Sleep Behavior, Physical Activity and Prehabilitation Interventions in Cancer

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Abstract

Colorectal cancer (CRC) is the third most frequent malignant disease worldwide, and surgery remains a fundamental aspect of oncological care. Sleep disorders impact a significant number of cancer patients undergoing surgical procedures. Up to 79.1% of patients complain of sleep disorders before surgery, reportedly twice as often as the general population. Sleep disorders are associated with adverse health outcomes and may affect patient recovery. Prehabilitation interventions, including a comprehensive treatment plan featuring lifestyle adjustment (exercise, nutrition, and psychosocial interventions), afford an opportunity for the patient to enhance their functional status, quality of life and surgical outcomes while waiting to begin cancer treatment or surgery. Sleep management may represent another key element, along with diet and physical activity, to promote lifestyle changes with benefits on health. The work in this thesis provides a deeper understanding of the complex interplay between sleep disturbances, physical activity, and prehabilitation interventions.

In the first study, a cross-sectional analysis of U.S. adult cancer survivors, we examined the associations between moderate to vigorous physical activity, sedentary behavior, and sleep-related outcomes. The results indicate that increasing physical activity and reducing sedentary behavior throughout the day may help reduce sleep complaints in cancer survivors. Developing and implementing strategies that encourage physical activity while reducing sedentary breaks is viable for improving sleep outcomes.

In the second study, we summarized the most recent evidence on the effects of preoperative exercise interventions on sleep outcomes in cancer patients in a systematic review. Most studies showed non-significant improvements in sleep disturbances. However, the substantial heterogeneity in interventions makes it difficult to draw definitive conclusions. Given the limited time for intervening during the preoperative period, physical activity alone may not be effective enough to improve sleep significantly.

In the third study, we aimed to investigate the potential effectiveness of multimodal prehabilitation, including exercise, nutrition, and psychological interventions, on sleep quality and duration during the preoperative period and up to 8-weeks after surgery in a pilot randomized controlled trial (RCT). Our findings identified small positive changes in perceived sleep quality

preoperatively; however, significant improvements in wakefulness during the night and sleep duration were objectively identified for specific subgroups. This study suggested that the multimodal prehabilitation approach might be more substantial for specific groups of patients, such as those with baseline physical performance limitations or anxiety.

Our fourth study, a secondary analysis of the previous study's data, revealed a bidirectional relationship between sleep and physical activity during prehabilitation. Active patients tend to sleep less at night, while those who sleep longer are less active the following day. Other sleep parameters, however, did not significantly affect daily physical activity levels.

In conclusion, multimodal prehabilitation may improve sleep quality for CRC patients before surgery and potentially sleep duration after surgery, particularly for those with high anxiety symptoms. Furthermore, sleep duration might influence physical activity levels preoperatively. This research underlines the importance of tailored interventions and sleep management in cancer patient lifestyle changes.

Résumé

Le cancer colorectal est la troisième maladie maligne la plus fréquente dans le monde, et la chirurgie reste un aspect fondamental de la prise en charge oncologique. Les troubles du sommeil touchent un nombre significatif de patients atteints de cancer subissant des interventions chirurgicales. Jusqu'à 79,1% des patients se plaignent de troubles du sommeil avant la chirurgie, soit deux fois plus souvent que la population générale. Les troubles du sommeil sont associés à des conséquences négatives sur la santé et peuvent affecter la récupération des patients. Les interventions de préhabilitation, y compris un plan de traitement complet comprenant des ajustements de mode de vie (exercice, nutrition et interventions psychosociales), offrent l'opportunité au patient d'améliorer son état fonctionnel, sa qualité de vie et les résultats chirurgicaux en attendant de commencer le traitement du cancer ou la chirurgie. La gestion du sommeil peut représenter un autre élément clé, avec l'alimentation et l'activité physique, pour promouvoir des changements de mode de vie bénéfiques pour la santé. Les travaux de cette thèse permettent une compréhension approfondie des interactions complexes entre les perturbations du sommeil, l'activité physique et les interventions de préhabilitation.

Dans la première étude, une analyse transversale des survivants du cancer adultes aux États-Unis, nous avons constaté que l'augmentation de l'activité physique et une réduction du comportement sédentaire tout au long de la journée pourraient aider à réduire les plaintes liées au sommeil chez les survivants du cancer. Des stratégies promouvant l'activité physique semblent améliorer le sommeil.

Dans la deuxième étude, nous avons résumé les preuves les plus récentes sur les effets des interventions d'exercice préopératoire sur les paramètres du sommeil chez les patients atteints de cancer dans une revue systématique. La plupart des études ont montré des améliorations non significatives des troubles du sommeil. Compte tenu du temps limité pour intervenir pendant la période préopératoire, l'activité physique seule peut ne pas être suffisamment efficace pour améliorer le sommeil de manière significative.

Dans la troisième étude, nous avons cherché à étudier l'efficacité potentielle de la préhabilitation multimodale, y compris l'exercice, la nutrition et les interventions psychologiques, sur la qualité et la durée du sommeil pendant la période préopératoire et jusqu'à

8 semaines après la chirurgie dans un essai pilote randomisé contrôlé (ECR). Nos résultats ont identifié de légèrs changements positifs dans la qualité du sommeil perçue en préopératoire ; cependant, des améliorations significatives de l'éveil pendant la nuit et de la durée du sommeil ont été objectivement identifiées pour des sous-groupes spécifiques. L'approche multimodale pourrait être particulièrement utile pour les patients ayant des limitations de performance ou de l'anxiété.

Notre quatrième étude, une analyse secondaire des données de l'étude précédente, a révélé une relation bidirectionnelle entre le sommeil et l'activité physique pendant la préhabilitation. Les patients actifs ont tendance à dormir moins la nuit, tandis que ceux qui dorment plus longtemps sont moins actifs le jour suivant. Cependant, d'autres paramètres du sommeil n'ont pas eu d'effet significatif sur les niveaux d'activité physique quotidienne.

En conclusion, la préhabilitation multimodale pourrait améliorer la qualité du sommeil pour les patients atteints de CRC avant la chirurgie et potentiellement la durée du sommeil après la chirurgie, en particulier pour ceux présentant des symptômes d'anxiété élevés. De plus, la durée du sommeil pourrait influencer les niveaux d'activité physique préopératoires. Cette recherche souligne l'importance des interventions personnalisées et de la gestion du sommeil dans les changements de style de vie des patients atteints de cancer.

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First and foremost, I profoundly appreciate Dr. A. Sender Liberman and Dr. Francesco Carli for embracing me into the Peri-Operative Program (POP) and providing an exceptional environment to grow as a young researcher. Your guidance has sparked my enthusiasm and motivated me to persevere.

