment option that improves aerobic fitness[112] and other aspects of quality of life such as anxiety, pain, and fatigue, all of which are associated sleep disturbance.[113-115] Exercise has been evaluated as a treatment for sleep disturbance in the healthy U.S. population[23,116] and a number of RCTs and observational studies have investigated exercise as a possible treatment for sleep

disturbance in cancer patients.[113,117-121] Exercise is generally accessible and a low-cost alternative treatment for sleep disturbance, but only three studies have investigated the relationship between exercise and sleep disturbance in individuals diagnosed with CRC: two observational studies[120,119] and one randomized controlled trial (RCT).[117] Of these studies, the RCT showed the most promising results for exercise, showing that an 8-week home-based exercise program improved sleep in a sample of stage IV colorectal *and* lung cancer patients.[117] Because the RCT included a mixture of individuals diagnosed with colorectal or lung cancer, the results of this study are not conclusive specifically for individuals diagnosed with CRC.

Two observational studies that explored the relationship between sleep and exercise did not find a statistically significant effect, but both studies were small, with 119 individuals diagnosed with colorectal, breast, or ovarian cancer [119] and 45 adults diagnosed with stage II or III CRC,[120] respectively, and sleep was not the primary outcome of the study; studies were not powered to detect differences in sleep outcomes. Because of the study designs, a causal effect of exercise on sleep disturbance could not be concluded.

There are a number of possible explanations for the inconsistent results between the RCT and observational studies including differences among participants in the study (e.g., cancer stage, cancer type), differences in exercise prescription of intensity and frequency, and differences in the slice of time during patients' cancer treatment trajectories. Another possible explanation is that exercise may be more effective in ameliorating sleep disturbance for some individuals and not for others, which could attenuate sleep outcomes between exercise treatment groups and usual care groups. Future randomized trials testing the effect of exercise on sleep disturbance in CRC should tailor the population of interest to patients whose sleep would benefit the most from exercise. Prior to conducting an RCT, it is important to identify the characteristics of CRC patients who may benefit most from an exercise intervention. Regression mixture models uncover possible variability among patients and provide a way to reveal relationships between sleep disturbance and exercise that may differ depending on severity of sleep disturbance.

This study builds on the published literature by examining the relationship between sleep and exercise in individuals diagnosed with CRC using observational patient-reported data from individuals

approximately 10 months after a diagnosis of non-metastatic colorectal cancer. The purpose of this study is two-fold. First, we investigated whether the relationship between exercise and sleep disturbance differed by *severity* of sleep disturbance in a sample of adults diagnosed with CRC. The second objective of this study was to evaluate the relationship between exercise and sleep disturbance specifically in a sample of adults diagnosed with stage I–III CRC in which it was hypothesized that patients whose exercise was categorized as moderately or highly active would experience less sleep disturbance than patients who did not exercise.

5.2 Methods

5.2.1 MY-Health Study Design

This secondary data analysis was conducted using data from the Measuring Your Health (MY-Health) study which included over 5000 patients enrolled between 2010 and 2012.[143] Potential study participants were identified from four SEER cancer registries located in three states: California (2 SEER registries), Louisiana, and New Jersey. Individuals age 21–84 years diagnosed with one of seven cancer types (colorectal, prostate, non-small cell lung, non-Hodgkin lymphoma, female breast, uterine, or cervical) within 6 to 13 months of diagnosis were invited to participate in the MY-Health study via mail. Participants completed questionnaires using mail-in hard copy questionnaires at two time points: The first data collection occurred approximately 10 months after diagnosis (mean = 9.73, range = 6-30 months) and the second data collection occurred around 17 months after diagnosis on average (mean = 17.42, range = 11-36 months). The MY-Health study oversampled racial/ethnic minorities and younger patients, and questionnaires were available in three languages (English, Spanish, Mandarin). Additional details on the study design and procedures were previously published.[143]

5.2.2 Participants

Patients who were identified as being diagnosed with stage I, II, or III colorectal cancer based on SEER information were included in the analyses for this study. Because exercise was the main independent variable of interest, the sample was further limited to patients who were able to perform physical activity, defined as patients who were able to get out of bed (based on a patient-reported survey question). The first round of data collection approximately 10 months on average after diagnosis included 734 patients, and 400 patients participated in the second round, which was collected approximately 17

months after diagnosis on average. For brevity, these data collection time points will be referred to as Month 10 and Month 17 respectively.

5.2.3 Measures

Dependent variable.

Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance items were administered to patients at Month 10 and Month 17. PROMIS Sleep Disturbance measures concepts included trouble staying asleep, not getting enough sleep, restlessness, feeling refreshed after sleep, and difficulty falling sleep. Results of the full psychometric evaluations of the PROMIS Sleep Disturbance item bank[144] and short forms[145] were previously published. A custom six-item short form was scored; the psychometric properties of the six-item form were evaluated in individuals enrolled in the MY-Health study (Cronbach's $\alpha = 0.88 – 0.95$).[146] PROMIS Sleep Disturbance is a continuous variable scored on a t-score metric with a mean of 50 and standard deviation (SD) of 10 based on the referent population (mixture of clinical and the general U.S. population[147]), and higher scores indicate worse sleep disturbance. Change in sleep disturbance was calculated by subtracting PROMIS Sleep Disturbance scores at 10 months from scores at 17 months after CRC diagnosis. Positive change is indicative of worsening sleep. The recall period was "the past 7 days." A recent study by Leung et al.[168] provided a cut point on PROMIS Sleep Disturbance indicative of clinically significant sleep disturbance (≥ 57, area under the curve = 0.92).

Independent variables.

Exercise.

The MY-Health study included three exercise-related survey items covering patient-perceived exercise intensity and patient-reported frequency of exercise in the previous 7 days. Exercise items were administered at Month 10 and Month 17 data collection, capturing patients' exercise routines during each slice of time during their treatment trajectory. Based on patients' responses to the exercise items, patients' exercise was categorized into one of four activity levels: (1) not active, (2) slightly active, (3) moderately active, and (4) highly active. The four exercise categories reflect the American College of Sports Medicine's (ACSM) recommendation that individuals diagnosed with cancer achieve 150 minutes of moderate-intensity exercise per week or 75 minutes of vigorous exercise per week.[15] Patients

classified in the “not active” or “slightly active” groups likely did not meet the minimum ACSM guideline of 150 minutes of moderate-intensity exercise per week or 75 minutes of vigorous exercise per week,[15] but patients in the “moderately active” or “highly active” groups likely met or exceeded the ACSM guideline. The primary independent variable of interest in each model, *exercise*, summarizes patients’ exercise routines at 10 and 17 months after CRC diagnosis. Exercise level was entered in the model as an indicator variable with “not active” as the reference category.

Patient-level factors associated with sleep disturbance.

The MY-Health dataset contains information on patient, disease, and treatment factors associated with sleep disturbance. There is an established link between cancer treatment and sleep disturbance, and some literature suggests that there is a relationship between time since treatment and sleep disturbance,[16-18,100,101] though the trajectory of sleep disturbance throughout and after treatment for adults with CRC is unknown. Cancer treatment type (e.g., surgery,[91] chemotherapy,[21,99] radiation) and most recent date of treatment were self-reported. Categorical variables were derived to capture current/recent treatment compared to no treatment or less-recent treatment. Categories were based on relevant physical recovery periods post-treatment and data availability. Time since chemotherapy was coded using four categories (i.e., currently receiving chemotherapy, chemotherapy 1–2 months ago, chemotherapy more than 2 months ago, never received chemotherapy). Time since surgery was coded using three categories (i.e., surgery occurred within 0–4 months, surgery occurred more than 4 months ago, never received surgery). Comorbid conditions[73] were self-reported and included in the models as a derived variable with three categories (i.e., no comorbid diseases, 1 comorbid disease, 2 or more comorbid diseases). Three PROMIS domains were included in the models as independent variables to assess aspects of health-related quality of life known to be associated with sleep disturbance:[73,79 80 81,90,92-95] Anxiety (11 items), Fatigue (14 items),[148] and Pain Interference (11 items).[149] These PROMIS measures were normed to the general U.S. population[147] and higher scores indicate worse anxiety, fatigue, and pain, respectively. Nausea severity was measured using a 5-point nausea[21] item from the FACT-G Physical Well-Being (PWB) subscale[150] with a recall period of the “past 7 days” and response choices ranging from 0 = “not at all” to 4 = “very much.” Although the nausea item has not been psychometrically evaluated as a single measure of nausea, the entire FACT-G PWB scale, which has

been evaluated extensively in cancer patients, covers concepts that overlap with PROMIS measures such as pain and fatigue. Therefore, only the nausea item was included in the models as a continuous variable. Other characteristics known to be associated with different levels of sleep disturbance were included in the models such as age at diagnosis,[2,21,97] sex,[72] time since diagnosis,[93] employment status,[84] and an indicator for living with children under 18[83,84] were included in the models. Age and race were also included in the model to account for the over-sampling of younger and minority persons from SEER registries. Race, employment status, and the living-with-child(ren) indicator were self-reported, and age at diagnosis, sex, and diagnosis date were obtained via SEER registry data.

Factors associated with exercise.

MY-Health variables also addressed determinants of exercise participation (treatment selection). Exercise participation is partially determined by patients' ability to perform activities,[153-155] thus patients' PROMIS Physical Function scores were included as a covariate in the model (higher scores indicate better physical function).[156] Social support is associated with participation in exercise and was measured using PROMIS Ability to Participate in Social Roles and Activities (higher scores represent fewer social limitations).[153-155,157] Higher weight is associated with less exercise, therefore body mass index (BMI) was derived from patient-reported weight and height.[72] Other factors already included in the model that are associated with participation in exercise and affect sleep include increased age, parenthood, sex, and race.[153-155]

5.2.4 Analyses

Patients' exercise information was captured at two time points in the MY-Health study. Therefore, analyses were conducted twice to assess the relationship between sleep disturbance and exercise level at two time points after CRC diagnosis. Month 10 analyses evaluate factors associated with sleep when patients are first transitioning out of CRC treatment. The second analysis employs the same variables and methods but using data that were collected on patients 17 months after diagnosis. This timeframe captures patients' experiences with sleep disturbance and their exercise participation as they transition out of treatment into a more stable recovery phase. Complete case analyses were conducted for all models. Due to missing data, 587 participants out of the 734 identified as diagnosed with stage I–III CRC

were included in the Month 10 analyses. For the follow-up assessment, approximately 7 months later, 356 participants were included in the Month 17 analyses.

Methods.

Descriptive statistics were tabulated. Relationships between candidate independent variables were evaluated for collinearity by calculating bivariate correlations and variance inflation factor (VIF) within multiple regression models. VIF values greater than 10 were considered a symptom of multicollinearity. The correlation coefficient between PROMIS Anxiety and PROMIS Depression was strong (r = 0.87), suggesting collinearity between scores; PROMIS Anxiety was included in the model and PROMIS Depression for simplicity (anxiety is associated with disturbed sleep, but depression is associated with both disturbed sleep and hypersomnia[169]). Although some categorical variables appear to be ordinal in nature, all categorical variables were entered into the model as indicator variables (except for the FACT-G PWB item, which was entered as a continuous variable) because categorical response choices/levels were not necessarily evenly spaced. Residuals were evaluated between candidate independent variables and PROMIS Sleep Disturbance to determine if higher-order terms needed to be included in the models.

Regression mixture models (RMMs)[158,159] are special cases of finite mixture models, which model weighted combinations of different distributions. With RMMs, the component membership to each distribution is unobservable (a latent variable). In this study, we employed RMMs to test if heterogeneity was present in the associations between sleep disturbance and exercise, specifically, if factors associated with sleep disturbance (especially exercise) varied by severity of sleep disturbance or another unknown mechanism (objective 1) at Month 10 and Month 17. RMMs were estimated using Dual Quasi-Newton optimization[162] and models ranging from one to two classes were evaluated. The final models (e.g., choice of number of classes) were chosen based on fit (smallest Bayesian Information Criterion Index (BIC)) and interpretability. RMMs are sensitive to starting values,[164] thus user-provided starting values were also tested to confirm the number of classes identified by SAS-generated starting values. If the single class model was identified, then multiple regression (which assumes one common class of sleep disturbance) was used to model factors associated with sleep disturbance. Regression coefficients were reviewed; a statistically significant coefficient on the exercise indicator variable signified a

relationship between sleep disturbance and exercise (objective 2). Objective 2 was assessed at approximately 10 and 17 months after CRC diagnosis.

A logistic regression was used to identify factors associated with patient survey completion at Month 10 (outcome = 1) versus participating in the Month 10 survey but not completing enough questions to be included in the analyses. The logistic regression model included patient characteristics at Month 10 that were related to sleep disturbance and potentially associated with survey compliance: sex, race, employment status, survey language, level of exercise activity, PROMIS Sleep Disturbance, and PROMIS Physical Functioning.

There was substantial patient attrition from the Month 10 survey data collection to Month 17 survey data collection; factors associated with patient persistence in survey participation from Month 10 data collection to Month 17 data collection were evaluated using descriptive statistics and logistic regression. Patients who participated in Month 10 and Month 17 survey administrations (outcome = 1) were compared with patients who participated in Month 10 but not Month 17 (outcome = 0) using logistic regression. The model included patient characteristics at Month 10 that were related to sleep disturbance and potentially associated with patient attrition: sex, race, employment status, survey language, level of exercise activity, PROMIS Sleep Disturbance, and PROMIS Physical Functioning. A sensitivity analysis was also conducted by including the Month 17 analysis sample in the Month 10 model (including variables that were collected at Month 10 only).

Another sensitivity analysis was conducted to describe the impact of including anxiety in the models instead of depression. Anxiety was removed from the Month 10 and Month 17 models and depression was added. Model results were compared.

Power.

Power to detect multiple classes was evaluated and confirmed using simulations based on MY-Health study data, which provided information about the covariance structure among the independent variables. Sub-samples were randomly drawn from the study dataset to simulate 1000 datasets for each of the parameter modifications in the simulation: overall sample size, numeric differences between coefficients in each latent class, variance of the error term used to simulate sleep disturbance scores, and proportion of sample within each class. A well-accepted rule of thumb for identifying minimally important

group differences on a PRO measure is the half standard deviation.[166,170] The half standard deviation of PROMIS Sleep Disturbance was approximately 5 points at Month 10. For classes to be meaningfully different, we anticipated that the classes should be separated at a minimum by the threshold for minimal important difference. For the Month 10 analyses, based on a sample size of 600, a mean difference between sleep disturbance scores in each class approximately 6 points apart, equal-size classes (i.e., proportion of patients in class 1 = 50% and proportion of patients in class 2 = 50%), and an error term of 3 or less, the power to detect multiple classes was 100%. When the variance of the error term used to compute the simulated sleep disturbance scores increased to 4, 5, or 8 and all other parameters were the same, power reduced to 61.1%, 9.2%, and 1.6%, respectively. Power to detect multiple classes was above 95% for all circumstances when the mean difference between simulated sleep disturbance between classes differed by approximately 9 and 17 points and the variance of the error term used to simulate sleep disturbance scores was less than 8. The proportion of the sample designated to each class was modified in the simulations but the effect on power was negligible. Regarding the Month 17 analyses, power to detect multiple classes was also evaluated for a sample size of 360. When the classes were of equal sizes, the mean difference between sleep disturbance scores in each class was almost 6 points apart and the variance of the error term used to simulate the sleep disturbance scores was 3 or less, then power to detect multiple classes was at least 94.1%. The proportion of the sample within each class had very little effect on power.

Power to detect the effect of exercise was calculated for a sample size of 600 and 350. When sample size was 600 and the partial correlation between exercise and sleep disturbance was 0.14 or greater, power was 0.93 or above. When the sample size was 600 and the partial correlation was very small (0.05), power was reduced to 23.2. When the sample size was 350 and the partial correlation was set at 0.20 or higher, power was 0.85 at the lowest. When the sample size was 350 and the partial correlation dipped to 0.14, power was 0.75.

Analysis conventions.

Regression coefficients were reviewed to describe the relationship between sleep disturbance and covariates in the models. An alpha of 0.05 or less was chosen as the criterion for statistical significance of the covariates in the RMMs. All analyses were performed using SAS version 9.3 (SAS

Institute Inc., Cary, NC, USA). More specifically, we used a SAS procedure called PROC FMM to fit RMMs.[163]

5.3 Results

Patient, disease, and treatment characteristics were similar for the Month 10 and Month 17 analysis samples (Table 5.1). The mean patient age at diagnosis was 62 years for participants in the Month 10 analysis. Approximately half the sample was female (Month 10: 52.5%, Month 17: 48.9%). Less than half of all study participants were working full-time, part-time, or were students (Month 10: 39.7%, Month 17: 37.1%). Sixty percent of patients had at least one comorbid condition (Month 10: 60.5%, Month 17 sample: 60.1%).

Descriptive statistics for variables entered in the RMM and multiple regression models were computed (Supplemental Table 5.1); data that were collected at the Month 17 data collection were entered in the Month 17 model. Almost two-thirds of the sample was moderately or highly active at Month 10 (60.3%) and over two-thirds of the sample was moderately or highly active at Month 17 (68.8%). Only 22.5% of patients were not active at Month 10 and 17.4% were not active at Month 17.

At both Month 10 and Month 17, mean PROMIS Sleep Disturbance scores hovered around the average scores observed in the referent population (i.e., patients who went to sleep clinics and healthy sleepers) (Month 10: mean = 50.4; Month 17 mean = 49.7). Applying Leung's cut point to our data (PROMIS Sleep Disturbance ≥ 57), we found that 24.0 and 20.8 percent of patients were likely experiencing clinically significant sleep disturbance at Month 10 and Month 17 respectively [data not shown].

The mean PROMIS Sleep Disturbance scores for each level of exercise follows the predicted pattern, with higher (more severe sleep disturbance) PROMIS Sleep Disturbance scores among patients reporting less exercise (No exercise mean: Month 10 = 53.0, Month 17 = 52.3) and lower (better sleep quality) PROMIS Sleep Disturbance scores among patients reporting more exercise (highly active mean: Month 10 = 48.5, Month 17 = 46.7) (Table 5.2). At Month 17, the difference between mean sleep disturbance scores in the not active group and the highly active group was 5.6 points, just above the threshold likely indicating a meaningful difference in sleep disturbance.

5.3.1 Regression Mixture Models

Model fit.