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Abbreviations

CRC	Colorectal cancer
IARC	International Agency for Research on Cancer
WHO	World Health Association
MSI	Microsatellite instability
CIMP	Methylator phenotype
CIN	Chromosomal instability
AJCC	American Joint Committee on Cancer
UICC	Union for International Cancer Control
TNM	Tumor node metastasis
ERAS	Enhanced Recovery After Surgery
ACSM	American College of Sports Medicine
N-REM	Non-rapid eye movement
REM	Rapid eye movement
ECG	Electroencephalogram
EMG	Electromyogram
EOC	Electrooculogram
SWS	Slow wave sleep
ICSD	International Classification of Sleep Disorders
PSG	Polysomnography
SOL	Sleep onset latency
WASO	Wake after sleep onset
TST	Total sleep time
SE	Sleep efficiency
PSQI	Pittsburgh Sleep Quality Index questionnaire
ISI	Insomnia Severity Index
ESS	Epworth Sleepiness Scale
GSDS	General Sleep Disturbance Scale
CV	Cardiovascular

T2DM	Type 2 diabetes
IL	Interleukin
TNF	Tumor necrosis factor
CRP	C-reactive protein
CTRA	Conserved transcriptional response to adversity
GH	Growth hormone
NF	Nuclear factor
SNS	Sympathetic nervous system
PRRs	Pattern recognition receptors
TLR4	Toll-like receptor 4
NDDs	Neurodegenerative diseases
POD	Postoperative delirium
POCD	Postoperative cognitive dysfunction
RCT	Randomized control trials
CBT-I	Cognitive-behavioral therapy for insomnia
PICO	Population, Intervention, Comparison, Outcomes
EORTC QLQ-C	European Organization for Research and Treatment Cancer Quality of Life Questionnaire Core
PRO	Patient-reported outcome
HADS	Hospital Anxiety and Depression Scale
MB	Mind-body
Ex	Exercise group
CG	Control group
NR	Not reported
NACT	Neoadjuvant chemoradiotherapy treatment
HR max	Maximal heart rate
MVPA	Moderate to vigorous physical activity
SOC	Standard of care
Prehab	Prehabilitation
CPET	Cardiopulmonary Exercise Testing
6MWT	6-Min walk test

ESPEN	European Society for Clinical Nutrition and Metabolism
TIB	Time in bed
CHAMPS	Community Health Activities Model Program for Seniors
SF-36	36-Item Short Form
WHODAS	World Health Organization Disability Assessment Schedule
PG-SGA	Patient-generated subjective global assessment
SD	Standard deviation
ICU	Intensive care unit
VZV	Varicella zoster virus
IQR	Interquartile range
CCI	Charlson Comorbidity Index
ASA	American Society of Anesthesiologists
N/A	Not applicable
GXT	Between group interaction
T	Main time effect
G	Main group effect
d	Size effect
T0	Baseline
T1	Preoperative
T2	4-week postoperative
T3	8-week postoperative
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
SB	Sedentary behavior
ACS	American Cancer Society
QoL	Quality of life
PA	Physical activity
NHANES	National Health and Nutrition Examination Survey
CAPI	Computer-Assisted Personal Interview
PHQ	Patient Health Questionnaire
AIC	Akaike information criterion

MET	Metabolic equivalent
MLM	Multilevel linear models
ICCs	Intraclass correlation coefficients
WS	Within-subject
BS	Between-subject
EMA	Ecological Momentary Assessment

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Statement of Originality and Contribution to Original Knowledge

In accordance with the guidelines of the Faculty of Graduate and Postdoctoral Studies of McGill University, this thesis is presented in a manuscript-based format. The research presented in this thesis constitutes original work, and collaboration from co-authors in the manuscripts are detailed in the section *Contribution of Authors*.

Contributions to original knowledge:

- This thesis is the first to examine the cross-sectional associations between moderate to vigorous physical activity (MVPA), sedentary behavior (SB) and sleep-related outcomes using a nationally representative sample of U.S. cancer survivors. It highlights the necessity of implementing long-term strategies to adjust both physical activity and sedentary behaviors to enhance sleep outcomes.
- We provided the first study that demonstrated the available empirical evidence of the impact of preoperative exercise training alone or as part of multimodal prehabilitation on sleep disturbances and sleep quality in cancer patients.
- This thesis provides the first study that discusses and assesses sleep behavior during the preoperative period and in a multimodal prehabilitation intervention approach.
- We are the first group conducting a randomized controlled trial to assess the impact of a multimodal prehabilitation program compared to a standard of care (SOC) group on sleep quality and parameters in colorectal cancer adults preoperatively and after surgery using self-reported and objective measures of sleep. Specifically, we demonstrated a small positive change in the perceived sleep quality only at the preoperative time point for the prehabilitation group, with more substantial improvements for specific subgroups.
- We are the first to report the sequence change between sleep parameters and physical activity in a multimodal prehabilitation intervention approach objectively determined and using intensive longitudinal data of 4 consecutive weeks.
- We present the first evidence of the negative bidirectional associations between sleep and physical activity and prove substantial heterogeneity within individuals during the preoperative period.

Contribution of Authors

All chapters of this thesis were written by Sarah Atoui and edited by Dr. A. Sender Liberman and Dr. Francesco Carli. The body of this thesis, Chapters 2, 3, 4 and 5, were prepared in manuscript format, and thus, the contributions of collaborating authors are detailed below.

Chapter 2: Exercise interventions in cancer patients with sleep disturbances scheduled for elective surgery: Systematic Review

- Sarah Atoui: Conceptualization; methodology; data curation; formal analysis; writing – original draft; and responding to revision requests.
- Miquel Coca-Martinez: Writing – data curation.
- Ibtisam Mahmoud: Data curation.
- Francesco Carli: Conceptualization, Writing – review & editing, supervision.
- A. Sender Liberman: Conceptualization, Writing – review & editing; supervision.

Chapter 3: Association between physical activity, sedentary behaviors and sleep-related outcomes among cancer survivors: a cross-sectional study

- Sarah Atoui: Study conception and design, data collection. statistical analysis; and responding to revision requests.
- Paquito Bernard: Study conception and design, technical advice on data collection, analysis, and manuscript revisions.
- Francesco Carli: Contributed to the design supervision and revisions of the manuscript.
- A. Sender Liberman: Contributed to the manuscript's design, supervision, and revisions.

Chapter 4: Does a Multimodal Prehabilitation Program Improve Sleep Quality and Duration in Patients Undergoing Colorectal Resection for Cancer? Pilot Randomized Control Trial

- Sarah Atoui: Study design, technical setup for the experiments, collection of samples, statistical analysis, writing the manuscript.
- Francesco Carli: Study design, supervision of data collection and evaluation of data and manuscript.
- Paquito Bernard: Technical advice on data manipulation, statistical analysis, and manuscript revision.
- Lawrence Lee: Collection of data (patient recruitment)
- Barry Stein: Collection of data (patient recruitment)
- Patrick Charlebois: Collection of data (patient recruitment)
- A. Sender Liberman: Originated the study as the principal investigator of a MITACS Accelerate grant, funding of studies, study design, supervision, evaluation, and manuscript revision.

Chapter 5: Bidirectional temporal associations between sleep parameters and physical activity levels in colorectal cancer patients during prehabilitation

- Sarah Atoui: Study design, technical setup for the experiments, collection of samples, statistical analysis, writing the manuscript.
- Paquito Bernard: Study conception and design, technical advice on data collection, analysis, and manuscript revisions.
- Francesco Carli: Study design, supervision of data collection and evaluation of data and manuscript.
- A. Sender Liberman: Originated the study as the principal investigator of a MITACS Accelerate grant, funding of studies, study design, supervision, evaluation, and manuscript revision.

Chapter 1: Introduction

Advances in cancer research have led to earlier detection and treatment of cancer, resulting in overall incidence and death rate reductions due to cancer (1). Despite improved treatment outcomes, however, cancer remains the leading cause of death in Canada (2). In Canada, lung, breast, prostate and colorectal cancers are the most diagnosed cancers (3). Accounting for all cancer deaths, colorectal is the second leading cause of cancer death (3). Cancer treatment has traditionally been directed toward prolonging the patient's survival and complete remission, especially in non-metastatic cancer cases. However, it has been associated with negative consequences for the patient's physical, emotional, and social life (4, 5). Colorectal cancer (CRC) treatment choice is based on several factors, including the stage, location, and the patient's conditions (6). However, surgery is an essential treatment and the traditional primary approach in most colorectal cancer diagnoses (7). Technological innovations have been introduced in colorectal surgery over the past decade and have significantly improved patient surgical outcomes (8, 9). Despite these advances, surgical and medical complications remain high, with incidence rates ranging from 25% to 60% (10). In addition to the systemic reaction of the surgical stress response involving hormonal, inflammatory and haematological changes (11), the physiological and chronological age, coexisting medical conditions, and potential psychological and social care issues complicate the treatment process of CRC patients, particularly in elderly ones (6).

Sleep disorders are common and significant complaints of cancer patients (12). Cancer patients' most common sleep complaints were identified by difficulty falling and staying asleep, with frequent and prolonged nighttime awakenings (12). Up to 60% of cancer patients complain of sleep disorders during diagnosis and treatment, which may persist for years after survivorship (13, 14). Cancer surgery is one of the related risk factors for sleep disorders. Preoperatively, up to 79% of patients complain of sleep disorders (15-17), a rate at least twice as frequent as in the general population (18). In addition to the physical (19-22) and psychological side effects (23-26), sleep disorders can adversely affect patient recovery, increase morbidity, and decrease hospitalization satisfaction (27, 28). Perioperative sleep management of patients is a relatively neglected field of research. A greater understanding of the preoperative sleep behavior of cancer patients is needed as it may help develop interventions and target patients' needs to improve their

general quality of life.

Prehabilitation is defined as the process of enhancing the individual's functional capacity to withstand an incoming stressor of inactivity associated with surgery (29), demonstrating several benefits for patients with different cancer entities (30-35). Previous research has shown that prehabilitation may improve cancer-related outcomes and reduce cancer-related healthcare costs (36). Structured exercise protocols represent a significant component of the prehabilitation program; additional elements, such as nutritional supplementation and psychosocial support, would also contribute to improved clinical outcomes (37). Grouping these interventions together is the premise of a multimodal prehabilitation program. Despite significant research focusing on the preoperative phase and prehabilitation interventions, limited research investigates sleep behavior during this period. Sleep is one of the complex physiological processes which plays a crucial role in many physiological processes, such as memory formation, optimal cognition, immune function, endocrine function, cardiovascular health, and mood (38). Identifying effective strategies to promote healthy sleep habits and reduce sleep disturbances in the preoperative period is essential. Furthermore, a better understanding of the movement change between behaviors can help design, test, optimize, and implement a multimodal program to maximize improvements in functional capacity and nutritional status before surgery. This thesis sought to investigate the impact of the prehabilitation intervention on sleep outcomes with a particular focus on physical activity.

This chapter briefly overviews colorectal cancer incidence and treatment strategies, then discusses the preoperative recovery and behavioral components pertinent to this thesis. The concept of prehabilitation and its rationale will be introduced, followed by the normal sleep pathway. Sleep disorders in the preoperative period will be presented, and the incidence, classification and assessment will be addressed. The introduction will be finished by identifying the critical role of managing sleep disorders during the preoperative period. Notably, the pathophysiological mechanisms of sleep disorders connected to immune and metabolic functions and neurodegenerative and psychiatric conditions will be discussed in detail. A cross-sectional study will be conducted to provide a general overview of the associations between moderate to vigorous physical activity, sedentary behavior, and sleep-related outcomes in U.S. adult cancer survivors. While this study offers valuable insights into these associations, our research aims to explore further a specific period for cancer patients: the preoperative phase. To achieve this, a

systematic review will be carried out, including a comprehensive investigation into the impact of preoperative exercise training alone or as part of multimodal prehabilitation on sleep disturbances and quality. Two original research articles will follow the literature review investigating the complex associations between prehabilitation, physical activity and sleep. Finally, Chapter 6 offers a comprehensive synthesis of findings connected and beyond the research context presented in this thesis.

1.1 Colorectal Cancer

1.1.1 Epidemiology

Colorectal cancer (CRC) is the third most frequent malignant disease around the world (1.85 million of new cases/year; 10.2% of total malignancies), according to the International Agency for Research on Cancer (IARC) of the World Health Association (WHO) (39). The worldwide incidence of CRC is anticipated to rise by an additional 20% to 2.2 million new cases annually by 2030 (40) to reach 3.2 million in 2040, based on the projection of aging, population growth, and human development (41). CRC is also the second most common cause of cancer-related death in both men and women in Canada and worldwide (42-44).

Although the lifetime risk is similar in men and women (45), in 2020, the global CRC incidence rate in men (23.4 cases per 100,000 persons) was 44% higher than in women (16.2 cases per 100,000 persons) (41). Colorectal cancer tends to occur in older patients, with approximately 60% diagnosed in patients aged ≥ 65 years, with a median age at diagnosis of 68 years (46). Recently, the incidence and mortality of CRC dramatically increased after the age of 50 years (86.3 versus 2.9, 40.9 versus 0.99 per 100,000 persons in 2020, respectively) (41). As the third most common malignancy, increasing CRC cases and rising incidence among younger generations (47, 48) represent a heavy financial burden and a substantial public health challenge (41). Indeed, screening is expected to significantly impact CRC incidence and mortality in the next 15 years (49). This effect is unlikely to be influenced by lifestyle, body fatness, dietary patterns (40), or new therapeutics (49). In 2007, Canada implemented structured programs for colorectal screening, which have since been established in most regions throughout the nation (50).

1.1.2 Pathophysiology and Clinical Presentation

Traditionally, three segments of cancer location define the subtypes of CRC: proximal colon, distal colon, and rectum (51, 52). Adenocarcinoma from mucus-producing cells is the most common type of CRC (53). CRCs also include other less common types of cancers: carcinoid tumors, gastrointestinal stromal tumors, lymphomas, and sarcomas.

CRC occurs due to multiple carcinogenic events: serrated lesions, adenoma-carcinoma sequence, and inflammation (54, 55). The unmanaged occurrence of carcinogenic events facilitates the progressive accumulation of genetic mutations and epigenetic modifications that drive the transformation of normal cells into uncontrolled adenoma and may eventually lead to CRC (41).

Genomic instability, a key factor responsible for global genetic aberrations and the consequent carcinogenesis, comprises three major aberrant events: microsatellite instability (MSI), CpG island methylator phenotype (CIMP), and chromosomal instability (CIN) (56). Therefore, specific single molecular markers are used to classify CRC patients into relevant clinical subtypes (57, 58).