RMMs were estimated to examine whether distinct classes of sleep disturbance were present. Models with one through four classes were estimated for the two cross-sectional models (Month 10 and Month 17). Table 5.3 presents BIC statistics for both models based on SAS-generated starting values. For the Month 10 and Month 17 models, the smallest BIC and AIC were associated with the one-class model. Therefore, a multivariable regression was chosen for the Month 10 and Month 17 models.

Relationship between sleep disturbance and exercise.

Month 10 model.

Table 5.4 presents the results of the Month 10 model. Although patients categorized as highly active or moderately active had positive coefficients in the model, which would suggest that more active individuals experienced worse sleep disturbance, this result was not statistically significant. Being retired (compared to working), worse anxiety, and worse fatigue had statistically significant relationships with worse sleep disturbance. Retirement was associated with PROMIS Sleep Disturbance score 2.4 points lower than working full-time, part-time, or being a student, a difference smaller than the five-point meaningful difference threshold. The positive coefficients on the anxiety and fatigue scales show that patients with less anxiety or fatigue experience less sleep disturbance. Although the coefficients on anxiety and fatigue were statistically significant, they were small (less than 1); a 25-point improvement in PROMIS Fatigue would be associated with a six-point improvement in PROMIS Sleep Disturbance.

Month 17 model.

Table 5.5 presents the results of the Month 17 cross-sectional model. Exercise levels did not exhibit statistically significant relationships with sleep disturbance. Anxiety and fatigue had statistically significant relationships with sleep disturbance such that worse anxiety and fatigue were associated with poorer sleep.

Sensitivity analysis: Anxiety and depression.

Due to the collinearity between anxiety and depression, a sensitivity analysis was conducted to test depression in the model instead of anxiety at Month 10 and Month 17. The models including depression (instead of anxiety) yielded almost identical results to the primary models at Month 10 [data not shown] with no statistically significant relationship between exercise and sleep disturbance and

statistically significant relationships between sleep disturbance and retirement (B = -2.6), depression (B = 0.20), and fatigue (B = 0.24). The Month 17 model including depression instead of anxiety yielded a very similar result compared to the Month 17 model including anxiety with statistically significant relationships between sleep disturbance and depression (B = 0.14) and fatigue (B = 0.36) [data not shown].

5.3.2 Missing Data and Patient Attrition

Due to missing data, 147 of the 734 CRC patients (stage I–III) included in the MY-Health study were removed from the RMM/multiple regression analyses, leaving 587 participants in the Month 10 analysis sample. The 147 patients who were not included in the Month 10 analyses were compared with the 587 patients who were included in the analyses using descriptive statistics and logistic regression (Supplemental Table 5.2). Being slightly active (OR = 2.43) (compared to those who were not active) and having a better physical functioning (OR = 1.03) were factors statistically significantly related to patient compliance completing survey questions at Month 10 and Month 17. Patients who identified as black were more likely to not complete survey items and not be included in the Month 10 analysis (OR = 0.60).

Patient attrition and missing data were factors in the size of the Month 17 analysis (n = 356), therefore patients who were included in the Month 17 analysis were compared with the 378 patients who participated in the Month 10 survey but were not included in the Month 17 analysis (due to patient attrition in survey participation or missing data) (Supplemental Table 5.3). Retirement (OR = 1.48) and more exercise activity ("slightly active" was the only statistically significant exercise category: OR = 1.66, but descriptive statistics imply that participants in the Month 17 analyses were more active overall) were factors associated with continued participation in the survey from Month 10 to Month 17, but identifying as "other or multiple" races (not white and not black) was associated with patient attrition/missing responses (OR = 0.51).

A sensitivity analysis was also conducted to describe the impact of patient attrition/missing data in the results of the Month 10 and Month 17 models: The Month 10 model was rerun including only patients were included in the Month 17 analyses (n = 356). Results were similar with similar magnitudes of regression coefficients and as in the primary Month 10 model, anxiety (B = 0.25) and fatigue (B = 0.19) were statistically significant. Some new statistically significant relationships emerged between sleep

disturbance and identifying as black (B = 3.1), having one comorbid condition (B = 0.03), and age at diagnosis (B = -0.13) [data not shown].

5.4 Discussion

This study builds on the published literature by examining the relationship between sleep and exercise specifically in individuals diagnosed with stage I, II, or III CRC using observational data representing patients' exercise habits without intervention. This study did not find a statistically significant relationship between sleep disturbance and exercise, and this relationship did not differ by *severity* of sleep disturbance. These findings provide evidence that the relationship between sleep disturbance and exercise is consistent at any level of sleep disturbance severity in this CRC sample, meaning that no specific subgroup of patients with normal, mild, moderate, or severe sleep disturbance (compared to healthy and non-healthy sleepers) emerged as being associated with any particular level of exercise (or lack of exercise).

Approximately 40% of individuals diagnosed with CRC in this study likely did not achieve the ACSM recommendations for exercise (150 minutes of moderate-intensity exercise per week or 75 minutes of vigorous exercise per week[15]) approximately 10 months after diagnosis. Although the exercise items presented some measurement limitations that precluded us from objectively categorizing patients as achieving or not achieving ACSM exercise recommended levels (e.g., *duration* of exercise not captured, items not psychometrically evaluated), patients classified in the "moderately active" or "highly active" groups likely met or exceeded ACSM guidelines. Nonetheless, the results of this study are similar to a large U.S. study using data from the 2009 Behavioral Risk Factor Surveillance System (BRFSS) survey showing that 40% of male and 30% of female CRC patients met the ACSM guidelines at least one year after diagnosis.[173] The same study reported that only 30% of female patients with CRC met or exceeded the ACSM guidelines. Patients who do not meet ACSM exercise guidelines are at higher risk for cancer-related mortality,[174] thus exercise is an important activity for individuals diagnosed with CRC regardless of the effect of exercise on sleep disturbance.

Previous research advocates exercise as beneficial to sleep in other cancer populations.[117,121,142] Much of the previously published research showing an exercise benefit was conducted with women diagnosed with breast cancer[140 141] or adults with mixed cancer diagnoses.[119 160 121] Patients may attribute

sleep disturbance to general cancer-related factors such as the anxiety of cancer diagnosis, but reasons for sleep disturbance vary by cancer site. For example, estrogen deficiency caused by treatments for breast cancer are associated with hot flashes and sweating, both known disrupters of sleep.[109] Xerostomia (mouth dryness) is often experienced by individuals diagnosed with head and neck cancer and has been shown to be determinantal to sleep in this population.[175] It is possible that exercise may be more effective in reducing particular aggravating factors of sleep disturbance in some cancer populations but not in others, thus explaining why exercise is associated with improved sleep disturbance in breast cancer or mixed cancer studies but not overwhelmingly so in CRC. Future research should focus evaluation of the relationship between sleep disturbance and exercise in specific cancer sites.

A previously published randomized trial found a statistically significant relationship between sleep disturbance and exercise in individuals diagnosed with stage IV lung cancer or CRC,[117] but two other observational studies did not find the same relationship between exercise and sleep. Stage IV patients were not included in our study because their treatment trajectories and HRQOL experiences are different from CRC patients diagnosed with non-metastatic disease; it is possible, even though Cheville's randomized trial and our study included CRC patients, that exercise is more efficacious in metastatic disease than in earlier stages. The first observational study, conducted by Lin and colleagues, included patients diagnosed with stage II or III CRC undergoing chemotherapy on a supervised exercise intervention compared to a usual-care group.[120] The supervised exercise intervention included 120 minutes of moderate-intensity exercise, less than the ACSM guidelines. Though patients could exercise outside of the supervised exercise program in the intervention group and in the usual-care group, exercise frequency, duration, and intensity was not measured, therefore complicating the interpretation of the results and the ability to draw conclusions about the relationship between amount of exercise and sleep disturbance. Patients were not randomized to their treatment groups and statistical models did not control for HRQOL-based factors such as anxiety, depression, fatigue, etc. The second observational study, conducted by Cho and colleagues, included women with breast, colorectal, or ovarian cancer beginning their first cycle of chemotherapy.[119] Cho did not find a statistically significant effect of exercise on sleep disturbance. The criteria for being classified as an exerciser was less stringent than the ACSM guidelines of 150 minutes of moderate-intensity exercise per week or 75 minutes of intense exercise per

week. Patients who exercised a minimum of three times a week for 20 minutes per session were classified as exercisers and compared against patients who did not meet these criteria. Similar to our study, both observational studies were faced with challenges in classifying patients as achieving exercise levels, which could affect mean differences between "treatment" groups. Cheville and colleagues did not collect information on patients' exercise routines in the control group, thus it is possible that as stage IV patients, the control group was less active than the patients in the "control" groups in the observational studies, separating the mean differences in sleep disturbance further in the randomized study than in the observational studies. Future observational studies should collect data on exercise frequency, intensity, and duration of exercise to more easily differentiate patients who achieve ACSM guidelines, providing more clarity on the differences in sleep disturbance between exercise groups. Although our study showed no statistically significant relationship between sleep disturbance and exercise, the results should not be considered conclusive because of the observational nature of this study and possible exercise measurement issues. Therefore, future prospective research may still be warranted.

In our study sample, we found a slight reduction in clinically significant sleep disturbance over the course of 7 months from approximately 24% to 21%. Although the trajectory of sleep disturbance severity over the full course of the cancer continuum is unknown in the CRC population, there is evidence of change in sleep disturbance over time in ovarian cancer.[18] Previous research also shows that exercise fluctuates over time after CRC diagnosis and exercise decreases during CRC treatment.[118] Given the likely fluctuation in sleep disturbance and exercise over time, future studies should prospectively collect data at different time windows to investigate possible temporal differences in the relationship between sleep disturbance and exercise. For example, patients undergo more drastic quality of life (and likely sleep outcome) changes immediately following diagnosis and through the active treatment phase than in the post-treatment recovery phase.

Holding the relationship between exercise and sleep disturbance constant, the results of the Month 10 and Month 17 models were very similar, with anxiety and fatigue moving in the same direction as sleep disturbance. These results suggest that there might be a symptom cluster at play, with symptoms of anxiety (and depression), fatigue, and sleep disturbance improving or worsening together, though the coefficients on fatigue and anxiety were very small. The direction of the relationship among

these symptoms is unclear, but the size of the coefficients suggest that a large change in fatigue would be associated with a small change in sleep disturbance. Retirement was associated with better sleep disturbance in the Month 10 model, but the relationship was not statistically significant in the Month 17 model. It is possible that missing data/patient attrition played into these results because retirement was strongly associated with participation in Month 17 data collection.

Other factors associated with patient attrition were being classified as “other or multiple” races and being less active. It is unclear why minority patients (non-white and non-black) were less likely to be in the Month 17 analyses, but a recent study on recruitment and retention strategies for minorities diagnosed with breast cancer suggests that barriers to survey participation may vary by race/ethinicity.[176]

The results of this study should be considered in light of some limitations. Patients were not randomized to participate in exercise, introducing selection bias. Although predictors of exercise participation were included in the models, the observational nature of this study limits the conclusions that can be drawn from analyses; instead of causal relationships, we can only infer associations. Therefore, independent variables, including exercise, are not necessarily predictors of sleep disturbance. There are a few omitted variables that that would be beneficial to include in the models discussed in this study, without which it is more difficult to control for selection into the exercise. The dataset did not include information on self-efficacy, one of the most important predictors of exercise. We also did not have access to an indicator for previous exercise habits prior to CRC diagnosis. Prior exercise habits are indicative of current or future exercise habits. Another omitted variable is information on patients’ physical activity, which is a much broader concept including any body movement that requires energy expenditure. Some patients may not exercise but engage in significant physical activity throughout the day. For example, some patients may walk to work, or have a labor-intensive job that involves heavy lifting. Exercise may be more relevant to patients with higher socioeconomic status because exercise is a planned, structured activity that requires time outside of other daily tasks and may also cost money. By only including exercise in the model, we may limit the conclusions and recommendations on exercise to patients above a certain socioeconomic threshold who have the means to exercise; some estimates may be biased because we are not including information on more general physical activity.

A strength of the MY-Health study was the inclusion of PROMIS measures, which were developed using rigorous qualitative and quantitative psychometric methods.[12,77,144,149] Using these data, we were able to include a wide range of HRQOL variables in our models to control for factors related to sleep disturbance and exercise participation beyond what most observational studies have included in previous research.

As a large community-based observational study, the MY-Health data provide information on experiences from a very diverse sample of patients who were evaluated during the course of usual care without controlled interventions. Understanding the relationship between sleep disturbance and exercise in patients with CRC 10 and 17 months after diagnosis is a building block to defining the trajectory of sleep disturbance and factors associated with sleep disturbance as patients transition off treatment.

5.5 Conclusion

The results of this study suggest a lack of significant relationship between exercise and sleep disturbance in individuals diagnosed with stage I, II and III CRC approximately 10 and 17 months after CRC diagnosis. A more granular understanding of this relationship could be evaluated through prospective research with longer follow up.

Table 5.1. Patient Characteristics at Month 10

Patient Characteristics Collected at Month 10	*Month 10 Analysis Sample (n = 587)*	*Month 17 Analysis Sample (n = 356)*
Age at diagnosis		
Mean (SD), Median, Min - Max	62.1 (12.4), 64.0, 22-84	63.5 (11.2), 65.0, 30-84
Sex		
Female	308 (52.5%)	174 (48.9%)
BMI		
Mean (SD), Median, Min - Max	28.8 (7.1), 27.4, 14-71	29.2 (7.3), 27.8, 17-71
Race		
Other (Asian, American Indian, Alaska native, Asian Hawaiian, Pacific Islander) or multiple	154 (26.2%)	71 (19.9%)
White	325 (55.4%)	215 (60.4%)
Black	108 (18.4%)	70 (19.7%)
Survey language		
English	531 (90.5%)	330 (92.7%)
Spanish or Chinese	56 (9.5%)	26 (7.3%)
Employment status		
Working full time, part time or student	233 (39.7%)	132 (37.1%)
Retired	250 (42.6%)	175 (49.2%)
Unemployed or disabled	104 (17.7%)	49 (13.8%)
Living status		
Live with child(ren) under 18 years old	97 (16.5%)	50 (14.0%)
Relevant comorbidities		
No comorbid conditions	232 (39.5%)	142 (39.9%)
1 comorbid condition	155 (26.4%)	94 (26.4%)
2 or more comorbid conditions	200 (34.1%)	120 (33.7%)
Cancer stage		
Stage I	169 (28.8%)	102 (28.7%)
Stage II	183 (31.2%)	117 (32.9%)
Stage III	235 (40.0%)	137 (38.5%)
Level of exercise activity		
Not active	132 (22.5%)	78 (22.0%)
Slightly active	101 (17.2%)	63 (17.8%)
Moderately active	271 (46.2%)	161 (45.5%)
Highly active	83 (14.1%)	52 (14.7%)
PROMIS Sleep Disturbance		
Mean (SD), Median, Min - Max	50.4 (9.7), 51.2, 30-75	49.5 (9.8), 50.3, 30-75
PROMIS Physical Functioning		
Mean (SD), Median, Min - Max	44.8 (9.1), 43.8, 15-62	45.1 (8.9), 44.6, 21-62

BMI = body mass index, max = maximum; min = minimum; PROMIS = Patient-Reported Outcomes Measurement Information System, SD = standard deviation.
Note: Percent calculated out of non-missing responses.

Table 5.2. Bivariate Relationship Between PROMIS Sleep Disturbance and Exercise Categories

	PROMIS Sleep Disturbance Scores at Month 10 (n = 587)						***PROMIS Sleep Disturbance Scores at Month 17 (n = 356)***					
Exercise Category	*N*	*Mean*	*SD*	*Median*	*Min*	*Max*	*N*	*Mean*	*SD*	*Median*	*Min*	*Max*
Not active	132	53.0	10.3	53.9	29.7	75.2	62	52.3	11.9	53.4	29.7	75.2
Slightly active	101	52.4	9.8	53.1	29.7	75.2	49	50.4	9.7	52.9	29.7	75.2
Moderately active	271	48.9	9.3	50.1	29.7	75.2	174	49.8	9.6	50.4	29.7	75.2
Highly active	83	48.5	8.8	48.8	29.7	71.6	71	46.7	9.5	48.0	29.7	68.7

PROMIS = Patient-Reported Outcomes Measurement Information System, SD = standard deviation, Min = minimum, Max = maximum.

Table 5.3. RMM Model Fit Statistics

	Month 10 model		***Month 17 model***	
Number of classes	***BIC***	***AIC***	***BIC***	***AIC***
1	4188.6	4070.4	2643.6	2539.0
2	4367.1	4126.4	2808.1	2595.0
3	4545.6	4182.4	2972.6	2651.0
4	4724.1	4238.4	3137.1	2707.0

RMM = Regression mixture model, BIC = Bayesian Information Criterion Index, AIC = Akaike Information Criterion.

Table 5.4. Multiple Regression Results, Month 10 model (n = 587)

Effect	*Categories*	*Estimate*	*Standard Error*	*Z*	*P value*
Intercept		35.799	7.48	4.78	<.0001
Exercise Group at Month 10	Highly active	1.564	1.15	1.36	0.1738
	Moderately active	0.451	0.86	0.53	0.5989
	Slightly active	-0.200	1.01	-0.20	0.8428
	Not active	ref	-	-	-
Months between chemotherapy and Month 10 data collection	1 = current	-0.286	0.96	-0.30	0.7650
	2 = 1-2 months	-1.540	0.92	-1.67	0.0956
	3 = > 2 months	-0.294	0.93	-0.31	0.7529
	0 = never	ref	-	-	-
Months between surgery and Month 10 data collection	1 = 0-4 months	-0.560	1.56	-0.36	0.7200
	2 = more than 4 months	-0.108	1.17	-0.09	0.9260
	0 = never	ref	-	-	-
Race (Collected at Month 10)	Black	1.362	0.86	1.59	0.1113
	Other (Asian, American Indian, Alaska native, Asian Hawaiian, Pacific Islander) or multiple	0.090	0.76	0.12	0.9059
	White	ref	-	-	-
Number of relevant comorbidities at Month 10	1 comorbid condition	1.517	0.80	1.91	0.0567
	2 or more comorbid conditions	0.826	0.81	1.03	0.3054
	No comorbid conditions	ref	-	-	-
Sex (Collected via SEER)	Female	0.363	0.64	0.56	0.5722
	Male	ref	-	-	-
Live with child under 18 years old at Month 10	Checked	1.070	0.93	1.15	0.2490
	Unchecked	ref	-	-	-
Employment at Month 10	Retired	-2.426	0.89	-2.72	0.0066
	Unemployed or disabled	-0.686	0.96	-0.72	0.4732
	Working full time, part time or student	ref	-	-	-
Months between diagnosis and Month 10 data collection		0.024	0.20	0.12	0.9034
Age at diagnosis (years) (Collected via SEER)		-0.059	0.04	-1.53	0.1266
BMI (Collected at Month 10)		0.046	0.05	1.00	0.3169
PROMIS Anxiety at Month 10		0.207	0.04	4.90	<.0001
PROMIS Fatigue at Month 10		0.243	0.06	4.38	<.0001
PROMIS Pain Interference at Month 10		0.044	0.04	1.04	0.2963
PROMIS Physical Functioning at Month 10		-0.099	0.06	-1.62	0.1063
PROMIS Social Functioning at Month 10		-0.081	0.06	-1.37	0.1706
FACT-G Physical Well-being Nausea Item at Month 10		0.014	0.41	0.03	0.9734
Variance		54.840	3.20	_	_

BMI = body mass index, FACT-G = Functional Assessment of Cancer Therapy-General, PROMIS = Patient-Reported Outcomes Measurement Information System, SD = standard deviation

Table 5.5. Multiple Regression Results, Month 17 (n = 356)

Effect	*Categories*	*Estimate*	*Standard Error*	*Z*	*P value*
Intercept		25.364	10.88	2.33	0.0197
Exercise group at Month 17	Highly active	-0.274	1.56	-0.18	0.8606
	Moderately active	0.427	1.27	0.34	0.7368
	Slightly active	0.149	1.61	0.09	0.9259
	Not active	ref	-	-	-
Months between chemotherapy and Month 17 data collection	1 = current	-0.899	2.22	-0.40	0.6857
	2 = 1-2 months	-0.944	2.27	-0.42	0.6769
	3 = > 2 months	-0.557	0.94	-0.59	0.5552
	0 = never	ref	-	-	-
Months between surgery and Month 17 data collection	1 = 0-4 months	-3.964	2.26	-1.76	0.0790
	2 = more than 4 months	-0.725	1.60	-0.45	0.6508
	0 = never	ref	-	-	-
Race (Collected at Month 10)	Black	-0.010	1.18	-0.01	0.9933
	Other (Asian, American Indian, Alaska native, Asian Hawaiian, Pacific Islander) or multiple	0.012	1.17	0.01	0.9920
	White	ref	-	-	-
Number of relevant comorbidities at Month 10	1 comorbid condition	1.754	1.11	1.58	0.1133
	2 or more comorbid conditions	-0.213	1.13	-0.19	0.8498
	No comorbid conditions	ref	-	-	-
Sex (Collected via SEER)	Female	-0.670	0.88	-0.76	0.4477
	Male	ref	-	-	-
Live with child under 18 years old at Month 10	Checked	-0.584	1.40	-0.42	0.6765
	Unchecked	ref	-	-	-
Employment at Month 10	Retired	-1.597	1.22	-1.31	0.1904
	Unemployed or disabled	-1.859	1.45	-1.28	0.2002
	Working full time, part time or student	ref	-	-	-
Months between diagnosis and Month 17 data collection		-0.002	0.22	-0.01	0.9942
Age at diagnosis (years) (Collected via SEER)		-0.075	0.06	-1.26	0.2069
BMI (Collected at Month 10)		0.092	0.06	1.46	0.1445
PROMIS Anxiety at Month 17		0.181	0.06	2.92	0.0035
PROMIS Fatigue at Month 17		0.331	0.08	4.28	<.0001
PROMIS Pain Interference at Month 17		0.091	0.06	1.58	0.1138
PROMIS Physical Functioning at Month 17		-0.053	0.08	-0.64	0.5254
PROMIS Social Roles and Activities at Month 17		0.022	0.08	0.26	0.7924
FACT-G Physical Well-being Nausea Item at Month 17		0.484	0.65	0.75	0.4550
Variance		62.954	4.72	_	_

BMI = body mass index, FACT-G = Functional Assessment of Cancer Therapy-General, PROMIS = Patient-Reported Outcomes Measurement Information System, SD = standard deviation

Supplemental Table 5.1. Descriptive Statistics for Variables Entered in RMM and Multiple Regression Models

Characteristic	*Month 10 (n = 587)*	*Month 17 (n = 356)*
Age at diagnosis (collected at Month 10)		
Mean (SD), Median, Min - Max	62.1 (12.4), 64.0, 22-84	63.5 (11.2), 65.0, 30-84
Sex (collected at Month 10)		
Female	308 (52.5%)	174 (48.9%)
BMI (collected at Month 10)		
Mean (SD), Median, Min - Max	28.8 (7.1), 27.4, 14-71	29.2 (7.3), 27.8, 17-71
Race (collected at Month 10)		
Other (Asian, American Indian, Alaska native, Asian Hawaiian, Pacific Islander) or multiple	154 (26.2%)	71 (19.9%)
White	325 (55.4%)	215 (60.4%)
Black	108 (18.4%)	70 (19.7%)
Employment status (collected at Month 10)		
Working full time, part time or student	233 (39.7%)	132 (37.1%)
Retired	250 (42.6%)	175 (49.2%)
Unemployed or disabled	104 (17.7%)	49 (13.8%)
Living status (collected at Month 10)		
Live with child(ren) under 18 years old	97 (16.5%)	50 (14.0%)
Relevant comorbidities (collected at Month 10)		
No comorbid conditions	232 (39.5%)	142 (39.9%)
1 comorbid condition	155 (26.4%)	94 (26.4%)
2 or more comorbid conditions	200 (34.1%)	120 (33.7%)
Level of exercise activity		
Not active	132 (22.5%)	62 (17.4%)
Slightly active	101 (17.2%)	49 (13.8%)
Moderately active	271 (46.2%)	174 (48.9%)
Highly active	83 (14.1%)	71 (19.9%)
Months Since Chemotherapy		
0 = never	263 (44.8%)	154 (43.3%)
1 = current	123 (21.0%)	16 (4.5%)
2 = 1-2 months	103 (17.5%)	15 (4.2%)
3 = > 2 months	98 (16.7%)	171 (48.0%)
Months Since Surgery		
0 = never	47 (8.0%)	30 (8.4%)
1 = 0-4 months	54 (9.2%)	26 (7.3%)
2 = more than 4 months	486 (82.8%)	300 (84.3%)
Months since diagnosis at data collection		
Mean (SD), Median, Min - Max	9.7 (1.6), 9.5, 6-21	17.3 (2.0), 17.0, 13-26
PROMIS Sleep Disturbance		
Mean (SD), Median, Min - Max	50.4 (9.7), 51.2, 30-75	49.7 (10.2), 51.4, 30-75
PROMIS Anxiety		
Mean (SD), Median, Min - Max	49.3 (10.7), 49.4, 36-84	48.2 (11.3), 48.3, 36-84
PROMIS Depression (in sensitivity analysis only)		
Mean (SD), Median, Min - Max	48.2 (10.3), 48.0, 36-81	47.2 (10.6), 46.4, 36-81
PROMIS Fatigue		
Mean (SD), Median, Min - Max	51.9 (10.3), 51.7, 29-78	49.7 (10.6), 49.9, 29-81
PROMIS Pain Interference		
Mean (SD), Median, Min - Max	52.9 (10.8), 54.6, 40-79	50.3 (10.4), 49.0, 40-79
PROMIS Physical Functioning		

Characteristic	*Month 10 (n = 587)*	*Month 17 (n = 356)*
Mean (SD), Median, Min - Max	44.8 (9.1), 43.8, 15-62	46.2 (9.7), 46.0, 15-62
PROMIS Ability to Participate in Social Roles and Activities		
Mean (SD), Median, Min - Max	49.9 (10.0), 49.4, 25-66	52.2 (10.6), 52.1, 25-66
FACT-G Physical Well-being Nausea Item		
Mean (SD), Median, Min - Max	0.6 (1.0), 0.0, 0-4	0.3 (0.8), 0.0, 0-4

BMI = body mass index, max = maximum; min = minimum; PROMIS = Patient-Reported Outcomes Measurement Information System, SD = standard deviation.
Note: Percent calculated out of non-missing responses.

Supplemental Table 5.2. Effect of Missing Responses at Month 10: Month 10 Descriptive Statistics

Patient Characteristics Collected at Month 10	*Patients who participated in survey at Month 10 but were not included in Month 10 analysis due to missing responses (n = 147)*	*Month 10 Analysis Sample (n = 587)*
Sex		
Female	73 (49.7%)	308 (52.5%)
Race		
Other (Asian, American Indian, Alaska native, Asian Hawaiian, Pacific Islander) or multiple	38 (25.9%)	154 (26.2%)
White (reference category)	68 (46.3%)	325 (55.4%)
Black	41 (27.9%)	108 (18.4%)*
Survey language		
English	130 (88.4%)	531 (90.5%)
Spanish or Chinese (reference category)	17 (11.6%)	56 (9.5%)
Employment status		
Working full time, part time or student (reference category)	41 (32.8%)	233 (39.7%)
Retired	65 (52.0%)	250 (42.6%)
Unemployed or disabled	19 (15.2%)	104 (17.7%)
Level of exercise activity		
Not active (reference category)	54 (38.6%)	132 (22.5%)
Slightly active	17 (12.1%)	101 (17.2%)*
Moderately active	53 (37.9%)	271 (46.2%)
Highly active	16 (11.4%)	83 (14.1%)
PROMIS Sleep Disturbance		
Mean (SD), Median, Min - Max	51.2 (9.9), 52.7, 30-75	50.4 (9.7), 51.2, 30-75
PROMIS Physical Functioning		
Mean (SD), Median, Min - Max	42.0 (10.3), 40.6, 15-62	44.8 (9.1), 43.8, 15-62*

Max = maximum; min = minimum; PROMIS = Patient-Reported Outcomes Measurement Information System, SD = standard deviation.
Note: Percent calculated out of non-missing responses.
* $p < 0.05$ in logistic regression.

Supplemental Table 5.3. Patient Attrition: Month 10 Descriptive Statistics

Patient Characteristics Collected at Month 10	*Patients who participated survey at Month 10 but were not included in Month 17 analysis due to patient attrition or missing responses (n = 378)*	*Month 17 Analysis Sample (n = 356)*
Sex		
Female	207 (54.8%)	174 (48.9%)
Race		
Other (Asian, American Indian, Alaska native, Asian Hawaiian, Pacific Islander) or multiple	121 (32.0%)	71 (19.9%)*
White (reference category)	178 (47.1%)	215 (60.4%)
Black	79 (20.9%)	70 (19.7%)
Survey language		
English	331 (87.6%)	330 (92.7%)
Spanish or Chinese (reference category)	47 (12.4%)	26 (7.3%)
Employment status		
Working full time, part time or student (reference category)	142 (39.9%)	132 (37.1%)
Retired	140 (39.3%)	175 (49.2%)*
Unemployed or disabled	74 (20.8%)	49 (13.8%)
Level of exercise activity		
Not active (reference category)	108 (29.0%)	78 (22.0%)
Slightly active	55 (14.7%)	63 (17.8%)*
Moderately active	163 (43.7%)	161 (45.5%)
Highly active	47 (12.6%)	52 (14.7%)
PROMIS Sleep Disturbance		
Mean (SD), Median, Min - Max	51.5 (9.6), 52.6, 30-75	49.5 (9.8), 50.3, 30-75
PROMIS Physical Functioning		
Mean (SD), Median, Min - Max	43.3 (9.8), 42.5, 15-62	45.1 (8.9), 44.6, 21-62

Max = maximum; min = minimum; PROMIS = Patient-Reported Outcomes Measurement Information System, SD = standard deviation.
Note: Percent calculated out of non-missing responses.
* $p < 0.05$ in logistic regression.

CHAPTER 6. RELATIONSHIP BETWEEN CHANGES IN SLEEP AND EXERCISE AS COLORECTAL CANCER SURVIVORS TRANSITION OFF TREATMENT (MANUSCRIPT 3)

6.1 Background

More than 1.1 million individuals in the United States are diagnosed with colorectal cancer (CRC)[5] and at least half of these patients experience decrements in sleep.[3] Consequences of sleep disturbance include decreased cognitive functioning[9] and fatigue,[10,11] loss in work productivity and work quality, and increased number of visits to health professionals.[14] Poor sleep is also linked to long-term implications such as being a risk factor for infectious diseases, cardiovascular diseases, and depression.[13]

Despite the negative ramifications associated with sleep disturbance, few treatment options are available to mitigate poor sleep. Cognitive behavioral therapy (CBT) and pharmacotherapies are the two most widely used treatment options for sleep disturbance. CBT is recommended by the American Academy of Sleep Medicine as a first-line therapy for patients with insomnia and includes relaxation therapy, sleep hygiene, and cognitive therapy. Unfortunately, there are an inadequate number of providers trained in CBT for sleep disturbance, and patient adherence issues pose considerable barriers to the adequacy of sleep treatment.[9] Pharmacologic treatments (e.g., benzodiazepine-receptor agonists, antidepressants, melatonin agonists) are associated with adverse daytime side effects such as sedation or dizziness. Although they should only be administered for 4 to 6 weeks,[21] cancer patients may experience disturbed sleep well beyond this period of time.[20] CRC patients using pharmacologic therapies to mitigate sleep disturbance are faced with either continuing pharmacologic treatment beyond the recommended 4 to 6 weeks or discontinue treatment before their sleep disturbance has been resolved.

Exercise is gaining support as a potential treatment for sleep disturbance in other populations. Exercise is a treatment option that, unlike CBT and pharmacologic treatments, is linked to additional benefits such as improved aerobic fitness.[112] In addition, exercise reduces anxiety, pain, and fatigue, all of which are associated with sleep disturbance.[113-115] Exercise has been evaluated as a treatment for sleep disturbance in the healthy U.S. population[23,116] and a number of RCTs and observational studies have

investigated exercise as a possible treatment for sleep disturbance in cancer patients.[113,117-121] Contrary to currently available treatments, exercise is generally accessible and less costly.

We are aware of only three studies that have investigated the relationship between exercise and sleep disturbance in individuals diagnosed with CRC.[120] [119] [117] Cheville and colleagues enrolled 66 patients diagnosed with stage IV colorectal *or* lung cancer and followed patients over the course of 8 weeks in a randomized control trial (RCT). They assessed a home-based exercise intervention in which patients exercised four or more days a week. The intervention resulted in a statistically significant improvement in sleep for the patients who participated in the exercise intervention versus those who were randomized to the usual care arm.[117] Because the RCT included a mixture of individuals diagnosed with colorectal or lung cancer, the results of this study are not conclusive specifically for individuals diagnosed with CRC. The two other studies assessing exercise did not find a statistically significant effect, but both studies were small, with 119 adults participants[119] and 45 adult participants,[120] respectively, and sleep was not the primary outcome of the study; studies were not powered to detect differences in sleep outcomes. The first of these studies by Cho and colleagues included women with colorectal, breast, or ovarian cancer.[119] The second study was a smaller observational study that included individuals diagnosed with stage II or III CRC and employed an opt-in exercise protocol such that participants were placed in a supervised exercise group or a usual care group based on their preference.[120] The supervised exercise group participated in moderate-intensity aerobic and resistance exercise for 12 weeks.[120] Exercise intensity, duration, and frequency were not reported for the usual care group.[120]

There are a number of possible explanations for the inconsistent results between these three studies including differences among participants enrolled in each study (e.g., cancer stage, cancer type), differences in exercise prescription of intensity and frequency, and differences in the slice of time during patients' cancer treatment trajectories. Another possible explanation is that exercise may be more effective in ameliorating sleep disturbance for some individuals and not for others, which could attenuate sleep outcomes between exercise treatment groups and usual care groups. Future randomized trials testing the effect of exercise on sleep disturbance in CRC should tailor the population of interest to patients whose sleep would stand to benefit the most from exercise. For example, patients who report

worse sleep may benefit the most from exercise. Without this information, future trials may enroll a patient sample that is too diverse and the effect of exercise may be lost in the average outcomes.

This study builds on the published literature by examining the relationship between sleep and exercise specifically in individuals diagnosed with CRC over a period of approximately 7 months as patients transition off of CRC treatment. Strenuous exercise has been shown to decrease during cancer treatment in individuals diagnosed with CRC, and the same study demonstrated that general physical activity levels likely increase to higher levels than before CRC diagnosis after treatment is complete.[177] However, the trajectory of sleep disturbance throughout and after treatment for patients with CRC is unknown. There is evidence in other cancer populations that cancer treatment is associated with a reduction and possible persistence of sleep disturbance,[16-18,21,99,101] but it is unclear if exercise may play a role in mitigating sleep disturbance over time for CRC patients. Therefore, this study focuses on change in sleep disturbance and change in exercise after cancer diagnosis. We used observational data that represents patients' exercise habits without intervention. Exercise activity was self-reported at two time points after CRC diagnosis, capturing change in exercise levels. Individuals enrolled in this study were recently diagnosed with stage I, II, or III CRC approximately 10 months after diagnosis, and their sleep and exercise were reassessed approximately 7 months later at roughly 17 months after diagnosis. This window of time represents an important aspect in patients' treatment trajectories as patients phase out of treatment and into survivorship when they may be more physically active.[177]

The purpose of this study is two-fold. First, we sought to uncover possible variability in the relationship between change in sleep and change in exercise among a sample of individuals diagnosed with CRC, informing patient enrollment in future controlled trials on exercise. We tested the hypothesis that the relationship between change in exercise activity and change in sleep disturbance differs by the magnitude of change in sleep disturbance from 10 to 17 months after diagnosis. The second objective of this study was to evaluate the relationship between change in exercise and change in sleep disturbance specifically in a sample of adults diagnosed with stage I–III CRC. The second hypothesis was that patients who increase exercise activity from 10 months to 17 months after diagnosis would experience a decline in sleep disturbance.