Staging for colorectal cancer follows the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor node metastasis (TNM) system, which is currently considered the robust prognostic parameter for patients with colorectal cancer (59).

Typically, stage I tumors are confined to the mucosa, submucosa and muscularis propria but do not invade through the muscularis propria fully. Stage II tumors, conversely, invade through the muscularis propria but do not have evidence of positive nodal status. Stage III tumors are associated with nodal involvement, while stage IV tumors stage IV tumors have metastasized. The overall 5-year survival was 65.2% in the United States from 1991 to 2000 (60) (Figure 1-1). The specific survival rate by stage was 93.2% for stage I, 82.5% for stage II, 59.5% for stage III, and 8.1% for stage IV. The advancements in understanding colorectal cancer (CRC) pathophysiology have led to increased treatment options (41) and thus have effectively inhibited cancer progression and prolonged overall survival (61).

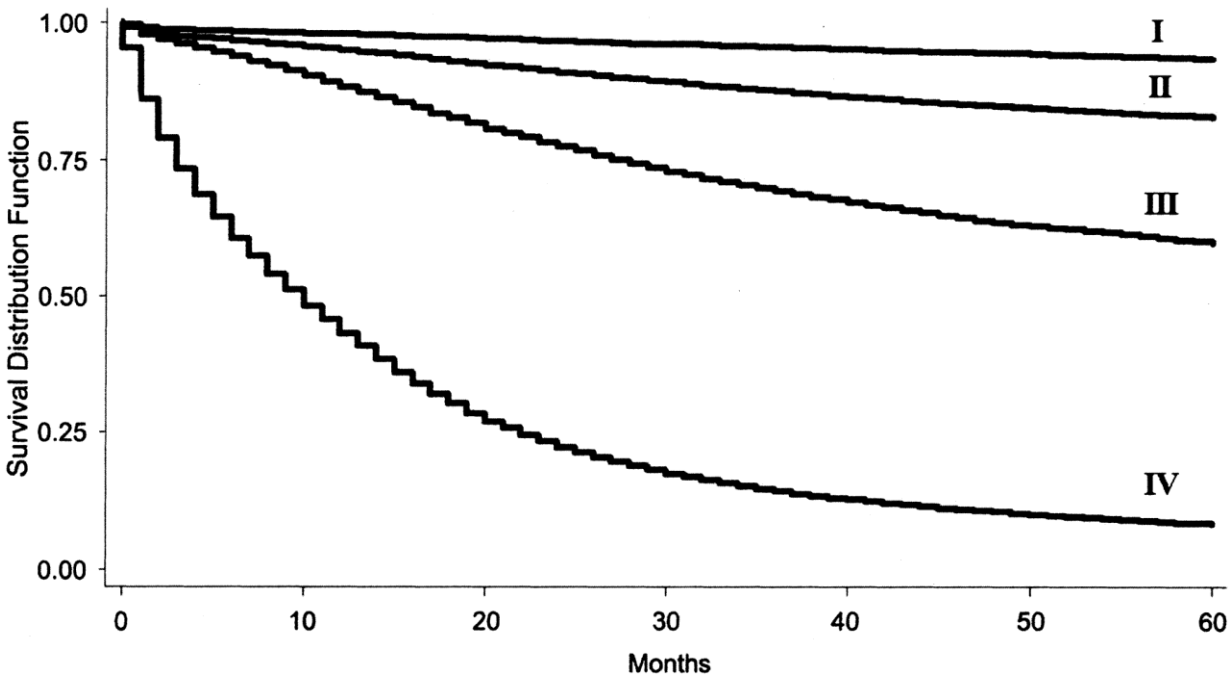

Figure 1-1: Five-year survival for American Joint Committee on Cancer fifth edition system stages I-IV (60).

1.1.3 Treatment Strategies

The stages at which CRC is diagnosed partly explain the differences in survival. Early detection is essential in preventing metastasis, reducing mortality, and improving prognosis and quality of future life (61). The symptoms of CRC only appear at the advanced stages; thus, screening is recommended for all average-risk individuals above 50 and earlier for those at higher risk (62). The current best evidence suggests using fecal occult blood testing yearly as a first-line strategy, followed by flexible sigmoidoscopy every 5 years (63). Most Canadian provinces have developed a systematic program using fecal occult blood testing as primary screening, followed by colonoscopy for any positive results (64).

Advancements have been made to better understand the pathophysiology of CRC and expand treatment options, including endoscopic resection, local surgical excision, targeted therapy, radiation therapy, ablative therapies, chemotherapy, and immunotherapy. Despite

alterations in the incidence patterns and the location of CRC within the colon or rectum, surgical intervention remains the reference-standard approach for treating early and even advanced cancer (43, 65). A wealth of technological innovations have been introduced in colorectal surgery over the past decade, significantly improving surgical outcomes for patients with CRC (8, 9). Therefore, the proportion of patient candidates for curative resection is rising along with improvements in anesthesia, surgical techniques, critical care and systemic therapy (66, 67).

In general, the surgical approach can be conducted either through a laparotomy involving a large abdominal incision or minimally invasive approaches, such as laparoscopy with or without robotic assistance, involving smaller, less invasive incisions. The procedure usually consists in resecting the tumor and rejoining the two ends of the colorectal sections. Occasionally, the affected area needs time to heal due to several patients, tumor and treatment factors. In that case, an ileostomy or colostomy may be created through an incision in the abdominal wall. CRC surgical resection is associated with a complication rate of up to 30.2% (68), which can lead to a significantly longer length of hospital stay (6 to 10 days) (69). With the extended bed rest that often follows surgery during hospitalization, older patients may experience several complaints, including fatigue (70), delirium, sleep difficulties (14) and cognitive and functional decline (10). Despite surgical resection being the primary treatment for colorectal cancer, it may be necessary to reduce the size of the tumor through neoadjuvant chemotherapy/and or radiotherapy prior to surgery to facilitate surgical resection. Due to the various treatment options available, such as surgery, chemotherapy, and radiotherapy, the relative survival rate of this population is 60% (71). The physical and mental stress patients experience during the treatment process can further cause functional decline and affect the quality of life (72). Therefore, it remains critical that these individuals are in optimal physical condition.

1.1.4 Preoperative Period and Functional Recovery

Most research aimed at expediting the healing process, like the Enhanced Recovery After Surgery (ERAS) protocol, has primarily concentrated on improving patients' conditions during the intra- and postoperative phases. However, studies support that low baseline functional capacity raises the likelihood of complications and prolongs the recovery process after major surgery (10). Emerging evidence suggests that patients' physiological and metabolic capacity can

be improved during the preoperative period (73). Therefore, optimizing the patient's health status before the stress of surgery is crucial for later recovery. The physical and mental components of the patient's health status are subsequently discussed.