6.2 Methods

6.2.1 MY-Health Study Design

This secondary data analysis was conducted using data from the Measuring Your Health (MY-Health) study which included over 5000 patients enrolled between 2010 and 2012.[143] Potential study participants were identified from four SEER cancer registries located in three states: California (2 SEER registries), Louisiana, and New Jersey. Individuals age 21–84 years diagnosed with one of seven cancers (i.e., colorectal, prostate, non-small cell lung, non-Hodgkin lymphoma, female breast, uterine, or cervical) within 6 to 13 months of diagnosis were invited to participate in the MY-Health study via mail. Participants completed questionnaires using mail-in hard copy questionnaires at two time points: The first data collection occurred approximately 10 months after diagnosis (mean = 9.73, range = 6-30 months), and the second data collection occurred 17 months after diagnosis, on average (mean = 17.42, range = 11-36 months). The MY-Health study oversampled race/ethnic minorities and younger patients, and questionnaires were available in three languages (English, Spanish, Mandarin). Additional details on the study design and procedures were previously published.[143]

6.2.2 Participants and Terminology

Patients who were identified as being diagnosed with stage I, II, or II colorectal cancer based on SEER confirmation were included in the analyses for this study. Because exercise was the main independent variable of interest, the sample was further limited to patients who were able to perform physical activity, defined as patients who were able to get out of bed (based on a patient-reported survey question). The first round of data collection approximately 10 months on average after diagnosis included 734 patients, and 400 patients participated in the second round, which was collected approximately 17 months after diagnosis on average. Although the exact time of data collection after CRC diagnosis varied, for brevity, the data collection rounds are referred to as “Month 10” and “Month 17” data collection.

6.2.3 Measures

Dependent variable.

PROMIS Sleep Disturbance items were administered to patients at Month 10 and Month 17. PROMIS Sleep Disturbance measures concepts such as trouble staying asleep, not getting enough sleep, restlessness, feeling refreshed after sleep, and difficulty falling sleep. Results of the full psychometric evaluations of the PROMIS Sleep Disturbance item bank[144] and short forms[145] were

previously published. A custom six-item short form was scored; the psychometric properties of the six-item form were evaluated in individuals enrolled in the MY-Health study (Cronbach's α = 0.88 – 0.95).[146] PROMIS Sleep Disturbance is a continuous variable scored on a t-score metric with a mean of 50 and standard deviation (SD) of 10 based on the referent population (mixture of clinical and the general U.S. population[147]), and higher scores indicate worse sleep disturbance. Change in sleep disturbance was calculated by subtracting PROMIS Sleep disturbance scores at 10 months from scores at 17 months after CRC diagnosis. Positive change is indicative of worsening sleep. The recall period was "the past 7 days". A recent study by Leung et al.[168] provided a cut point on PROMIS Sleep Disturbance indicative of clinically significant sleep disturbance (≥ 57, area under the curve = 0.92).

Independent variables.

Exercise.

The MY-Health study included three exercise-related survey items covering patient-perceived exercise intensity and patient-reported frequency of exercise in the previous 7 days. Exercise items were administered at Month 10 and Month 17 data collection. Based on patients' responses to these questions, patients' exercise was categorized into one of four activity levels: (1) not active, (2) slightly active, (3) moderately active, and (4) highly active. The four exercise categories reflect the American College of Sports Medicine's (ACSM) recommendation that individuals diagnosed with cancer achieve 150 minutes of moderate-intensity exercise per week or 75 minutes of vigorous exercise per week.[15] Patients classified in the "not active" or "slightly active" groups likely did not meet the minimum ACSM guideline of 150 minutes of moderate-intensity exercise per week or 75 minutes of vigorous exercise per week,[15] but patients in the "moderately active" or "highly active" groups likely met or exceeded the ACSM guideline. The primary independent variable of interest, change in exercise, summarizes the change in exercise categories from 10 to 17 months after CRC diagnosis. Change in exercise was entered in the model as a categorical variable with five categories: (1) less active by 2 or 3 exercise categories, (2) less active by 1 exercise category, (3) no change in exercise activity, (4) more active by 1 exercise category, and (5) more active by 2 or 3 exercise categories.

Patient-level factors associated with sleep disturbance.

The MY-Health dataset contains information on patient, disease, and treatment factors associated with sleep disturbance. Cancer treatment has been linked with decrements in sleep quality, and some studies suggest that recovery from treatment (i.e., time since treatment) is predictor of sleep quality.[16-18,100,101] The trajectory of sleep disturbance throughout and after treatment for adults with CRC is unknown, thus this information will be included in the models to account for the possible effect of CRC treatment on sleep disturbance. Cancer treatment type (e.g., surgery, chemotherapy, radiation) and most recent date of treatment were self-reported at Month 17 data collection. Categorical variables were derived to capture current/recent treatment compared to no treatment or less-recent treatment. Treatment trajectory categories were based on relevant physical recovery periods post-treatment and data availability. Time since chemotherapy was coded using four categories (i.e., currently receiving chemotherapy, chemotherapy 1–2 months ago, chemotherapy more than 2 months ago, never received chemotherapy [reference category]). Time since surgery was coded using three categories (i.e., surgery occurred within 0–4 months, surgery occurred more than 4 months ago, never received surgery [reference category]). Comorbid conditions[73] were self-reported and included in the models as a derived variable with three categories (i.e., no comorbid diseases [reference category], 1 comorbid disease, 2 or more comorbid diseases). Four PROMIS domains were included in the models as independent variables to assess aspects of health-related quality of life known to be associated with sleep disturbance:[73,79 80 81,90,92-95] Anxiety (11 items), Depression (10 items), Fatigue[148] (14 items), and Pain Interference (11 items).[149] These PROMIS measures were normed to the general U.S. population[147] and higher scores indicate worse anxiety, depression, fatigue, and pain, respectively. PROMIS change scores (Month 17 – Month 10) were entered in the model as continuous variables with positive change indicating a worsening symptom. Nausea severity was measured using a five-point nausea[21] item from the FACT-G Physical Well-Being (PWB) subscale[150] with a recall period of the “past 7 days” and response choices ranging from 0 = “not at all” to 4 = “very much.” Although the nausea item has not been psychometrically evaluated as a single measure of nausea, the entire FACT-G PWB scale, which has been evaluated extensively in cancer patients,[178-180] covers concepts that overlap with PROMIS measures such as pain and fatigue. Therefore, only the nausea item was included in the models. Change in nausea severity was entered in

the model as a continuous variable. Other characteristics known to be associated with sleep disturbance were included in the models such as age at diagnosis,[2,21,97] sex,[72] time since diagnosis at Month 17 data collection,[93] employment status at Month 10 (i.e., working, retired, unemployed/disabled [reference category]),[84] and an indicator for living with children under 18 (collected during Month 10 data collection)[83,84] were included in the models. Age and race were also included in the model to account for the over-sampling of younger and minority persons from SEER registries. Race, employment status, and the living-with-child(ren) indicator were self-reported, and age at diagnosis, sex, and diagnosis date were obtained via SEER registry data.

Factors associated with exercise.

MY-Health variables also addressed determinants of exercise participation (treatment selection). Exercise participation is partially determined by patients' ability to perform activities,[153-155] thus patients' change PROMIS Physical Function scores (from Month 10 to Month 17) was included as a covariate in the model (positive change indicates improvement).[156] Social support is associated with participation in exercise and was measured using PROMIS Ability to Participate in Social Roles and Activities;[153-155,157] change in social support was entered in the model as a continuous variable (positive change indicates improvement). Higher weight is associated with less exercise, therefore body mass index (BMI) was derived from patient-reported weight and height (collected at Month 10 only).[72] Other factors already included in the model that are associated with participation in exercise and affect sleep include increased age, parenthood, sex, and race.[153-155]

6.2.4 Analyses

Methods.

Descriptive statistics were calculated and tabulated. Relationships between candidate independent variables were evaluated for collinearity by calculating bivariate correlations and variance inflation factor (VIF) within multiple regression models. VIF values greater than 10 were considered a symptom of multicollinearity. Residuals were evaluated between candidate independent variables and change in sleep disturbance to determine if higher-order terms needed to be included in the models.

Regression mixture models (RMMs)[158,159] are special cases of finite mixture models, which model weighted combinations of different distributions. With RMMs, the component membership to each

distribution is unobservable (a latent variable). We employed RMMs to test if heterogeneity was present in the relationship between change in sleep disturbance and change in exercise. (For example, if factors associated with sleep disturbance (especially exercise) varied by magnitude of change in sleep disturbance.) RMMs were estimated using Dual Quasi-Newton optimization.[162] Models ranging from one to four classes were evaluated. The final models (e.g., choice of number of classes) were chosen based on fit (e.g., smallest Bayesian Information Criterion Index (BIC), Akaike Information Criterion (AIC)) and interpretability. RMMs are sensitive to starting values,[164] thus user-provided starting values were also tested to confirm the number of classes identified by SAS-generated starting values. If only one class of sleep disturbance was identified, then multiple regression (which assumes one common class of sleep disturbance) was used to model factors associated with change in sleep disturbance.

Sensitivity analyses. Patients classified as having no change in exercise may have participated in a range of exercise activity from not participating in any exercise 10 and 17 months after diagnosis to being classified as highly active at 10 and 17 months after diagnosis. Therefore, a sensitivity analysis was conducted to evaluate the relationship between constant exercise, change in exercise and change in sleep disturbance. Six exercise categories were derived and included in an RMM model analogous to the primary model described above except with a six-category exercise variable instead of a five-level exercise variable: (1) less active by 2 or 3 exercise categories, (2) less active by 1 exercise category, (3) no change in exercise activity – persistently not active or slightly active [reference category], (4) no change in exercise activity – persistent moderately or highly active, (5) more active by 1 exercise category, and (6) more active by 2 or 3 exercise categories.

Although collinearity analyses (Pearson correlations, VIF) did not identify collinearity issues among independent variables, HRQOL-related variables such as anxiety, depression, and fatigue are known to be highly correlated. A sensitivity analysis was conducted to test the exclusion of PROMIS Anxiety from the model because it yielded the largest VIF (VIF = 2.13) and the strongest correlations with other HRQOL change variables (PROMIS Anxiety change and PROMIS Depression change: r = 0.69; PROMIS Anxiety change and PROMIS Fatigue change: r = 0.43).

Patient attrition. Factors associated with patient attrition in survey participation from Month 10 data collection to Month 17 were evaluated using logistic regression. Patients who participated in Month

10 and Month 17 survey administrations (outcome = 1) were compared with patients who participated in Month 10 but not Month 17 (outcome = 0) using logistic regression. The model included patient characteristics at Month 10 that were related to sleep disturbance and potentially associated with patient attrition: sex, race, employment status, survey language, level of exercise activity, PROMIS Sleep Disturbance, and PROMIS Physical Functioning.

Power.

Power to detect multiple classes was evaluated and confirmed using simulations based on random samples drawn from the MY-Health study data, providing information about the covariance structure among the independent variables. Sub-samples were randomly drawn from the study dataset to simulate 1000 datasets for each of the parameter modifications in the simulation: overall sample size, numeric differences between coefficients in each latent class, variance of PROMIS Sleep Disturbance, and proportion of sample within each class. A well-accepted rule of thumb for identifying minimally important group differences on a patient-reported outcome is the half standard deviation.[166,170] The half standard deviation of PROMIS Sleep Disturbance at Month 10 was approximately 5 points. For classes to be meaningfully different, we anticipated that the classes should be separated at a minimum by the threshold for minimal important difference. Based on a sample size of 300 and a mean difference between sleep disturbance scores in each class approximately 6 points (5.5) apart, a simulated sleep disturbance error variance between 1 and 7, and equal class sizes (proportion of sample in class 1 = 50%, proportion of sample in class 2 = 50%), the power to detect multiple classes was 100%. When the distance between coefficients in each class dropped below 1.5 and the error variance of the simulated sleep disturbance variable was 4 or more, power reduced to below 70%. The proportion of the sample designated to each class was modified in the simulations but the effect on power was negligible.

Power to detect the effect of exercise was calculated for a sample size of 300. When the partial correlation between exercise and sleep disturbance was 0.20 or greater, power was 0.94 or above. When the sample size was 300 and the partial correlation was very small (0.05 or 0.14), power was reduced to .14 and .69 respectively.

Analysis conventions.

Complete case analyses were conducted for all models: due to missing data, 348 participants were included in the analyses. Regression coefficients were reviewed to describe the relationship between sleep disturbance and covariates in the models. An alpha of 0.05 or less was chosen as the criterion for statistical significance of the covariates in the RMMs. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). More specifically, we used a SAS procedure called PROC FMM to fit RMMs.[163]

6.3 Results

Patient, disease, and treatment characteristics at Month 10 are presented in Table 6.1. The mean patient age at diagnosis was 63 years (SD = 11.3, range from 30 to 84 years) and approximately half the sample was female (48.6%). Almost 30% (28.4%) of the sample was diagnosed with Stage I disease, 33% was diagnosed with Stage II CRC (32.5%), and almost 40% (39.1%) of the sample was diagnosed with Stage III CRC. The median number of months between data collections was 7.4 (range = 5.5 to 15.2) [data not shown]. Mean PROMIS Sleep Disturbance scores were similar to the average scores observed in the referent population (i.e., patients who went to sleep clinics and healthy sleepers) at Month 10 with a mean of 49.5. Applying Leung's cut point, 21.6% and 20.1% of the Month 10 and Month 17 samples respectively were likely experiencing clinically-significant sleep disturbance [data not shown]. Almost two-thirds of the sample was classified as having participated in "moderately active" or "highly active" exercise at Month 10 (60.9%), and only 21.6% of patients were not active at all at Month 10.

Descriptive statistics for all variables entered in the models (that were not already present in Table 6.1) are presented in Table 6.2. A little over half the sample (52.3%) was classified as having no change in exercise activity, while 29.8% of patients increased activity levels, and 17.8% participated in less active exercise at Month 17 compared to Month 10. Mean change in PROMIS Sleep Disturbance from Month 10 to Month 17 was 0 (SD = 7.1) and ranged from -25 (improvement) to 19 (worsening).

The bivariate relationship between change in sleep disturbance and change in exercise is presented in Table 6.3. The mean change in PROMIS Sleep Disturbance scores for patients who increased activity from month 10 to 17 were negative (PROMIS Sleep Disturbance score for more active by 1 exercise category: -0.57, More active by 2 or 3 exercise categories: -0.96), indicating improvement.

There was little change in mean PROMIS Sleep Disturbance scores for the patients that did not change exercise categories (mean = 0.15) or who were less active (0.04).

6.3.1 Regression Mixture Models

Model fit.

RMMs were estimated to determine whether distinct classes of sleep disturbance were present. Models with one to four classes were estimated. The smallest BIC and AIC were associated with the two-class model (one-class: AIC = 2308.8, BIC =2424.2; two-class: AIC = 2069.8, BIC = 2304.8, three-class: AIC = 2156.5, BIC = 2510.9, four-class: AIC = 2432.6, BIC = 2906.5,). The two-class model chosen using SAS starting values (Supplemental Table 6.1) included one large class (mixing probability = 0.90) and a small class (mixing probability = 0.10). The regression coefficients for the smallest class were all statistically significant and the variance for smallest class was less than 0.001 suggesting that class 2 included outliers only. Therefore, a multiple regression (one-class model) was chosen for the analysis.

Sleep disturbance and exercise.

Multiple regression results are presented in Table 6.4. Change in exercise level was not statistically significantly associated with change in sleep disturbance from months 10 to 17. Change in fatigue and sleep disturbance at Month 10 had statistically significant relationships with change in sleep disturbance from Month 10 to Month 17. Patients reporting less fatigue were significantly more likely to report improved sleep quality, but the coefficient was small (change in fatigue = 0.15); a 35-point improvement in PROMIS Fatigue would be associated with a 5.3-point improvement in PROMIS Sleep Disturbance. Poor sleep disturbance 10 months after diagnosis was associated with improvement in sleep disturbance from 10 to 17 months after CRC diagnosis (B = -0.23).

Sensitivity analysis. Similar to the primary model, the smallest AIC and BIC fit statistics were associated with a two-class model, but the second class was comprised of only 20 patients and regression coefficients in class 2 were mostly statistically significant and uninterpretable suggesting that class 2 contained outliers. Therefore, a multiple regression (one-class model) was chosen for the sensitivity analysis. Neither an increase in exercise from 10 to 17 months or persistent moderately or highly active exercisers were statistically associated with change in sleep disturbance. Change in fatigue and sleep disturbance at Month 10 had statistically significant relationships with change in sleep

disturbance from 10 to 17 months after diagnosis. Results of the sensitivity analysis are presented in Supplemental Table 6.2.

For the sensitivity analysis evaluating the removal of PROMIS Anxiety, results were very similar to the primary model, with coefficients of similar magnitude. PROMIS Sleep Disturbance at Time 1 and change in PROMIS Fatigue were statistically significant in both models ($p < 0.01$ in both models) [data not shown]. Change in PROMIS Depression was not statistically significant in the primary model, but was statistically significant in the sensitivity analyses ($B = 0.11$, $p = 0.02$) [data not shown].

Patient attrition.

A total of 734 individuals diagnosed with stage I, II, or III CRC participated in the 10 Month data collection, but only 348 participants were included in the models due to missing responses and patient survey attrition by the 17 month data collection (leaving 386 patients not included in the models). We compared patient characteristics for patients who were included in the RMM/multiple regression models ($n = 348$), with patients who were not included in the models due to missing values or survey attrition ($n = 386$). Overall, factors associated with patient survey adherence were very similar to factors associated with survey attrition (Supplemental Table 6.3). Only two patient characteristics were statistically significant in the model: being retired (OR = 1.69) and race other than white or black (OR = 0.53). The odds of patients completing the Month 17 survey were 70% higher for patients who were retired compared to patients who were unemployed or disabled, and patients who characterized themselves as of other/multiple races (not black or white) were 47% less likely to complete the 17 Month survey.

6.4 Discussion

This study builds on the published literature by examining the relationship between change in sleep and change in exercise specifically in individuals diagnosed with stage I, II, or III CRC using patient-reported observational data on patients' exercise habits without intervention. The results of this study show no statistically significant relationship between change in patient-reported sleep disturbance and change in exercise among CRC patients 10 to 17 months from diagnosis. Further, we found the relationship between sleep and exercise did not differ by *magnitude of change* of sleep disturbance, meaning that no specific subgroup of patients with more improvement or more worsening in sleep disturbance emerged as being associated with any particular change in level of exercise. The sensitivity

analysis further confirmed these findings and also showed that there was not a strong relationship between change in sleep disturbance and persistent exercise likely at or above the ACSM guidelines between 10 and 17 months after diagnosis.

The exercise items presented some measurement limitations that precluded us from objectively categorizing patients as achieving or not achieving ACSM exercise recommendations (e.g., *duration* of exercise not captured, items not psychometrically evaluated). Nonetheless, descriptive statistics show that a larger proportion of CRC patients in this sample increased exercise between 10 and 17 months after diagnosis compared to the proportion that decreased exercise levels. Approximately 40% of individuals diagnosed with CRC in this study likely did not achieve the ACSM recommendations for exercise (150 minutes of moderate-intensity exercise per week or 75 minutes of vigorous exercise per week[15]) approximately 10 months after diagnosis. Between Month 10 and Month 17, almost 30% of the sample increased exercise categories by at least one level and only 18% reduced exercise activity. These results reflect an early study on exercise habits in CRC survivors showing that after treatment, CRC patients increase exercise on average.[118]

A previously published randomized trial including individuals diagnosed with stage IV lung cancer or CRC found that sleep disturbance decreased for patients in the exercise arm on average and patients in the usual care arm did not experience much change in sleep disturbance.[117] After 8 weeks on the exercise intervention, there was a statistically significant difference between sleep quality in the study arms. Stage IV patients were not included in our study because their treatment trajectories and HRQOL experiences are different from CRC patients diagnosed with non-metastatic disease; it is possible, even though Cheville's randomized trial and our study included CRC patients, that exercise is more efficacious in metastatic disease than in earlier stages or that there is something inherently different about the effect of exercise on sleep in individuals with lung cancer (approximately 50% of Cheville's sample). Also, measurement limitations of the exercise items in our study likely contribute to the differences in results.

By evaluating patient attrition in survey participation, we gained insight on research participation patterns for future prospective research studies in CRC samples. We found that retirement is associated with patient survey adherence. This finding is consistent with the literature;[181] patients with more leisure time on hand may be more willing to participate in surveys than patients who are employed or

unemployed/disabled. Being classified as a minority (non-white and non-black) was associated with survey attrition. Although the reasons for this finding are unknown for the MY-Health study, a recent study on recruitment and retention strategies for minorities diagnosed with breast cancer suggests that barriers to participation may vary by race/ethinicity.[176]

There are a few omitted variables that would be beneficial to include in the models discussed in this study, without which it is more difficult to control for selection into the exercise. The dataset did not include information on self-efficacy, one of the most important predictors of exercise, though challenging to measure. We also did not have access to an indicator for exercise habits prior to CRC diagnosis. Prior exercise habits are indicative of current or future exercise habits. Another omitted variable is information on patients' physical activity, which is a much broader concept including any body movement that requires energy expenditure. Some patients may not exercise but engage in significant physical activity throughout the day. For example, some patients may walk to work or have a labor-intensive job that involves heavy lifting. Exercise may be more relevant to patients with higher socioeconomic status because exercise is a planned, structured activity that requires time outside of other daily tasks and may also cost money. By only including exercise in the model, we limit the conclusions and recommendations on exercise to patients above a certain socioeconomic threshold who have the means to exercise; some estimates may be biased because we are not including information on more general physical activity.

The exercise items presented some measurement limitations that introduce measurement error in the models. Duration of exercise was not captured and although the exercise items were not psychometrically evaluated. Further, there is evidence that patients overestimate or exaggerate self-reported exercise (social desirability),[182] also introducing bias into the models.

Although polysomnography is considered the gold standard for sleep assessment, as a lab-based measure, polysomnography is burdensome to track changes in sleep quality over time and it may not adequately characterize sleep disturbance during real-life situations out of the lab.[13] PROMIS Sleep Disturbance scale addresses this weakness because it is a short (six-item) questionnaire that assessed sleep quality during real-life situations outside of the lab.

As a community-based observational study, the MY-Health data provide information on experiences from a very diverse sample of patients who were evaluated during the course of usual care

without controlled interventions. Understanding the relationship between sleep disturbance and exercise in patients with CRC is a building block to developing controlled trials for treatment of sleep disturbance. This information can be used to design future randomized control trials aimed at mitigating sleep disturbance.

6.5 Conclusion

This research addresses exercise at a critical time of change in the cancer continuum for CRC patients, the transition to survivorship when patients' daily lives are less controlled by the negative impacts of treatment and they may have the capacity to increase exercise frequency or intensity. The results of this study suggest that as CRC patients transition off treatment, change in exercise levels are not closely tied to change in sleep disturbance from approximately 10 to 17 months after diagnosis, but that fatigue is associated with sleep disturbance. It is possible that this result is time-dependent; future studies should investigate the relationship between exercise and sleep disturbance during other time windows in the cancer continuum, especially before and during treatment when patients typically experience worse HRQOL. Knowledge of exercise duration or previous exercise habits may provide better understanding of the association between exercise and sleep disturbance in individuals diagnosed with CRC.

Table 6.1. Patient Characteristics at Month 10

Characteristic	*Month 10 (n = 348)*
Age at diagnosis	
Mean (SD), Median, Min - Max	63.4 (11.3), 65.0, 30-84
Sex	
Female	169 (48.6%)
BMI	
Mean (SD), Median, Min - Max	29.2 (7.4), 27.9, 17-71
Race and ethnicity	
Non-Hispanic White	177 (50.9%)
Non-Hispanic Black	63 (18.1%)
Other	108 (31.0%)
Employment status	
Working full time, part time or a student	131 (37.6%)
Retired	169 (48.6%)
Unemployed or disabled	48 (13.8%)
Living status	
Live with child(ren) under 18 years old	50 (14.4%)
Relevant comorbidities	
No comorbid conditions	140 (40.2%)
1 comorbid condition	92 (26.4%)
2 or more comorbid conditions	116 (33.3%)
Cancer stage	
Stage I	99 (28.4%)
Stage II	113 (32.5%)
Stage III	136 (39.1%)
Level of exercise activity	
Not active	75 (21.6%)
Slightly active	61 (17.5%)
Moderately active	160 (46.0%)
Highly active	52 (14.9%)
Months Since Chemotherapy	
0 = never	154 (45.8%)
1 = current	72 (21.4%)
2 = 1-2 months	65 (19.3%)
3 = > 2 months	45 (13.4%)
Months Since Surgery	
0 = never	21 (6.5%)
1 = 0-4 months	28 (8.7%)
2 = more than 4 months	272 (84.7%)
Radiation	
Ever received radiation	58 (17.0%)
Months since diagnosis at data collection	
Mean (SD), Median, Min - Max	9.5 (1.3), 9.4, 6-15
PROMIS Sleep Disturbance	
Mean (SD), Median, Min - Max	49.5 (9.7), 50.2, 30-75
PROMIS Anxiety	
Mean (SD), Median, Min - Max	47.6 (10.2), 47.4, 36-84
PROMIS Depression	
Mean (SD), Median, Min - Max	46.6 (9.7), 45.2, 36-72
PROMIS Fatigue	
Mean (SD), Median, Min - Max	51.2 (10.2), 51.4, 29-78
PROMIS Pain Interference	
Mean (SD), Median, Min - Max	51.9 (10.8), 52.5, 40-79

Characteristic	*Month 10 (n = 348)*
PROMIS Physical Functioning	
Mean (SD), Median, Min - Max	45.1 (8.8), 44.7, 21-62
PROMIS Ability to Participate in Social Roles and Activities	
Mean (SD), Median, Min - Max	50.6 (9.8), 50.1, 25-66
FACT-G Physical Well-being Nausea Item	
Mean (SD), Median, Min - Max	0.5 (0.9), 0.0, 0-4

BMI = body mass index, FACT-G = Functional Assessment of Cancer Therapy-General, max = maximum; min = minimum; PROMIS = Patient-Reported Outcomes Measurement Information System, SD = standard deviation;
Note: Percent calculated out of non-missing responses.

Table 6.2. Descriptive Statistics for Variables Collected at Month 17 or Describing Change

Characteristic	*n = 348*
Change in exercise activity (Month 17 – Month 10)[a]	
Less active by 2 or 3 exercise categories	18 (5.2%)
Less active by 1 exercise category	44 (12.6%)
No change	182 (52.3%)
Persistently not active or slightly active[a]	49 (14.1%)
Persistently moderately or highly active[a]	133 (38.2%)
More active by 1 exercise category	68 (19.5%)
More active by 2 or 3 exercise categories	36 (10.3%)
Months between chemotherapy and Month 17 data collection	
0 = never	149 (42.8%)
1 = current	15 (4.3%)
2 = 1-2 months	15 (4.3%)
3 = > 2 months	169 (48.6%)
Months between surgery and Month 17 data collection	
0 = never	29 (8.3%)
1 = 0-4 months	25 (7.2%)
2 = more than 4 months	294 (84.5%)
Months since diagnosis at Month 17 data collection	
Mean (SD), Median, Min - Max	17.3 (2.0), 17.0, 13-26
Change in PROMIS Sleep Disturbance (Month 17 - Month 10) [a]	
Mean (SD), Median, Min - Max	0.0 (7.1), 0.0, -25-19
Change in PROMIS Anxiety (Month 17 - Month 10)	
Mean (SD), Median, Min - Max	0.4 (8.8), 0.0, -26-28
Change in PROMIS Depression (Month 17 - Month 10)	
Mean (SD), Median, Min - Max	0.6 (8.4), 0.0, -23-29
Change in PROMIS Fatigue (Month 17 - Month 10)	
Mean (SD), Median, Min - Max	-1.6 (8.2), -1.2, -24-24
Change in PROMIS Pain Interference (Month 17 - Month 10)	
Mean (SD), Median, Min - Max	-1.8 (9.1), 0.0, -38-25
Change in PROMIS Physical Functioning (Month 17 - Month 10)	
Mean (SD), Median, Min - Max	1.2 (6.1), 0.2, -22-24
Change in PROMIS Ability to Participate in Social Roles and Activities (Month 17 - Month 10)	
Mean (SD), Median, Min - Max	1.6 (8.4), 0.7, -23-26
Change in FACT-G Physical Well-being Nausea Item (Month 17 - Month 10)	
Mean (SD), Median, Min - Max	-0.2 (0.9), 0.0, -4-3

BMI = body mass index, FACT-G = Functional Assessment of Cancer Therapy-General, max = maximum; min = minimum; PROMIS = Patient-Reported Outcomes Measurement Information System, SD = standard deviation;
Note: Percent calculated out of non-missing responses.
[a] Subset of the "No change" category.
[b] Change in PROMIS Sleep Disturbance from Month 10 to Month 17 was the dependent variable of interest. PROMIS Sleep Disturbance at Month 10 was also entered in the model (see Table 1 for descriptive statistics).

Table 6.3. Mean Change in PROMIS Sleep Disturbance by Change in Exercise Categories (n = 348)

		Change in PROMIS Sleep Disturbance				
Change in Exercise Categories	*N*	*Mean*	*SD*	*Median*	*Minimum*	*Maximum*
Less active by 2 or 3 exercise categories	18	2.61	8.09	2.0	-14.8	19.2
Less active by 1 exercise category	44	0.04	7.97	1.4	-20.0	12.6
No change	182	0.15	7.18	0.0	-25.0	19.0
Persistently not active or slightly active[a]	49	-0.7	6.9	0.0	-21.7	15.8
Persistently moderately or highly active[a]	133	0.5	7.3	0.0	-25.0	19.0
More active by 1 exercise category	68	-0.57	6.77	0.0	-22.3	14.2
More active by 2 or 3 exercise categories	36	-0.96	5.49	0.0	-10.8	9.8

PROMIS = Patient-Reported Outcomes Measurement Information System, SD = standard deviation.
[a] Subset of the “No change” category.

Table 6.4. Multiple Regression Results: Relationship between Change in PROMIS Sleep Disturbance and Change in Exercise (n = 348)

Effect	*Categories*	*Estimate*	*Standard Error*	*Z*	*P value*
Intercept		7.488	5.06	1.48	0.1390
Exercise group change (Month 17 - Month 10)	Less active by 1 exercise category	0.365	1.08	0.34	0.7355
	Less active by 2 or 3 exercise categories	2.579	1.57	1.64	0.1006
	More active by 1 exercise category	-0.024	0.91	-0.03	0.9791
	More active by 2 or 3 exercise categories	0.318	1.20	0.26	0.7913
	No change	ref	-	-	-
Months between chemotherapy and Month 17 data collection	1 = current	1.502	1.72	0.87	0.3823
	2 = 1-2 months	0.515	1.76	0.29	0.7694
	3 = > 2 months	0.151	0.76	0.20	0.8422
	0 = never	ref	-	-	-
Months between surgery and Month 17 data collection	1 = 0-4 months	-2.570	1.77	-1.45	0.1458
	2 = more than 4 months	-0.451	1.25	-0.36	0.7185
	0 = never	ref	-	-	-
Race (Collected at Month 10)	Black	-0.421	0.90	-0.47	0.6418
	Other or multiple	-0.292	0.89	-0.33	0.7438
	White	ref	-	-	-
Number of relevant comorbidities at Month 10	1 comorbid condition	0.915	0.89	1.03	0.3046
	2 or more comorbid conditions	-0.258	0.85	-0.30	0.7610
	No comorbid conditions	ref	-	-	-
Sex (Collected via SEER)	Female	-0.073	0.69	-0.11	0.9147
	Male	ref	-	-	-
Live with child under 18 years old at Month 10	Checked	-0.383	1.09	-0.35	0.7247
	Unchecked	ref	-	-	-
Employment at Month 10	Retired	-1.297	0.95	-1.37	0.1710
	Unemployed or disabled	-0.636	1.11	-0.58	0.5651
	Work	ref	-	-	-
Months between diagnosis and Month 17 data collection		0.124	0.17	0.73	0.4681
Age at diagnosis (years) (Collected via SEER)		0.012	0.05	0.26	0.7931
BMI (Collected at Month 10)		0.070	0.05	1.46	0.1451
PROMIS Sleep Disturbance at Month 10		-0.225	0.04	-6.01	<.0001
PROMIS Anxiety change (Month 17 - Month 10)		0.091	0.06	1.63	0.1034
PROMIS Depression change (Month 17 - Month 10)		0.055	0.06	0.98	0.3267
PROMIS Fatigue change (Month 17 - Month 10)		0.152	0.05	2.87	0.0042
PROMIS Pain Interference change (Month 17 - Month 10)		-0.007	0.04	-0.16	0.8740
PROMIS Physical Functioning (Month 17 - Month 10)		0.006	0.07	0.09	0.9287
PROMIS Social Roles and Activities (Month 17 - Month 10)		-0.083	0.06	-1.51	0.1322
FACT-G Physical Well-being Nausea Item change (Month 17 - Month 10)		0.065	0.39	0.17	0.8688
Variance		37.481	2.84	_	_

BMI = body mass index, FACT-G = Functional Assessment of Cancer Therapy-General, PROMIS = Patient-Reported Outcomes Measurement Information System.

Supplemental Table 6.1. Regression Mixture Model: Two-Class Solution (n = 348)

Effect	*Categories*	*Estimate*	*Standard Error*	*Z*	*P value*
CLASS 1					
Intercept		11.934	4.42	2.70	0.0069
Exercise group change (Month 17 - Month 10)	Less active by 1 exercise category	1.310	0.93	1.40	0.1601
	Less active by 2 or 3 exercise categories	2.741	1.37	2.00	0.0459
	More active by 1 exercise category	0.526	0.78	0.68	0.4985
	More active by 2 or 3 exercise categories	0.611	1.03	0.59	0.5538
	No change	ref	-	-	-
Months between chemotherapy and Month 17 data collection	1 = current	1.990	1.58	1.26	0.2089
	2 = 1-2 months	0.126	1.49	0.08	0.9324
	3 = > 2 months	1.226	0.65	1.89	0.0588
	0 = never	ref	-	-	-
Months between surgery and Month 17 data collection	1 = 0-4 months	-4.562	1.50	-3.05	0.0023
	2 = more than 4 months	-0.885	1.09	-0.82	0.4147
	0 = never	ref	-	-	-
Race (Collected at Month 10)	Black	0.235	0.79	0.30	0.7675
	Other or multiple	-0.098	0.76	-0.13	0.8974
	White	ref	-	-	-
Number of relevant comorbidities at Month 10	1 comorbid condition	0.707	0.77	0.92	0.3564
	2 or more comorbid conditions	0.024	0.75	0.03	0.9742
	No comorbid conditions	ref	-	-	-
Sex (Collected via SEER)	Female	-0.351	0.59	-0.59	0.5525
	Male	ref	-	-	-
Live with child under 18 years old at Month 10	Checked	-0.322	0.93	-0.34	0.7303
	Unchecked	ref	-	-	-
Employment at Month 10	Retired	-1.599	0.83	-1.92	0.0553
	Unemployed or disabled	-0.487	0.96	-0.50	0.6140
	Work	ref	-	-	-
Months between diagnosis and Month 17 data collection		-0.025	0.15	-0.17	0.8664
Age at diagnosis (years) (Collected via SEER)		-0.011	0.04	-0.28	0.7805
BMI (Collected at Month 10)		0.052	0.04	1.29	0.1960
PROMIS Sleep Disturbance at Month 10		-0.212	0.03	-6.43	<.0001
PROMIS Anxiety change (Month 17 - Month 10)		0.032	0.05	0.68	0.4957
PROMIS Depression change (Month 17 - Month 10)		0.119	0.05	2.55	0.0109
PROMIS Fatigue change (Month 17 - Month 10)		0.147	0.05	3.22	0.0013
PROMIS Pain Interference change (Month 17 - Month 10)		0.057	0.04	1.56	0.1187
PROMIS Physical Functioning (Month 17 - Month 10)		0.041	0.06	0.66	0.5065
PROMIS Social Roles and Activities (Month 17 - Month 10)		-0.068	0.05	-1.40	0.1616

Effect	*Categories*	*Estimate*	*Standard Error*	*Z*	*P value*
FACT-G Physical Well-being Nausea Item change (Month 17 - Month 10)		0.125	0.33	0.38	0.7042
CLASS 2					
Intercept		-9.666	0.08	-124.50	<.0001
Exercise group change (Month 17 - Month 10)	Less active by 1 exercise category	-2.479	0.02	-160.19	<.0001
	Less active by 2 or 3 exercise categories	-2.798	0.03	-84.37	<.0001
	More active by 1 exercise category	-3.229	0.01	-255.15	<.0001
	More active by 2 or 3 exercise categories	-4.383	0.02	-188.91	<.0001
	No change	ref	-	-	-
Months between chemotherapy and Month 17 data collection	1 = current	-6.736	0.02	-323.86	<.0001
	2 = 1-2 months	11.958	0.03	389.64	<.0001
	3 = > 2 months	-11.591	0.01	-954.33	<.0001
	0 = never	ref	-	-	-
Months between surgery and Month 17 data collection	1 = 0-4 months	23.975	0.04	674.37	<.0001
	2 = more than 4 months	0.450	0.02	19.58	<.0001
	0 = never	ref	-	-	-
Race (Collected at Month 10)	Black	2.852	0.01	222.71	<.0001
	Other or multiple	-12.519	0.02	-614.23	<.0001
	White	ref	-	-	-
Number of relevant comorbidities at Month 10	1 comorbid condition	1.306	0.02	62.23	<.0001
	2 or more comorbid conditions	0.442	0.01	30.55	<.0001
	No comorbid conditions	ref	-	-	-
Sex (Collected via SEER)	Female	0.819	0.02	53.70	<.0001
	Male	ref	-	-	-
Live with child under 18 years old at Month 10	Checked	1.563	0.02	78.12	<.0001
	Unchecked	ref	-	-	-
Employment at Month 10	Retired	1.340	0.01	144.91	<.0001
	Unemployed or disabled	-0.324	0.02	-20.74	<.0001
	Work	ref	-	-	-
Months between diagnosis and Month 17 data collection		1.544	0.00	789.55	<.0001
Age at diagnosis (years) (Collected via SEER)		0.173	0.00	290.80	<.0001
BMI (Collected at Month 10)		-0.387	0.00	-373.38	<.0001
PROMIS Sleep Disturbance at Month 10		-0.319	0.00	-587.71	<.0001
PROMIS Anxiety change (Month 17 - Month 10)		0.923	0.00	786.40	<.0001
PROMIS Depression change (Month 17 - Month 10)		-1.284	0.00	-779.49	<.0001
PROMIS Fatigue change (Month 17 - Month 10)		-0.470	0.00	-624.54	<.0001
PROMIS Pain Interference change (Month 17 - Month 10)		-0.115	0.00	-251.80	<.0001
PROMIS Physical Functioning (Month 17 - Month 10)		-0.341	0.00	-550.93	<.0001
PROMIS Social Roles and Activities (Month 17 - Month 10)		-0.167	0.00	-282.60	<.0001

Effect	*Categories*	*Estimate*	*Standard Error*	*Z*	*P value*
FACT-G Physical Well-being		1.223	0.01	131.89	<.0001
Nausea Item change (Month 17 - Month 10)					
Variance Class 1		24.858	1.98	_	_
Variance Class 2		0.000293	0.000072	_	_

BMI = body mass index, FACT-G = Functional Assessment of Cancer Therapy-General, PROMIS = Patient-Reported Outcomes Measurement Information System.