1.1.5 Exercise Intervention

The beneficial effects of exercise interventions can be primarily attributed to the enhancement of patients' preoperative cardiovascular reserve capacity, which is crucial for the body's ability to withstand systemic perturbations (74-76). Furthermore, exercise interventions are recognized for their ability to decrease the levels of monocytes in both the circulation and tissues and inhibit the production of proinflammatory cytokines, thus creating an environment with anti-inflammatory properties (77-79). The American College of Sports Medicine (ACSM) and the American Heart Association recommend that regular physical activity is essential for healthy aging and should include moderate-intensity aerobic activity for 30 minutes five times per week, along with strengthening, balance, and flexibility exercises (80). Furthermore, increasing weekly habitual PA levels to $\geq$ 150 min of moderate or $\geq$ 75 min of vigorous PA contributes to several positive health benefits, including reducing body fat and waist circumference (81). Engaging in regular physical activity helps to provide a protective effect against many functional limitations (82). Regular physical activity and exercise help maintain physiological capacity and enhance functional abilities (83, 84). Multiple studies have demonstrated that exercise training can be successfully implemented during the preoperative period to improve physical recovery after surgery (85, 86).

Physical activity can be assessed objectively (directly measured, primarily through accelerometry) and subjectively (self-reports, e.g., questionnaires or diaries). Multiple types of accelerative devices, especially accelerometers, are used worldwide to capture the amount of physical activity subjects perform in everyday life. However, objective measures are also limited and cannot be viewed as the gold standard (87). Whereas most activities are captured easily (e.g., whole-body movement), other activities are complex. Situations in which participants sit and perform physical activity (e.g., cycling, certain forms of weightlifting exercise) are typically underestimated. However, new software algorithms help to accurately classify movement patterns (e.g., cycling, taking the bus) and, in so doing, enhance the precision of estimating

energy consumption. Retrospective questionnaires were used to estimate the typical level of physical activity or the number of minutes of vigorous exercise engaged during the last 2 weeks are subject to considerable measurement error, including item interpretation, recall bias, and social desirability effects (88). Accordingly, several authors caution against studies relying solely on self-reported physical activity (87, 89, 90).

While physical activity is a crucial component of a healthy lifestyle, it is essential to consider the broader spectrum of daily behavior. One of the critical components of everyday life is the amount of time spent on sedentary activities. Sedentary behavior is those activities that do not increase energy expenditure substantially above the resting level, such as sitting, lying down, or viewing TV (91). Interestingly, being physically active does not necessarily negate the detrimental effects of prolonged sedentary behavior (92). For instance, an individual might fulfill or even surpass the recommended guidelines for physical activity. However, suppose a significant portion of their daily routine is spent in a sedentary posture, such as sitting or reclining. In that case, they remain susceptible to negative health consequences, including, but not limited to, cardiovascular ailments and metabolic disorders, specifically in older adults (93-95). Moreover, evidence suggests that the relationship between sedentary behavior and all-cause and cardiovascular disease mortality is independent of physical activity levels (96). These findings indicate the importance of promoting physical activity and reducing sedentary behaviors at older ages to improve physical fitness, which results in enhanced functioning of older adults.

1.1.6 Nutritional Intervention

Nutritional status can influence postoperative morbidity and mortality (97). Preoperative energy reserves, such as lean body mass, are necessary to sustain the mobilization of reserves caused by stress (98, 99). This is critical for maintaining physiological strength and integrity (100). Patients with low reserves, including those who are malnourished, frail and/or sarcopenic (muscle-depleted), are at higher risk during surgery and may have a reduced ability to manage the additional demands during the surgical procedure (101, 102). Identifying and addressing dietary deficiencies before surgery has been a longstanding practice that has significantly improved surgical outcomes (103). The nutrition aspect during the preoperative period primarily focuses on preventing and treating malnutrition (100). Furthermore, adequate daily protein may improve

exercise gains (exercise capacity, body protein, strength) to enhance physiological reserve and functional capacity (100).

1.1.7 Psychological Support

Experienced psychological stress before surgery is common and expected for patients undergoing surgery (104). However, preoperative surgical distress patients tend to be physically inactive, resulting in lower functional capacity (105). Furthermore, patients presenting with anxiety symptoms require more anesthesia (106). Thus, an increased need for anesthesia could lead to opioid-related side effects, including nausea, which can delay hospital discharge (107, 108). Engaging patients early in the recovery process and providing patients with tools, such as deep breathing, may manage psychological stress and promote resilience during the preoperative period (109, 110).

1.2 Normal Sleep Pathway

Regular sleep is a complex and critical physiological process necessary for life (111) and typically occupies one-third of our lives, playing a fundamental role in physical, mental, and emotional health (112). Human sleep includes nonrapid eye movement sleep (N-REM) and REM sleep (113) (Figure 1-2). N-REM can be subdivided into three stages: N1, N2, and N3 (114). Each stage differs in its electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG) signature. Sleep begins with N-REM at N1 (light sleep). This light sleep stage accounts for 5%–10% of total sleep in adults, N2 accounts for 45%–55%, and N3 for 15%–25%. N3, the most restful stage, is called deep or slow wave sleep (SWS), with the body being least metabolically active during this period. REM sleep accounts for 20%–25% of total sleep in adults, whereas N-REM sleep accounts for the rest. NREM and REM sleep occur alternatively in cycles of around 90 minutes at night (115). Each phase must be completed to have a restful sleep; otherwise, sleep disruption will result (116).

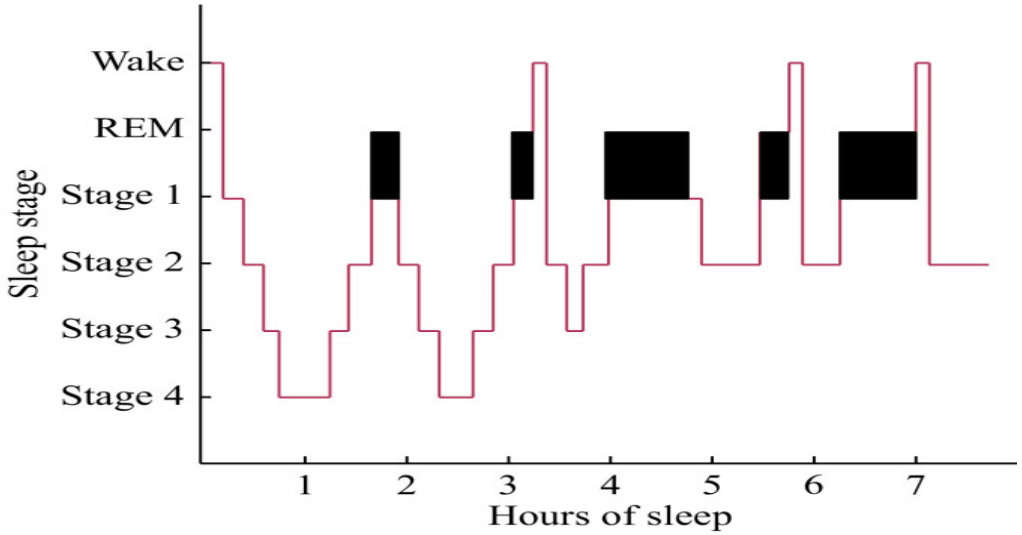

Figure 1-2: A hypnogram of a typical young adult. N1=stage 1, N2=stage 2, and N3=stage 3+stage 4 (27).