Supplemental Table 6.2. Multiple Regression Results: Sensitivity Analysis for Six Exercise Categories Assessing the Relationship Between Sleep Disturbance and Exercise Change/Persistence (n = 349)

Effect	*Categories*	*Estimate*	*Standard Error*	*Z*	*P value*
Intercept		7.651	5.16	1.48	0.1383
Exercise group change (Month 17 - Month 10)	Less active by 1 exercise category	0.048	1.34	0.04	0.9713
	Less active by 2 or 3 exercise categories	2.269	1.76	1.29	0.1976
	More active by 1 exercise category	-0.284	1.20	-0.24	0.8130
	More active by 2 or 3 exercise categories	0.425	1.43	0.30	0.7655
	No change, moderately/highly active	-0.390	1.08	-0.36	0.7186
	No change, not/slightly active	ref	-	-	-
Months between chemotherapy and Month 17 data collection	1 = current	1.383	1.73	0.80	0.4229
	2 = 1-2 months	0.398	1.76	0.23	0.8214
	3 = > 2 months	-0.015	0.76	-0.02	0.9846
	0 = never	ref	-	-	-
Months between surgery and Month 17 data collection	1 = 0-4 months	-2.512	1.78	-1.41	0.1576
	2 = more than 4 months	-0.402	1.26	-0.32	0.7497
	0 = never	ref	-	-	-
Race (Collected at Month 10)	Black	-0.300	0.91	-0.33	0.7431
	Other or multiple	-0.322	0.90	-0.36	0.7195
	White	ref	-	-	-
Number of relevant comorbidities at Month 10	1 comorbid condition	0.930	0.90	1.04	0.2997
	2 or more comorbid conditions	-0.208	0.86	-0.24	0.8091
	No comorbid conditions	ref	-	-	-
Sex (Collected via SEER)	Female	-0.150	0.69	-0.22	0.8272
	Male	ref	-	-	-
Live with child under 18 years old at Month 10	Checked	-0.504	1.09	-0.46	0.6446
	Unchecked	ref	-	-	-
Employment at Month 10	Retired	-1.150	0.95	-1.21	0.2260
	Unemployed or disabled	-0.682	1.11	-0.61	0.5389
	Work full time, part time or student	ref	-	-	-
Months between diagnosis and Month 17 data collection		0.154	0.17	0.89	0.3725
Age at diagnosis (years) (Collected via SEER)		0.006	0.05	0.12	0.9041
BMI (Collected at Month 10)		0.059	0.05	1.22	0.2227
PROMIS Sleep Disturbance at Month 10		-0.218	0.04	-5.82	<.0001
PROMIS Anxiety change (Month 17 - Month 10)		0.083	0.06	1.49	0.1370
PROMIS Depression change (Month 17 - Month 10)		0.060	0.06	1.06	0.2875
PROMIS Fatigue change (Month 17 - Month 10)		0.159	0.05	2.99	0.0028
PROMIS Pain Interference change (Month 17 - Month 10)		-0.008	0.04	-0.20	0.8385
PROMIS Physical Functioning (Month 17 - Month 10)		0.001	0.07	0.02	0.9828

Effect	*Categories*	*Estimate*	*Standard Error*	*Z*	*P value*
PROMIS Social Roles and Activities (Month 17 - Month 10)		-0.076	0.06	-1.36	0.1729
FACT-G Physical Well-being Nausea Item change (Month 17 - Month 10)		0.075	0.40	0.19	0.8504
Variance		37.798	2.86	_	_

BMI = body mass index, FACT-G = Functional Assessment of Cancer Therapy-General, PROMIS = Patient-Reported Outcomes Measurement Information System.

Supplemental Table 6.3. Participant Survey Attrition: Comparison of Month 10 Descriptive Statistics and Logistic Regression Results

Patient Characteristic	*Patients who participated at Month 10 but not in analysis (n = 386)*	*Patients who participated in Month 10 data collection and were included in analysis (n = 348)*	*Odds Ratio*	*95% Wald Confidence Limits*
Sex				
Female (compared to males)	212 (54.9%)	169 (48.6%)	0.830	0.611 - 1.128
Race				
Black	83 (21.5%)	66 (19.0%)	0.711	0.474 - 1.065
Other/multiple	123 (31.9%)	69 (19.8%)	0.527*	0.362 - 0.769
White	180 (46.6%)	213 (61.2%)	Ref	
Employment status				
Work	143 (39.3%)	131 (37.6%)	1.201	0.751 - 1.921
Retired	146 (40.1%)	169 (48.6%)	1.685*	1.072 - 2.648
Unemployed or disabled	75 (20.6%)	48 (13.8%)	Ref	
Survey Language				
English (compared to Spanish or Chinese)	338 (87.6%)	323 (92.8%)	1.495	0.866 - 2.582
Level of exercise activity				
Not active	111 (29.3%)	75 (21.6%)	Ref	
Slightly active	57 (15.0%)	61 (17.5%)	1.623	0.994 - 2.649
Moderately active	164 (43.3%)	160 (46.0%)	1.124	0.749 - 1.688
Highly active	47 (12.4%)	52 (14.9%)	1.199	0.685 - 2.099
PROMIS Sleep Disturbance				
Mean (SD), Median, Min - Max	51.4 (9.7), 52.6, 30-75	49.5 (9.7), 50.2, 30-75	0.996	0.978 - 1.014
PROMIS Physical Functioning				
Mean (SD), Median, Min - Max	43.4 (9.8), 42.4, 15-62	45.1 (8.8), 44.7, 21-62	1.012	0.991 - 1.033

BMI = body mass index, FACT-G = Functional Assessment of Cancer Therapy-General, PROMIS = Patient-Reported Outcomes Measurement Information System, Ref = reference category.
*p < 0.05.

CHAPTER 7. CONCLUSIONS

7.1 Summary of Findings

This dissertation represents the first attempt to evaluate sleep disturbance specifically in individuals diagnosed with stage I, II, and III CRC. Using data from the population-based MY-Health study, we examined sleep disturbance approximately 10 and 17 months after diagnosis. Overall, we sought to identify factors (patient, disease, and CRC treatment characteristics) associated with severity of sleep disturbance and to examine the relationship between sleep disturbance and exercise. We also sought to uncover possible heterogeneity in the relationships between sleep disturbance severity (and magnitude of change in sleep disturbance) and patient, disease, and treatment characteristics and exercise. Specific findings from each dissertation manuscript are summarized below.

The objective of Manuscript 1 (Chapter 4) was to identify patient, disease, and treatment characteristics associated with of sleep disturbance (and change in sleep disturbance) in individuals diagnosed with stage I, II, or III CRC. Specifically, we investigated whether there was heterogeneity in patient, disease, and treatment characteristics across severity of sleep disturbance, and then we identified correlates of sleep disturbance with a focus on chemotherapy. We evaluated these relationships with sleep disturbance at approximately 10 months after diagnosis, and then we looked at change in sleep disturbance from around 10 to 17 months after CRC diagnosis. We found that patient, disease, and treatment characteristics associated with sleep disturbance did not differ depending on the severity of sleep disturbance. In addition, the presence of 2 or more comorbid conditions, working patients (full-time, part-time, or students), anxiety, pain, and fatigue were correlates of poorer sleep disturbance in patients diagnosed with CRC regardless of how mild or severe sleep disturbance was 10 months after diagnosis. Patient, disease, and treatment characteristics did not vary by *magnitude* of change in sleep disturbance. Poorer sleepers at Month 10 reported greater improvement in sleep disturbance from Month 10 to Month 17, and worsening anxiety and fatigue were also indicators of worsening sleep disturbance over time. We hypothesized that current or recent chemotherapy would be associated with worse sleep outcomes

compared to no chemotherapy. The results of our analyses (non-statistically significant coefficients) did not support this hypothesis.

In Manuscript 2 (Chapter 5), we investigated whether the relationship between exercise and sleep disturbance differed by *severity* of sleep disturbance at approximately 10 and 17 months after CRC diagnosis. The second objective of Manuscript 2 was to evaluate the relationship between sleep disturbance and exercise at about 10 and 17 months post-diagnosis. It was hypothesized that patients whose exercise was categorized as moderately or highly active would experience less sleep disturbance than patients who did not exercise. We found that the relationship between sleep disturbance and exercise was consistent at any level of sleep disturbance severity (at about 10 and 17 months after diagnosis), meaning that no specific subgroup of patients with normal, mild, moderate or severe sleep disturbance (compared to healthy and non-healthy sleepers) emerged as being associated with any particular level of exercise (or lack of exercise). Further, we did not find evidence that more exercise was associated with better sleep quality at around 10 and 17 months after CRC diagnosis.

In Manuscript 3 (Chapter 6), we sought to uncover possible variability in the relationship between change in sleep and change in exercise and to evaluate the relationship between change in exercise and change in sleep disturbance. We found a weak (and non-statistically significant) relationship between change in sleep disturbance and change in exercise, and this relationship did not differ by *magnitude of change* of sleep disturbance from approximately 10 to 17 months after CRC diagnosis, meaning that no specific subgroup of patients with more improvement or more worsening in sleep disturbance emerged as being associated with any particular increase or decrease in exercise category (or lack of exercise).

7.2 Strengths and Limitations

The MY-Health study provided a large and demographically diverse sample of individuals diagnosed with CRC and included a fairly comprehensive set of HRQOL measures relevant to cancer (e.g., sleep disturbance, pain, anxiety, depression, fatigue). Although the MY-Health study was not representative of the SEER population, including higher proportions of younger and non-white participants, the study sample was uniquely diverse, providing context to results from studies with less-generalizable samples (e.g., women only,[119] non-U.S. sample[120]). The MY-Health study design also

allowed us to evaluate sleep disturbance at two important time points after CRC diagnosis, as patients were transitioning off treatment and when most patients were transitioning to survivorship.

The MY-Health study collected information on HRQOL using PROMIS measures, which were developed using rigorous qualitative and quantitative psychometric methods.[12,77,144,149] In particular, PROMIS Sleep Disturbance was the outcome variable in all primary dissertation analyses. In contrast to polysomnography, the gold-standard lab-based objective measure of sleep, PROMIS Sleep Disturbance, is a brief (less burdensome) measure of sleep quality from the patient perspective that tracks real-life sleep outside of the lab.[13]

The results of this study should be considered in light of some limitations:

Approximately 50% of patients were lost to follow-up from the Month 10 to Month 17 data collections. Minorities were more likely to not participate in the follow-up survey and retirees were more likely to participate in both study data collections. In Manuscript 2, more-active patients participated in the Month 17 data collection, though the only statistically significant difference was among the slightly active exercise group. When patient attrition is not completely at random or missing at random, parameter estimates may be biased.

Endogeneity is a complicating factor for observational studies investigating HRQOL. Anxiety, depression, pain, fatigue, and sleep disturbance are known to be closely related and effects could be bi-directional. For example, pain may cause sleep disturbance, but if sleep disturbance is severe, it could cause pain due to increased inflammation or inability of the body to heal with less sleep. Endogeneity limits the conclusions that can be drawn from regression analyses: regression coefficients represent *associations* between sleep disturbance and the independent variables; independent variables were not necessarily predictors of sleep disturbance.

Observational studies limit our ability to draw causal conclusions about the impact of exercise on sleep disturbance. However, a randomized study evaluating exercise as we did in Manuscripts 2 and 3 that compared exercise at or above ACSM recommendations to no exercise would be ethically infeasible because patients should not be denied the opportunity to exercise given its many benefits. Exercise is associated with clear cardiovascular and quality of life benefits,[136,138,137,139] and without exercise, patients are at higher risk for developing additional comorbid conditions (e.g., heart disease, type 2 diabetes).[183]

A common limitation of secondary data analysis is omitted variables, which may bias model estimates. We did not have information on self-efficacy, one of the most important predictors of exercise. Although difficult to measure, a measure of self-efficacy would be beneficial to include because it would increase our ability to control for selection into the exercise. We also did not have access to an indicator for exercise habits prior to CRC diagnosis. Prior exercise habits are indicative of current or future exercise habits and would be helpful in controlling for selection into exercise.

Although the exercise items provided information on frequency of exercise, they did not address duration of exercise. Duration is important because a 10-minute regimen could result in very different physiological effects than a 60-minute regimen. Another limitation of the exercise questions is that exercise intensity is subjectively assigned by the patients. In exercise physiology, exercise intensity is objectively quantified using validated measures. The exercise questions did not undergo psychometric evaluation; it is possible that one patient's definition of "vigorous" activity is different from another patient's definition. Or that (some) people have a tendency to overreport how much they exercise.[184]

Another omitted variable is information on patients' physical activity, which is a much broader concept including any body movement that requires energy expenditure. Some patients may not exercise but engage in significant physical activity throughout the day. For example, some patients may walk to work or have a labor-intensive job that involves heavy lifting. Exercise may be more relevant to patients with higher socioeconomic status because exercise is a planned, structured activity that requires time outside of other daily tasks and may also cost money. By only including exercise in the model, we limit the conclusions and recommendations on exercise to patients above a certain socioeconomic threshold who have the means to exercise; some estimates may be biased because we are not including information on more general physical activity.

7.3 Policy Implications and Future Directions

An unexpected finding from this dissertation was that CRC patients in our sample experienced sleep decrements at about the same severity level as the PROMIS referent group, which included community-based and clinical samples.[171] Previous literature suggested that sleep disturbance would be more severe in CRC patients than in the general population. In previously published literature, the prevalence of sleep disturbance or insomnia in the cancer population was estimated to be approximately

three times higher than the general population,[49] and results from an RCT estimated that half of individuals diagnosed with CRC experience decrements in sleep.[3] To put our results in context, a recent study by Leung et al.[168] provided a cut point on PROMIS Sleep Disturbance indicative of clinically significant sleep disturbance (area under the curve = 0.92; PROMIS Sleep Disturbance ≥ 57). Applying Leung's cut point to our data, approximately 24% and 21% of CRC patients in the sample were likely experiencing clinically significant sleep disturbance at Month 10 and Month 17, respectively. Average sleep disturbance was not alarmingly severe compared to a more general sample (general and clinical population), but put in context using the cut point for clinically significant sleep disturbance, 1 in 4 patients from our sample would likely have benefited from a sleep intervention at Month 10, suggesting that sleep disturbance is not just a problem in CRC but also a general public health problem. The trajectory of sleep disturbance severity is not known during much of the CRC cancer continuum. Future research should focus on other slices of time in the CRC continuum when sleep disturbance may be more severe, such as the first six months after diagnosis when patients are undergoing treatment.

Results of our analyses from Manuscript 1 show a link between sleep disturbance and other aspects of HRQOL such as anxiety, depression, fatigue, and pain. In the exercise-focused manuscripts (2 and 3), we continued to find a relationship between sleep disturbance and fatigue, underscoring the concordance between sleep and other aspects of HRQOL identified in other cancers.[106-108] Interestingly, the correlation coefficients on the HRQOL-related variables in our studies were small, suggesting that although there was a statistically significant relationship between sleep disturbance and other aspects of HRQOL, screening or treating clinically significant anxiety, depression, fatigue, or pain does not necessarily lead to identifying or improving sleep disturbance (and vice versa). Although sleep disturbance is prevalent in the cancer population, most individuals diagnosed with cancer do not have conversations with their clinicians about their sleep difficulties.[167] Together, these results suggest that screening for sleep disturbance is warranted, and the fluctuation in sleep disturbance severity from Month 10 to Month 17 provides evidence that sleep screening should occur throughout the cancer continuum, a recommendation mirrored in *Clinical Practice Guidelines in Oncology*:[185] "Survivors should be screened for possible sleep disorders at regular intervals, especially when they experience a change in clinical

status or treatment"[185] and in recent study of insomnia in cancer survivors, which called for systematic interventions to increase standardized screening for sleep disorders.[186]

We found that 40% of the study sample was likely not achieving ACSM exercise recommendations for exercise 10 months after diagnosis. Although the exercise questions presented some limitations, these results are consistent with previous studies showing that cancer survivors likely do not meet strength and aerobic guidelines.[187] Even though our studies did not identify a relationship between exercise and sleep disturbance, the clear cardiovascular and quality of life benefits[136,138,137,139] of exercise in the cancer population support the need for interventions to motivate patients to exercise.

A set of recommendations for designing clinical trials on exercise in the cancer population was published last year that stated, "It is also important to recruit patients to studies based on their need for improvement in the selected outcome, rather than the 'all comers' approach."[188] Our studies addressed this concern by evaluating possible heterogeneity among sleep disturbance and exercise, as well as heterogeneity among patient, disease, and treatment characteristics and sleep disturbance. We did not find evidence of subgroups of CRC patients whose sleep might benefit from exercise more than others. RMMs represent a powerful statistical tool for identifying heterogeneity, and future research should continue to employ this statistical tool to identify patients that may stand to benefit from a treatment more than others.

Although our studies did not find a relationship between exercise and sleep disturbance, our results suggest that for some patients, severity of sleep disturbance diminishes from 10 to 17 months after CRC diagnosis. Previous research by Courneya and colleagues shows fluctuations in exercise activity after diagnosis.[118] Future studies should evaluate the relationship between sleep disturbance and exercise at different time points in the CRC continuum. Exercise has many other benefits for physical and mental health, thus we do not recommend any policy associated with decreasing or not exercising.

This is the first study we are aware of that provides a threshold for meaningful differences between groups of patients on the PROMIS Sleep Disturbance scale. PRO thresholds are important for interpreting classes derived from RMMs as well as treatment effects in future randomized studies. In lieu of anchor-based thresholds, we calculated a preliminary distribution-based threshold (half standard deviation at Month 10) to provide context on group differences. The threshold derived from this

dissertation should be reevaluated using other methods (including additional distribution-based methods and, more important, methods including the patient perspective), in other CRC samples (especially in patients with stage IV disease because they were not included in this dissertation), and during other time points during the cancer continuum.

In conclusion, this dissertation provides important information on two policy-related issues. First, CRC patients should be screened for sleep disturbance throughout the cancer continuum because sleep disturbance is a general public health problem and no strong patient, CRC, or CRC-related treatment factors could be used to identify possible sleep disturbance in the clinic. Second, exercise has clear health benefits and although this study does not provide evidence that exercise is associated with better sleep quality, CRC patients should continue to be encouraged to exercise.

REFERENCES

1. Palesh OG, Roscoe JA, Mustian KM, et al: Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center-Community Clinical Oncology Program. J Clin Oncol 28:292-8, 2010

2. Palesh O, Peppone L, Innominato PF, et al: Prevalence, putative mechanisms, and current management of sleep problems during chemotherapy for cancer. Nat Sci Sleep 4:151-162, 2012

3. Innominato PF, Spiegel D, Ulusakarya A, et al: Subjective sleep and overall survival in chemotherapy-naïve patients with metastatic colorectal cancer. Sleep Med 16:391-8, 2015

4. Centers for Disease Control and Prevention: Colorectal Cancer Statistics, https://www.cdc.gov/cancer/colorectal/statistics/. Accessed February 10, 2016.

5. National Cancer Institute: SEER Stat Fact Sheets: Colon and Rectum Cancer, http://seer.cancer.gov/statfacts/html/colorect.html. Accessed January 15, 2016

6. LeMasters T, Madhavan S, Sambamoorthi U, et al: A population-based study comparing HRQoL among breast, prostate, and colorectal cancer survivors to propensity score matched controls, by cancer type, and gender. Psychooncology 22:2270-82, 2013

7. Wilson TR, Birks YF, Alexander DJ: A qualitative study of patient perspectives of health-related quality of life in colorectal cancer: comparison with disease-specific evaluation tools. Colorectal Dis 12:762-9, 2010

8. Dunn J, Lynch B, Rinaldis M, et al: Dimensions of quality of life and psychosocial variables most salient to colorectal cancer patients. Psychooncology 15:20-30, 2006

9. Winkelman JW: CLINICAL PRACTICE. Insomnia Disorder. N Engl J Med 373:1437-44, 2015

10. Mota DD, Pimenta CA, Caponero R: Fatigue in colorectal cancer patients: prevalence and associated factors. Rev Lat Am Enfermagem 20:495-503, 2012

11. Roscoe JA, Kaufman ME, Matteson-Rusby SE, et al: Cancer-related fatigue and sleep disorders. Oncologist 12 Suppl 1:35-42, 2007

12. Flynn KE, Shelby RA, Mitchell SA, et al: Sleep-wake functioning along the cancer continuum: focus group results from the Patient-Reported Outcomes Measurement Information System (PROMIS((R))). Psychooncology 19:1086-93, 2010

13. Irwin MR: Why sleep is important for health: a psychoneuroimmunology perspective. Annu Rev Psychol 66:143-72, 2015

14. Manocchia M, Keller S, Ware JE: Sleep problems, health-related quality of life, work functioning and health care utilization among the chronically ill. Qual Life Res 10:331-45, 2001

15. American Cancer Society: Colorectal Cancer Facts & Figures 2014-2016, http://www.cancer.org/acs/groups/content/documents/document/acspc-042280.pdf Accessed September 13, 2016

16. Liu L, Rissling M, Natarajan L, et al: The longitudinal relationship between fatigue and sleep in breast cancer patients undergoing chemotherapy. Sleep 35:237-45, 2012

17. Sanford SD, Wagner LI, Beaumont JL, et al: Longitudinal prospective assessment of sleep quality: before, during, and after adjuvant chemotherapy for breast cancer. Support Care Cancer 21:959-67, 2013

18. Bezjak A, Tu D, Bacon M, et al: Quality of life in ovarian cancer patients: comparison of paclitaxel plus cisplatin, with cyclophosphamide plus cisplatin in a randomized study. J Clin Oncol 22:4595-603, 2004

19. Savard J, Liu L, Natarajan L, et al: Breast cancer patients have progressively impaired sleep-wake activity rhythms during chemotherapy. Sleep 32:1155-60, 2009

20. Arndt V, Merx H, Stegmaier C, et al: Quality of life in patients with colorectal cancer 1 year after diagnosis compared with the general population: a population-based study. J Clin Oncol 22:4829-36, 2004

21. Savard J, Savard M-H, Ancoli-Israel S: in Kryger M, Roth T, Dement W, et al (eds): *Principles and practice of sleep medicine* (ed Sixth). Philadelphia, PA, Elsevier, 2017

22. Ancoli-Israel S, Liu L, Rissling M, et al: Sleep, fatigue, depression, and circadian activity rhythms in women with breast cancer before and after treatment: a 1-year longitudinal study. Support Care Cancer 22:2535-45, 2014

23. King AC, Oman RF, Brassington GS, et al: Moderate-intensity exercise and self-rated quality of sleep in older adults. A randomized controlled trial. JAMA 277:32-7, 1997

24. Schmitz KH, Courneya KS, Matthews C, et al: American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 42:1409-26, 2010

25. Reeve BB, Mitchell SA, Dueck AC, et al: Recommended patient-reported core set of symptoms to measure in adult cancer treatment trials. J Natl Cancer Inst 106, 2014

26. Howell D, Fitch M, Bakker D, et al: Core domains for a person-focused outcome measurement system in cancer (PROMS-Cancer Core) for routine care: a scoping review and Canadian Delphi Consensus. Value Health 16:76-87, 2013

27. Centers for Disease Control and Prevention: CDC - What Is Colorectal Cancer?, http://www.cdc.gov/cancer/colorectal/basic_info/what-is-colorectal-cancer.htm Accessed 2016.

28. United States Census Bureau: Population estimates, July 1, 2014, (V2014), www.census.gov/quickfacts/map/PST045214/44 Accessed 2016.

29. American Cancer Society: Key Statistics for Colorectal Cancer, https://www.cancer.org/cancer/colon-rectal-cancer/about/key-statistics.html Accessed February 3, 2017.

30. Centers for Disease Control and Prevention: CDC - What Are the Risk Factors for Colorectal Cancer?, http://www.cdc.gov/cancer/colorectal/basic_info/risk_factors.htm Accessed 2016.

31. American Cancer Society: Colorectal cancer risk factors, http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-risk-factors Accessed 2016.

32. Schernhammer ES, Laden F, Speizer FE, et al: Night-shift work and risk of colorectal cancer in the nurses' health study. J Natl Cancer Inst 95:825-8, 2003

33. American Cancer Society: What is colorectal cancer?, http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-what-is-colorectal-cancer Accessed 2016.

34. Centers for Disease Control and Prevention: CDC - What Are the Symptoms of Colorectal Cancer?, http://www.cdc.gov/cancer/colorectal/basic_info/symptoms.htm Accessed 2016.

35. United States Preventitive Services Task Force: Final Update Summary: Colorectal Cancer: Screening - US Preventive Services Task Force, http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/colorectal-cancer-screening Accessed 2016.

36. Centers for Disease Control and Prevention: CDC - What Should I Know About Screening for Colorectal Cancer?, http://www.cdc.gov/cancer/colorectal/basic_info/screening/index.htm Accessed 2016.

37. Centers for Disease Control and Prevention: Colorectal Cancer Screening Basic Fact Sheet, http://www.cdc.gov/cancer/colorectal/pdf/Basic_FS_Eng_Color.pdf Accessed 2016.

38. American Cancer Society: Colorectal Cancer Prevention and Early Detection, http://www.cancer.org/cancer/colonandrectumcancer/moreinformation/colonandrectumcancerearlydetection/colorectal-cancer-early-detection-acs-recommendations Accessed June 24, 2016.

39. American Cancer Society: Colorectal Cancer Facts & Figures 2014-2016, 2016

40. Siegel R, Desantis C, Jemal A: Colorectal cancer statistics, 2014. CA Cancer J Clin 64:104-17, 2014

41. American Cancer Society: Colorectal cancer stages. http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-staged Accessed 2016.

42. American Cancer Society: Treatment of colon cancer, by stage. http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-treating-by-stage-colon Accessed 2016.

43. American Cancer Society: Treatment of rectal cancer, by stage. http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-treating-by-stage-rectum Accessed 2016.

44. American Cancer Society: What are the survival rates for colorectal cancer, by stage? http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-survival-rates Accessed 2016.

45. Quach C, Sanoff HK, Williams GR, et al: Impact of colorectal cancer diagnosis and treatment on health-related quality of life among older Americans: a population-based, case-control study. Cancer 121:943-50, 2015

46. Baker F, Haffer SC, Denniston M: Health-related quality of life of cancer and noncancer patients in Medicare managed care. Cancer 97:674-81, 2003

47. Maguire R, Hanly P, Hyland P, et al: Understanding burden in caregivers of colorectal cancer survivors: what role do patient and caregiver factors play? Eur J Cancer Care (Engl), 2016

48. Hanly P, Maguire R, Hyland P, et al: Examining the role of subjective and objective burden in carer health-related quality of life: the case of colorectal cancer. Support Care Cancer 23:1941-9, 2015

49. Irwin MR: Depression and insomnia in cancer: prevalence, risk factors, and effects on cancer outcomes. Curr Psychiatry Rep 15:404, 2013

50. Otte JL, Carpenter JS, Manchanda S, et al: Systematic review of sleep disorders in cancer patients: can the prevalence of sleep disorders be ascertained? Cancer Med 4:183-200, 2015

51. Savard J, Ivers H, Savard MH, et al: Cancer treatments and their side effects are associated with aggravation of insomnia: Results of a longitudinal study. Cancer 121:1703-11, 2015

52. Jansen F, van Uden-Kraan CF, Braakman JA, et al: A mixed-method study on the generic and ostomy-specific quality of life of cancer and non-cancer ostomy patients. Support Care Cancer 23:1689-97, 2015

53. Sanoff HK, Morris W, Mitcheltree AL, et al: Lack of Support and Information Regarding Long-Term Negative Effects in Survivors of Rectal Cancer. Clin J Oncol Nurs 19:444-8, 2015

54. Jansen L, Koch L, Brenner H, et al: Quality of life among long-term (>/=5 years) colorectal cancer survivors--systematic review. Eur J Cancer 46:2879-88, 2010

55. Foster C, Haviland J, Winter J, et al: Pre-Surgery Depression and Confidence to Manage Problems Predict Recovery Trajectories of Health and Wellbeing in the First Two Years following Colorectal Cancer: Results from the CREW Cohort Study. PLoS One 11:e0155434, 2016

56. Scarpa M, Di Cristofaro L, Cortinovis M, et al: Minimally invasive surgery for colorectal cancer: quality of life and satisfaction with care in elderly patients. Surg Endosc 27:2911-20, 2013

57. National Cancer Institute: FDA Approval for Oxaliplatin - National Cancer Institute, 2016

58. Tofthagen C, Donovan KA, Morgan MA, et al: Oxaliplatin-induced peripheral neuropathy's effects on health-related quality of life of colorectal cancer survivors. Support Care Cancer 21:3307-13, 2013

59. Tsunoda A, Nakao K, Tsunoda Y, et al: Health-related quality of life of colorectal cancer patients receiving oral UFT plus leucovorin compared with those with surgery alone. Int J Clin Oncol 15:153-60, 2010

60. Chau I, Norman AR, Cunningham D, et al: Longitudinal quality of life and quality adjusted survival in a randomised controlled trial comparing six months of bolus fluorouracil/leucovorin vs. twelve weeks of protracted venous infusion fluorouracil as adjuvant chemotherapy for colorectal cancer. Eur J Cancer 41:1551-9, 2005

61. Brant JM, Beck SL, Dudley WN, et al: Symptom trajectories during chemotherapy in outpatients with lung cancer colorectal cancer, or lymphoma. Eur J Oncol Nurs 15:470-7, 2011

62. Evans RG, Stoddart GL: Producing health, consuming health care. Soc Sci Med 31:1347-63, 1990

63. Evans RG, Stoddart GL: Consuming research, producing policy? Am J Public Health 93:371-9, 2003

64. Hennessy DA, Flanagan WM, Tanuseputro P, et al: The Population Health Model (POHEM): an overview of rationale, methods and applications. Popul Health Metr 13:24, 2015

65. Evans R: A retrospective on the "New Perspective". J Health Polit Policy Law 7:325-44, 1982

66. Wisk LE, Gangnon R, Vanness DJ, et al: Development of a novel, objective measure of health care-related financial burden for U.S. families with children. Health Serv Res 49:1852-74, 2014

67. Wong ES, Liu CF: The relationship between local area labor market conditions and the use of Veterans Affairs health services. Bmc Health Services Research 13, 2013

68. MacDonald SE, Newburn-Cook CV, Allen M, et al: Embracing the population health framework in nursing research. Nursing Inquiry 20:30-41, 2013

69. Thompson CW: Activity, exercise and the planning and design of outdoor spaces. Journal of Environmental Psychology 34:79-96, 2013

70. Berke EM, Vernez-Moudon A: Built environment change: a framework to support health-enhancing behaviour through environmental policy and health research. Journal of Epidemiology and Community Health 68:586-590, 2014

71. Statistics BoL: American Time Use Survey: Charts by Topic: Sleep, 2016

72. Colten HR, Altevogt BM, Institute of Medicine (U.S.). Committee on Sleep Medicine and Research.: Sleep disorders and sleep deprivation : an unmet public health problem. Washington, DC, Institute of Medicine : National Academies Press, 2006

73. Bliwise D, Scullin M: Normal Aging, in Kryger M, Roth T, Dement WC, et al (eds): Principles and practice of sleep medicine (ed Sixth). Philadelphia, PA, Elsevier, 2017

74. American Academy of Sleep Medicine: International Classification of Sleep Disorders – Third Edition (ICSD-3) (ed 3rd edition). Darien, IL, American Academy of SLeep Medicine, 2014

75. Sateia MJ, Thorpy MJ: Classification of Sleep Disorders, Principles and Practice of Sleep Medicine, 2017, pp 618-626

76. Harris B, Ross J, Sanchez-Reilly S: Sleeping in the arms of cancer: a review of sleeping disorders among patients with cancer. Cancer J 20:299-305, 2014

77. National Institutes of Health: PROMIS Methodology, http://www.nihpromis.org/science/methodology Accessed December 4, 2015.