1.3 Preoperative Sleep Disorder in Cancer

1.1.1. Incidence and Prevalence

Sleep disorders are prevalent in perioperative patients. About 8.8–79.1% of patients complain of sleep disorders before the surgery (15-17), a rate that has been reported as double that of the general population (117). Patients report sleep disorders both before treatment (118) and during cancer treatment (119). Moreover, the incidence of sleep disorders may differ by the types of surgery and disease. For instance, among lung cancer patients undergoing surgery, 49.7% had sleep disturbance one year after surgery (16). On the other hand, during the preoperative period, 59% of patients with different types of cancer reported having a sleep disorder (28% with insomnia syndrome), and at 18 months after surgery, the prevalence declined but remained significant (36%) (14). Another study looking at cancer patients in various stages of treatment found that 45% reported a sleep problem in the prior month (119). Half of them described the sleep problems as being either moderate, severe, or unbearable. The sleep difficulties reported were diverse, with around 90% of the patients complaining of awakening during the night, approximately 85% reporting sleeping fewer hours than usual, 75% having trouble falling back asleep, and 39% indicating napping at unusual times, such as in the late morning or early afternoon.

Despite the considerable incidence and prevalence of sleep disorders that pose a significant risk to public health, there is inadequate comprehension, insufficient identification, and poor management of these disorders, particularly among cancer patients during the perioperative period.

1.1.2. Classification of Sleep Disorders

Generally, sleep disorders related to surgery can be divided into two main categories: chronic insufficient sleep and sleep disorders during hospitalization. According to the International Classification of Sleep Disorders, version 3 (ICSD-3), sleep disorders can be categorized based on clinical symptoms (120, 121). Sleep disturbances include insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, sleep-related movement disorders, circadian rhythm sleep disorders, parasomnias, physiological (organic) sleep disorders, and other sleep disorders not due to a known substance or physiological condition, environmental sleep disorder, etc. (122-124). As there are a variety of sleep categories, this thesis introduces the common clinical type of sleep disorder defined as disruptions in nighttime sleep or wakefulness that include a variety of clinical conditions (e.g., insomnia) (125). Insomnia is the most common type of sleep disorder, particularly in perioperative patients, characterized by difficulties initiating, maintaining, and consolidating sleep, with poor overall sleep quality (126, 127). Clinical chronic sleep disorder lasts for more than 3 months, while a short-term sleep disorder lasts for <3 months. Sleep disturbances and insomnia are indicated by a sleep onset latency (SOL), or the amount of time it takes to fall asleep of > 30 min (128); wake after sleep onset (WASO), or the amount of time awake during the night after initiating sleep of > 30 min (129); total sleep time (TST), or amount of spent asleep during the night of ≤ 6.5 h (130) and sleep efficiency (SE), or the percentage of time asleep while in bed of < 85% (131). SE is the most important index of sleep consolidation/fragmentation as calculated by [TST/ (SOL +WASO duration +TST)] x 100% (132).

1.1.3. Methods for Assessing Sleep Quality and Duration

The gold standard for recording sleep is polysomnography (PSG), which measures brain waves, eye movement, muscle tension, and often respiration, heart rate, and leg movements during overnight sleep. Although not invasive, PSG recordings can be complex, particularly for cancer

patients that usually are exhausted or in pain (133). Therefore, few studies have used PSG to study sleep in cancer. Because PSGs can be challenging to record, actigraphy is an alternative method many researchers use to analyze sleep and wake patterns (134). An actigraph is a device similar in size to a watch worn on the wrist that records body movement using motion-sensitive accelerometry. Unique algorithms can estimate sleep and wake times from body movement. Studies show that Actigraphy is highly reliable, particularly for measuring total sleep time (TST) and sleep efficiency (SE) compared to PSG recordings (135).

Sleep disorder might be assessed through ActiGraph by evaluating parameters used to describe and quantify different aspects of sleep, such as its duration, quality, and architecture. Example data are presented in figure 1-3. The lightly shaded sleep period identifies the time in bed; the darker shaded period means the time asleep. The top chart in figure 1.4 shows a high sleep efficiency with only brief disturbances noted by physical movement. In contrast, the second chart indicates much lower sleep efficiency with prolonged interruptions of wakefulness and delayed sleep onset, resulting in disturbed sleep (136).

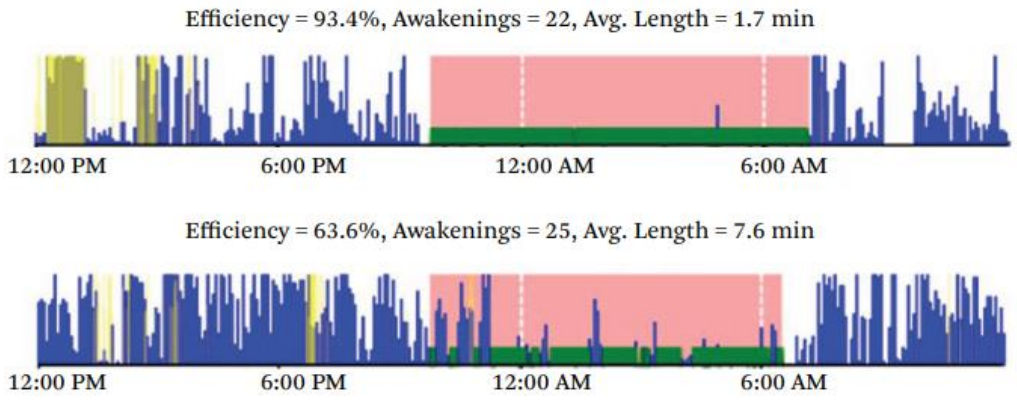

Figure 1-3: Actigraph Sleep Data, normal (Top) and disturbed (Bottom) nights of sleep (136). Note: Movement activity where a lightly shaded area identifies the period in bed and a darker shaded area means time asleep.

Sleep disorders may also be subjectively assessed and are mainly measured by the scales the Pittsburgh Sleep Quality Index questionnaire (PSQI), Insomnia Severity Index (ISI), Athens Insomnia Scale, Epworth Sleepiness Scale (ESS), General Sleep Disturbance Scale (GSDS). In clinical studies, the most used assessment is PSQI (137). PSQI can evaluate seven sleep areas, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month. The

severity of sleep quality is based on scoring 19 items in these seven areas, with higher scores indicating worse sleep. However, PSQI is used to evaluate sleep quality over one month. Another assessment tool for sleep disorders is ISI (138), a self-rated scale measuring insomnia symptoms and consequences. The items were designed to assess the severity of sleep-onset, sleep maintenance difficulties, satisfaction with current sleep pattern, interference with daily functioning, noticeability impairment, and degree of distress or concern caused by sleep disorder. The severity of insomnia is also based on the total score of these items. Both questionnaires have demonstrated high reliability and validity among cancer patients (139, 140).

1.4 Why it is Important to Address Sleep Disorders During the Preoperative Period?

Sleep disorders, which can occur during the perioperative period, affect many cancer patients undergoing surgery. Sleep disorders can adversely affect patient recovery, increase morbidity, and decrease hospitalization satisfaction (27, 28). Sleep disorders, notably short or long sleep durations, are associated with adverse health outcomes and all-cause mortality with a U-shaped relationship (141-143). Indeed, epidemiological, and experimental data support the association of sleep disorder with the risk of cardiovascular (CV) (hypertension and coronary artery disease) and metabolic (obesity, type 2 diabetes (T2DM)) diseases (19-22). Sleep disorder is also associated with psychopathological and psychiatric disorders, including negative mood and mood regulation, psychosis, anxiety, suicidal behavior, and depression risk (23-26). Furthermore, sleep profoundly affects endocrine, metabolic, and immune pathways, critical in developing and progressing chronic diseases (144-146).

Perioperative sleep management of patients is a relatively neglected field of research. Here will be reviewing significant, meaningful pathways impacting preoperative care and surgical outcomes. We hope to stimulate interest and research into this critical area by raising awareness of this topic.

1.1.4. Sleep Disorder and Immune-Related Outcomes

Most sleep disorders in cancer patients are associated with the activation of inflammatory responses (147). Experimental studies found that short sleep duration may alter immune responses (148) and upregulate several proinflammatory cytokines and chemokines, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) (149, 150).

Whereas IL-6 may help reduce inflammation by activating anti-inflammatory cytokines, short sleep duration actually triggers the production of IL-6 and TNF-α within cells, which affects the production of other inflammatory cytokines in the body (151). Many of these cytokines and chemokines, including those mentioned, are all encoded by target genes of the IKK-β-dependent NF-κB-activation pathway and are associated with tumor development and progression (152). Bidirectional communication between the brain and peripheral tissues and organs allows the brain to regulate the inflammatory activity, which can, in turn, influence neural processes within the brain and impact sleep. When this dynamic is induced by sustained sleep disturbance, a feed-forward sleep dysregulation can occur, which may activate the conserved transcriptional response to adversity (CTRA). CTRA activation increases proinflammatory gene expression and risk for inflammation-related disorders such as cardiovascular disease, cancer, and major depressive disorder. Conversely, it leads to decreased antiviral gene expression and increased risk of infectious diseases (153) (Figure 1-4). These findings may also affect the understanding of associations between insomnia, sleep disturbances, and cancer patients (154).

In the context of surgery, major surgical trauma is thought to be accompanied by a period of postoperative immunosuppression, predisposing patients to infection (155, 156). The postoperative inflammatory response causes neuroinflammation (157), which is thought to contribute to the postoperative sleep disturbances that surgical patients experience. No previous study has investigated this question in cancer patients undergoing surgery. However, administration of IL-1 into the lateral ventricle of rabbits resulted in the suppression of REM sleep, increased non-REM sleep and hyperthermia, similar to the changes observed in postoperative patients (158, 159). The sleep disturbance observed was attenuated by the pre-treatment with an IL-1 receptor antagonist (158). On the other hand, low levels of IL-6 at night were associated with more restorative sleep (160). Some cytokines involved in the surgical inflammatory response likely play a role in postoperative sleep disturbance. Laparoscopic surgery induces a less potent surgical inflammatory response than open surgery (161). This may help explain changes in EEG-sleep patterns observed after laparoscopic cholecystectomy (162).

1.1.5. Endocrine/Metabolic Changes Associated with Sleep Disorders

A meta-analysis included 11 cross-sectional studies and three cohort studies that found that short (<6 hours (163)) and long sleep (>9 hours (164)) increases the risk of metabolic syndrome (165).

Furthermore, a systematic review and meta-analysis (166), including 13 studies involving 300,202 patients found that short and long sleep duration increased the risk of obesity by 14% and 15%, respectively; the risk of hypertension was increased by 16% and 13%, respectively. Short sleep duration also increases the risk of hyperglycemia by 12% (156).

The mechanism of sleep loss causing metabolic dysregulation may be multifactorial. Changes in hormonal secretion profiles may affect glucose regulation (167). Growth hormone (GH) and cortisol are two hormones that have an impact on glucose regulation. GH is typically elevated at the sleep onset latency (SOL), with the highest levels during slow wave sleep (SWS). In contrast, cortisol levels significantly increase during the second half of sleep, predominantly in REM sleep (168, 169). Following sleep deprivation, the sleep-associated GH pulse is significantly reduced or eliminated (170). On the other hand, some experimental research found increased cortisol production at night during short sleep (171-173), a hormone that can cause insulin resistance and promote weight gain, hyperglycemia and hypertension. Studies have shown an increase in cortisol levels in the evening after just one night of sleep deprivation contributes to glucose dysregulation (174). Another possible mechanism is inflammation. As discussed above, experimental sleep deprivation has been found to alter the immune response and increase proinflammatory markers such as IL-6, TNF-α, and CRP (150, 175). Thus, prolonged sleep disturbances can lead to systemic low-grade inflammations associated with various diseases with inflammatory components, such as metabolic syndrome (166). Uncontrolled disease processes might mediate the association between long-term sleep duration and elevated inflammatory status. Establishing causality and elucidating the underlying mechanisms of sleep loss and metabolic dysregulation may help to manage metabolic disorders such as glucose dysregulation during the preoperative period.

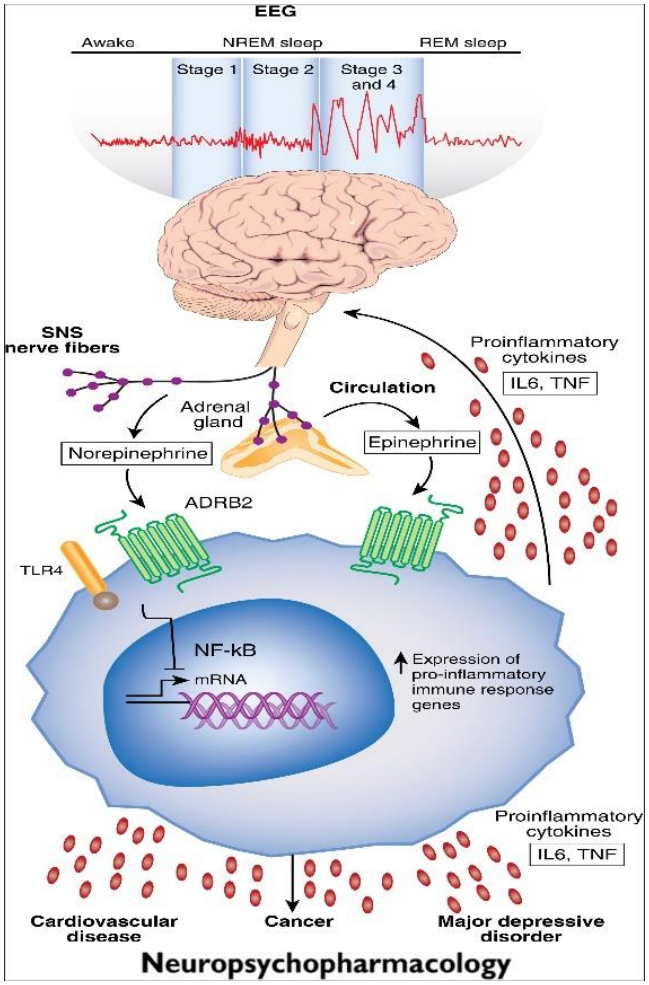

Figure 1-4: Immune consequences of sleep deprivation. Following a night of sleep loss, nerve fibers from the sympathetic nervous system (SNS) release the neurotransmitter norepinephrine into primary and secondary lymphoid organs and stimulate the adrenal gland to release stored epinephrine into the systemic circulation. Both neuromediators stimulate leukocyte adrenergic receptors (e.g., ADRB2) and activate nuclear factor (NF)-κB-mediated inflammatory programs. Intrinsic circuits detect microbes via pattern recognition receptors (PRRs) such as the toll-like receptor 4 (TLR4) and stimulate inflammatory gene expression via transcription factors such as nuclear factor (NF)-κB. The production of proinflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) occurs (153).