78. PROMIS: Domain Frameworks: PROMIS Adult Self-Reported Health, http://www.nihpromis.org/measures/domainframework1#sri Accessed November 14, 2015

79. Twomey F, O'Brien T, O'Reilly M, et al: An Observational Research Study to Evaluate the Impact of Breakthrough Cancer Pain on the Daily Lives and Functional Status of Patients. Ir Med J 108:174-6, 2015

80. Beck SL, Dudley WN, Barsevick A: Pain, sleep disturbance, and fatigue in patients with cancer: using a mediation model to test a symptom cluster, Oncol Nurs Forum, 2005, pp 542

81. Cheng KK, Lee DT: Effects of pain, fatigue, insomnia, and mood disturbance on functional status and quality of life of elderly patients with cancer. Crit Rev Oncol Hematol 78:127-37, 2011

82. Htoo A, Talwar A, Feinsilver SH, et al: Smoking and sleep disorders. Med Clin North Am 88:1575-91, xii, 2004

83. Filtness AJ, MacKenzie J, Armstrong K: Longitudinal change in sleep and daytime sleepiness in postpartum women. PLoS One 9:e103513, 2014

84. Strine TW, Chapman DP: Associations of frequent sleep insufficiency with health-related quality of life and health behaviors. Sleep Med 6:23-7, 2005

85. Aslan O, Sanisoglu Y, Akyol M, et al: Subjective sleep quality of cancer patients. J buon 15:708-14, 2010

86. Gellis LA, Lichstein KL, Scarinci IC, et al: Socioeconomic status and insomnia. J Abnorm Psychol 114:111-8, 2005

87. Lund HG, Reider BD, Whiting AB, et al: Sleep patterns and predictors of disturbed sleep in a large population of college students. J Adolesc Health 46:124-32, 2010

88. Smagula SF, Stone KL, Fabio A, et al: Risk factors for sleep disturbances in older adults: Evidence from prospective studies. Sleep Med Rev 25:21-30, 2016

89. LeBlanc M, Beaulieu-Bonneau S, Merette C, et al: Psychological and health-related quality of life factors associated with insomnia in a population-based sample. J Psychosom Res 63:157-66, 2007

90. Bardwell WA, Profant J, Casden DR, et al: The relative importance of specific risk factors for insomnia in women treated for early-stage breast cancer. Psychooncology 17:9-18, 2008

91. Savard J, Villa J, Ivers H, et al: Prevalence, natural course, and risk factors of insomnia comorbid with cancer over a 2-month period. J Clin Oncol 27:5233-9, 2009

92. Colagiuri B, Christensen S, Jensen AB, et al: Prevalence and predictors of sleep difficulty in a national cohort of women with primary breast cancer three to four months postsurgery. J Pain Symptom Manage 42:710-20, 2011

93. Mystakidou K, Parpa E, Tsilika E, et al: How is sleep quality affected by the psychological and symptom distress of advanced cancer patients? Palliat Med 23:46-53, 2009

94. Yennurajalingam S, Chisholm G, Palla SL, et al: Self-reported sleep disturbance in patients with advanced cancer: Frequency, intensity, and factors associated with response to outpatient supportive care consultation--A preliminary report. Palliat Support Care 13:135-43, 2015

95. Mercadante S, Girelli D, Casuccio A: Sleep disorders in advanced cancer patients: prevalence and factors associated. Support Care Cancer 12:355-9, 2004

96. McMillan SC, Tofthagen C, Morgan MA: Relationships among pain, sleep disturbances, and depressive symptoms in outpatients from a comprehensive cancer center. Oncol Nurs Forum 35:603-11, 2008

97. Palesh OG, Roscoe JA, Mustian KM, et al: Prevalence, Demographics, and Psychological Associations of Sleep Disruption in Patients With Cancer: University of Rochester Cancer Center–Community Clinical Oncology Program, J Clin Oncol, 2010, pp 292-8

98. Savard J, Savard M-H, Ancoli-Israel: *Principles and Practice of Sleep Medicine.* [electronic resource]. Philadelphia, PA, Elsevier, 2017

99. Alfano CM, Lichstein KL, Vander Wal GS, et al: Sleep duration change across breast cancer survivorship: associations with symptoms and health-related quality of life. Breast Cancer Res Treat 130:243-54, 2011

100. Kozachik SL, Bandeen-Roche K: Predictors of patterns of pain, fatigue, and insomnia during the first year after a cancer diagnosis in the elderly. Cancer Nurs 31:334-44, 2008

101. Van Onselen C, Paul SM, Lee K, et al: Trajectories of sleep disturbance and daytime sleepiness in women before and after surgery for breast cancer. J Pain Symptom Manage 45:244-60, 2013

102. Fan G, Filipczak L, Chow E: Symptom clusters in cancer patients: a review of the literature. Curr Oncol 14:173-9, 2007

103. Portenoy RK, Thaler HT, Kornblith AB, et al: Symptom prevalence, characteristics and distress in a cancer population. Qual Life Res 3:183-9, 1994

104. Dodd MJ, Miaskowski C, Paul SM: Symptom clusters and their effect on the functional status of patients with cancer, Oncology nursing forum, 2001, pp 465-470

105. Ferrans CE, Zerwic JJ, Wilbur JE, et al: Conceptual model of health-related quality of life. J Nurs Scholarsh 37:336-42, 2005

106. Sanford SD, Beaumont JL, Butt Z, et al: Prospective longitudinal evaluation of a symptom cluster in breast cancer. J Pain Symptom Manage 47:721-30, 2014

107. Ho SY, Rohan KJ, Parent J, et al: A longitudinal study of depression, fatigue, and sleep disturbances as a symptom cluster in women with breast cancer. J Pain Symptom Manage 49:707-15, 2015

108. Lin S, Chen Y, Yang L, et al: Pain, fatigue, disturbed sleep and distress comprised a symptom cluster that related to quality of life and functional status of lung cancer surgery patients. J Clin Nurs 22:1281-90, 2013

109. Savard J, Morin CM: Insomnia in the context of cancer: a review of a neglected problem. J Clin Oncol 19:895-908, 2001

110. Palesh O, Aldridge-Gerry A, Zeitzer JM, et al: Actigraphy-measured sleep disruption as a predictor of survival among women with advanced breast cancer. Sleep 37:837-42, 2014

111. Rosekind MR, Gregory KB, Mallis MM, et al: The cost of poor sleep: workplace productivity loss and associated costs. J Occup Environ Med 52:91-8, 2010

112. Tran H, Lin C, Yu F, et al: A multicenter study on the relative effectiveness of a 12-week physical training program for adults with an oncologic diagnosis. Support Care Cancer, 2016

113. Mishra SI, Scherer RW, Snyder C, et al: Exercise interventions on health-related quality of life for people with cancer during active treatment. Cochrane Database Syst Rev 8:Cd008465, 2012

114. Gopalakrishna A, Longo TA, Fantony JJ, et al: Lifestyle factors and health-related quality of life in bladder cancer survivors: a systematic review. J Cancer Surviv, 2016

115. Dennett AM, Peiris CL, Shields N, et al: Moderate-intensity exercise reduces fatigue and improves mobility in cancer survivors: a systematic review and meta-regression. J Physiother, 2016

116. Chang JJ, Pien GW, Stamatakis KA, et al: Association between physical activity and insomnia symptoms in rural communities of southeastern Missouri, Tennessee, and Arkansas. J Rural Health 29:239-47, 2013

117. Cheville AL, Kollasch J, Vandenberg J, et al: A home-based exercise program to improve function, fatigue, and sleep quality in patients with Stage IV lung and colorectal cancer: a randomized controlled trial. J Pain Symptom Manage 45:811-21, 2013

118. Courneya KS, Friedenreich CM: Relationship between exercise pattern across the cancer experience and current quality of life in colorectal cancer survivors. J Altern Complement Med 3:215-26, 1997

119. Cho MH, Dodd MJ, Cooper BA, et al: Comparisons of exercise dose and symptom severity between exercisers and nonexercisers in women during and after cancer treatment. J Pain Symptom Manage 43:842-54, 2012

120. Lin KY, Shun SC, Lai YH, et al: Comparison of the effects of a supervised exercise program and usual care in patients with colorectal cancer undergoing chemotherapy. Cancer Nurs 37:E21-9, 2014

121. Mishra SI, Scherer RW, Geigle PM, et al: Exercise interventions on health-related quality of life for cancer survivors. Cochrane Database Syst Rev 8:CD007566, 2012

122. Sylvia LG, Bernstein EE, Hubbard JL, et al: A Practical Guide to Measuring Physical Activity. J Acad Nutr Diet 114:199-208, 2014

123. Hardy LL, Hills AP, Timperio A, et al: A hitchhiker's guide to assessing sedentary behaviour among young people: deciding what method to use. J Sci Med Sport 16:28-35, 2012

124. Jones LW, Eves ND, Haykowsky M, et al: Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. Lancet Oncol 9:757-65, 2008

125. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 167:211-77, 2003

126. Story C, Bryant AL, Phillips B, et al: Comparison of Methods for Determining Aerobic Exercise Intensity Using Heart Rate in Acute Leukemia Patients Prior to Induction Chemotherapy. Biol Res Nurs 18:432-8, 2016

127. Pettee Gabriel K, McClain JJ, Schmid KK, et al: Reliability and convergent validity of the past-week Modifiable Activity Questionnaire. Public Health Nutr 14:435-42, 2010

128. Besson H, Brage S, Jakes RW, et al: Estimating physical activity energy expenditure, sedentary time, and physical activity intensity by self-report in adults. Am J Clin Nutr 91:106-14, 2009

129. Blair SN, Haskell WL, Ho P, et al: Assessment of habitual physical activity by a seven-day recall in a community survey and controlled experiments. Am J Epidemiol 122:794-804, 1985

130. Bouchard C, Tremblay A, Leblanc C, et al: A method to assess energy expenditure in children and adults. Am J Clin Nutr 37:461-7, 1983

131. Courneya KS: Physical Activity and Cancer Survivorship: Frameworks, Overview and Key Questions, Physical Activity and Cancer Survivorship: A workshop for researchers. Rizzo Conference Center, Chapel Hill NC, 2016

132. American College of Sports Medicine.: Medicine and science in sports and exercise. Baltimore, etc., Lippincott Williams & Wilkins, pp volumes

133. Amireault S, Godin G, Lacombe J, et al: The use of the Godin-Shephard Leisure-Time Physical Activity Questionnaire in oncology research: a systematic review. BMC Med Res Methodol 15:60, 2015

134. Amireault S, Godin G, Lacombe J, et al: Validation of the Godin-Shephard Leisure-Time Physical Activity Questionnaire classification coding system using accelerometer assessment among breast cancer survivors. J Cancer Surviv 9:532-40, 2015

135. Amireault S, Godin G: The Godin-Shephard leisure-time physical activity questionnaire: validity evidence supporting its use for classifying healthy adults into active and insufficiently active categories. Percept Mot Skills 120:604-22, 2015

136. Casla S, Lopez-Tarruella S, Jerez Y, et al: Supervised physical exercise improves VO2max, quality of life, and health in early stage breast cancer patients: a randomized controlled trial. Breast Cancer Res Treat 153:371-82, 2015

137. Courneya KS, Vardy JL, O'Callaghan CJ, et al: Effects of a Structured Exercise Program on Physical Activity and Fitness in Colon Cancer Survivors: One Year Feasibility Results from the CHALLENGE Trial. Cancer Epidemiol Biomarkers Prev 25:969-77, 2016

138. Chen HM, Tsai CM, Wu YC, et al: Randomised controlled trial on the effectiveness of home-based walking exercise on anxiety, depression and cancer-related symptoms in patients with lung cancer. Br J Cancer 112:438-45, 2015

139. Lee J, Lee M, Hong S, et al: Association between physical fitness, quality of life, and depression in stage II-III colorectal cancer survivors. Support Care Cancer 23:2569-77, 2015

140. Mehnert A, Veers S, Howaldt D, et al: Effects of a physical exercise rehabilitation group program on anxiety, depression, body image, and health-related quality of life among breast cancer patients. Onkologie 34:248-53, 2011

141. Rogers LQ, Hopkins-Price P, Vicari S, et al: Physical activity and health outcomes three months after completing a physical activity behavior change intervention: persistent and delayed effects. Cancer Epidemiol Biomarkers Prev 18:1410-8, 2009

142. Roveda E, Vitale JA, Bruno E, et al: Protective Effect of Aerobic Physical Activity on Sleep Behavior in Breast Cancer Survivors. Integr Cancer Ther, 2016

143. Jensen RE, Moinpour CM, Keegan TH, et al: The Measuring Your Health Study: Leveraging Community-Based Cancer Registry Recruitment to Establish a Large, Diverse Cohort of Cancer Survivors for Analyses of Measurement Equivalence and Validity of the Patient Reported Outcomes Measurement Information System®(PROMIS®) Short Form Items. Psychological Test and Assessment Modeling 58:99, 2016

144. Buysse DJ, Yu L, Moul DE, et al: Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. Sleep 33:781-92, 2010

145. Yu L, Buysse DJ, Germain A, et al: Development of short forms from the PROMIS sleep disturbance and Sleep-Related Impairment item banks. Behav Sleep Med 10:6-24, 2011

146. Jensen R, King-Kallimanis B, Sexton E, et al: Measurement properties of PROMIS Sleep Disturbance short forms in a large, ethnically diverse cancer cohort. Psycholocial Test and Assessment Modeling 58:353-370, 2016

147. Health Measures: Interpret Scores: PROMIS, 2016

148. Reeve BB, Pinheiro LC, Jensen RE, et al: Psychometric Evaluation of the PROMIS® Fatigue Measure in an Ethnically and Racially Diverse Population-Based Sample of Cancer Patients. PSYCHOLOGICAL TEST AND ASSESSMENT MODELING 58, 2016

149. Cella D, Riley W, Stone A, et al: The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol 63:1179-94, 2010

150. Cella DF, Tulsky DS, Gray G, et al: The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. Journal of Clinical Oncology 11:570-579, 1993

151. Galvao DA, Newton RU: Review of exercise intervention studies in cancer patients. J Clin Oncol 23:899-909, 2005

152. Battaglini C, Reeve B, McMurray R, et al: Personal communication to develop exercise categories, (ed Telephone, email and in-person meeting to specify derived exercise categories), 2016

153. Sherwood NE, Jeffery RW: The behavioral determinants of exercise: implications for physical activity interventions. Annu Rev Nutr 20:21-44, 2000

154. Bauman AE, Sallis JF, Dzewaltowski DA, et al: Toward a better understanding of the influences on physical activity: the role of determinants, correlates, causal variables, mediators, moderators, and confounders. Am J Prev Med 23:5-14, 2002

155. Sallis JF, Hovell MF: Determinants of exercise behavior. Exerc Sport Sci Rev 18:307-30, 1990

156. Patient-reported Outcomes Measurement Information System: PROMIS Physical Function Scoring Manual,

https://www.assessmentcenter.net/documents/PROMIS%20Physical%20Function%20Scoring%20Manual.pdf Accessed November 18, 2016.

157. Patient-reported Outcomes Measurement Information System: PROMIS Ability to Participate in Social Roles and Activities Scoring Manual, https://www.assessmentcenter.net/documents/PROMIS%20Ability%20to%20Participate%20in%20Social%20Roles%20and%20Activities%20Scoring%20Manual.pdf Accessed November 18, 2016.

158. Schlattmann P: Medical applications of finite mixture models [electronic resource]. [Berlin], Springer-Verlag, 2009

159. Frühwirth-Schnatter S: Finite mixture and Markov switching models. New York, Springer, 2006

160. Tang MF, Liou TH, Lin CC: Improving sleep quality for cancer patients: benefits of a home-based exercise intervention. Support Care Cancer 18:1329-39, 2009

161. Bonate PL: Analysis of pretest-posttest designs. Boca Raton, Chapman & Hall/CRC, 2000

162. SAS Institute: Algorithm Descriptions, https://support.sas.com/documentation/cdl/en/statug/63962/HTML/default/viewer.htm#statug_introcom_a0000003374.htm Accessed February 16, 2017

163. Kessler D, McDowell A: Introducing the FMM Procedure for Finite Mixture Models. SAS Global Forum, 2012

164. Y ZHaH: Finite Mixture Models and Their APplications: A Review. Austin Biom and Biostat 2:1-6, 2015

165. Van Horn ML, Jaki T, Masyn K, et al: Evaluating differential effects using regression interactions and regression mixture models. Educ Psychol Meas 75:677-714, 2015

166. Norman GR, Stratford P, Regehr G: Methodological problems in the retrospective computation of responsiveness to change: The lesson of Cronbach. Journal of Clinical Epidemiology 50:869-879, 1997

167. Engstrom CA, Strohl RA, Rose L, et al: Sleep alterations in cancer patients. Cancer Nurs 22:143-8, 1999

168. Leung YW, Brown C, Cosio AP, et al: Feasibility and diagnostic accuracy of the Patient-Reported Outcomes Measurement Information System (PROMIS) item banks for routine surveillance of sleep and fatigue problems in ambulatory cancer care. Cancer 122:2906-17, 2016

169. American Psychiatric Association., American Psychiatric Association. DSM-5 Task Force.: Diagnostic and statistical manual of mental disorders : DSM-5 (ed 5th). Washington, D.C., American Psychiatric Association, 2013

170. Norman GR, Sloan JA, Wyrwich KW: Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 41:582-92, 2003

171. Patient-reported Outcomes Measurement Information System: PROMIS Sleep Disturbance Scoring Manual, https://www.assessmentcenter.net/documents/PROMIS%20Sleep%20Disturbance%20Scoring%20Manual.pdf Accessed July 8, 2015.

172. Leung YW, Brown C, Cosio AP, et al: Feasibility and diagnostic accuracy of the Patient-Reported Outcomes Measurement Information System (PROMIS) item banks for routine surveillance of sleep and fatigue problems in ambulatory cancer care. Cancer, 2016

173. LeMasters TJ, Madhavan SS, Sambamoorthi U, et al: Health behaviors among breast, prostate, and colorectal cancer survivors: a US population-based case-control study, with comparisons by cancer type and gender. J Cancer Surviv 8:336-48, 2014

174. Haydon AM, Macinnis RJ, English DR, et al: Effect of physical activity and body size on survival after diagnosis with colorectal cancer. Gut 55:62-7, 2005

175. Shuman AG, Duffy SA, Ronis DL, et al: Predictors of poor sleep quality among head and neck cancer patients. Laryngoscope 120:1166-72, 2010

176. Ashing-Giwa K, Rosales M: Recruitment and retention strategies of African American and Latina American breast cancer survivors in a longitudinal psycho-oncology study. Oncol Nurs Forum 39:E434-42, 2012

177. Chung JY, Lee DH, Park JH, et al: Patterns of physical activity participation across the cancer trajectory in colorectal cancer survivors. Support Care Cancer 21:1605-12, 2013

178. Fairclough DL, Cella DF: Functional Assessment of Cancer Therapy (FACT-G): non-response to individual questions. Qual Life Res 5:321-9, 1996

179. Mullin V, Cella D, Chang CH, et al: Development of three African language translations of the FACT-G. Qual Life Res 9:139-49, 2000

180. Winstead-Fry P, Schultz A: Psychometric analysis of the Functional Assessment of Cancer Therapy-General (FACT-G) scale in a rural sample. Cancer 79:2446-52, 1997

181. Mein G, Johal S, Grant RL, et al: Predictors of two forms of attrition in a longitudinal health study involving ageing participants: an analysis based on the Whitehall II study. BMC Med Res Methodol 12:164, 2012

182. Adams SA, Matthews CE, Ebbeling CB, et al: The effect of social desirability and social approval on self-reports of physical activity. Am J Epidemiol 161:389-98, 2005

183. Lee IM, Shiroma EJ, Lobelo F, et al: Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 380:219-29, 2012

184. Sallis JF, Saelens BE: Assessment of physical activity by self-report: status, limitations, and future directions. Res Q Exerc Sport 71 Suppl 2:1-14, 2000

185. Denlinger CS, Ligibel JA, Are M, et al: Survivorship: Sleep Disorders, Version 1.2014: Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 12:630-42, 2014

186. Zhou ES, Partridge AH, Syrjala KL, et al: Evaluation and treatment of insomnia in adult cancer survivorship programs. J Cancer Surviv, 2016

187. Ottenbacher A, Yu M, Moser RP, et al: Population Estimates of Meeting Strength Training and Aerobic Guidelines, by Gender and Cancer Survivorship Status: Findings From the Health Information National Trends Survey (HINTS). J Phys Act Health 12:675-9, 2014

188. Kilari D, Soto-Perez-de-Celis E, Mohile SG, et al: Designing exercise clinical trials for older adults with cancer: Recommendations from 2015 Cancer and Aging Research Group NCI U13 Meeting. J Geriatr Oncol 7:293-304, 2016