1.1.6. Sleep Disorder and Neurodegenerative Diseases (NDDs)

Perioperative sleep disturbances induce structural changes in the brain, possibly contributing to cognitive impairment (176). Clinical findings indicate that perioperative sleep disorders significantly increase the risk of postoperative complications, including postoperative delirium (POD) and postoperative cognitive dysfunction (POCD), especially in elderly patients (177, 178).

Potential pathophysiological mechanisms involve neuro-immune dysregulation. Neuroinflammation following sleep deprivation has been studied as a pathogenic mechanism potentially mediating the association between sleep deprivation and neurodegenerative processes (179-182). Low-grade neuroinflammation, as indexed by increased levels of pro-inflammatory mediators (e.g., TNF-α, IL-1β, and COX-2) and activation of astrocytes and microglia, primary immune cells in the brain, was detected in the hippocampus and piriform cortex regions of the brain of chronic sleep-deprived rats along with neurobehavioral alterations (anxiety, learning, and memory impairments). The catabolic process of cytoplasmic components (altered autophagy) contributes to the aggregation and accumulation of β-amyloid (Aβ), cytoskeleton-related protein τ, and synuclein in neuronal cells and tissues (183). Acute and chronic experimental sleep deprivation resulted in brain Aβ accumulation and plaque formation, a specific pathological change in Alzheimer's disease process, the most common type of dementia (184-186). Epidemiological studies also suggest disturbed sleep may increase the risk of Parkinson's disease (187, 188). Much like Aβ in Alzheimer's, abnormal levels of α-synuclein are typical to Parkinson's disease, the second most common NDD (189).

Altogether, the increased risk of NDDs (e.g., Alzheimer's disease, and Parkinson's disease) due to lack of sleep could be linked to the induction of inflammation in the brain and disorders of systemic innate and adaptive immunity (190). However, no human investigations have yet confirmed the mediating role of immune dysregulation in association between sleep disorders and the risk or outcomes of NDDs. Future studies should further investigate the role of perioperative sleep-disturbance-associated neurodegenerative disease.

1.1.7. Sleep Disorder and Mental Diseases

During the preoperative period, risk factors for anxiety and depression include waiting for hospitalization, fear of death, preoperative pain, cancer diagnosis itself, surgery risk and

complication, and postoperative recovery (191, 192). Sleep disturbance is a significant symptom and complication of most mental illnesses (193). Patients with depression symptoms show decreased slow-wave sleep and disinhibition of REM sleep both in REM density and total REM sleep time (194). Preoperative anxiety can increase perioperative pain and intraoperative anesthetic requirements (195), thus leading to higher Visual Analogue Scale (VAS) pain scores after surgery, long-term pain, and increased opioid use (196), which has a confounding negative effect on sleep (197). However, it is unclear whether sleep disorders are secondary to or comorbid with pain and/or the medications used to mitigate pain, anxiety, and depression in cancer patients (12). On the other hand, sleep disorder is also associated with an increased risk of psychopathological and psychiatric disorders, including negative mood, psychosis, anxiety, suicidal behavior, and the risk of depression (23-26).

The biological pathways between sleep disorders and mental diseases, specifically anxiety and depression, are not fully understood. However, one of the possible mechanisms is inflammation. As discussed before, sleep disorder contributes to increased levels of inflammatory cytokines (e.g., IL-6 and TNF) throughout the day (150, 175). However, a strong relationship between inflammation and depression has also been observed (198-200). Sleep disturbance may increase one's vulnerability to depression by augmenting affective sensitivity to cytokines and possibly by altering neural sensitivity to inflammation (153). Previous studies show that sleep disorders may lead to a significant increase in depressive symptoms in patients with inflammatory conditions (201, 202), which suggests that inflammation might also serve as a vulnerability factor in which subsequent exposure to sleep disturbance triggers an increase in depressive symptoms (202). Perioperative mental diseases, sleep disturbance, and post-operative pain can create a vicious circle (193), and their interactions are complex.

1.5 Conclusion

Regular sleep is crucial for maintaining immune function integrity and favoring a homeostatic immune against inflammatory triggers (153, 203). Thus, sleep disorders may result in deregulated immune responses with increased pro-inflammatory pathways, contributing to increased risk or worsening of infection and inflammation-related chronic diseases (204). A better knowledge of the influence of preoperative sleep disorders and inflammatory biological mechanisms is crucial, particularly in cancer patients during the preoperative period. These investigations may translate scientific knowledge into the preoperative clinic to prioritize health issues and develop strategies and policies for subject risk stratification.

1.6 Prehabilitation

Traditionally, attempts have been made to improve the recovery process by implementing interventions after surgery. Nevertheless, the postoperative period may not be the most suitable time to introduce interventions to hasten recovery (205). The preoperative period might be an appropriate time to intervene in the factors contributing to recovery (72, 205). The individual's active engagement in the preparation process may benefit one’s physical function and emotional distress surrounding the anticipation of surgery and recovery (37, 72). Prehabilitation can be defined as the process of enhancing the individual's functional capacity to withstand an incoming stressor of inactivity associated with surgery (29) (Figure 1-5).

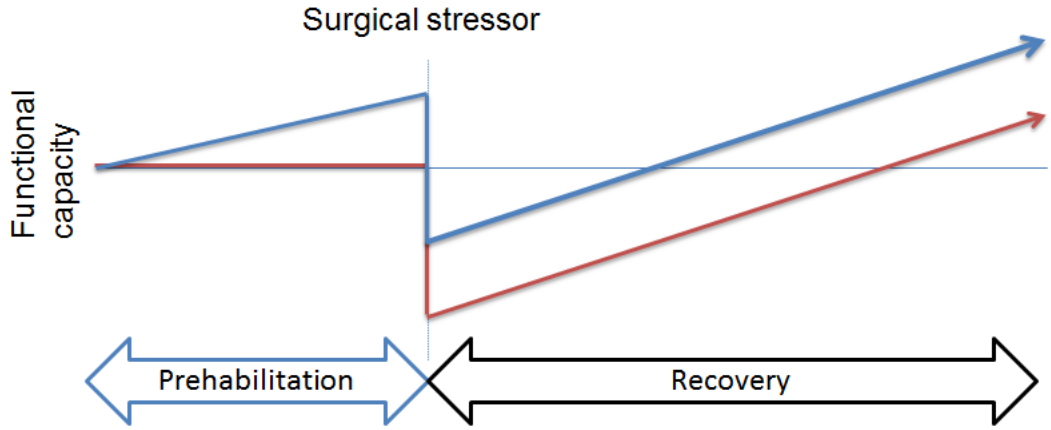

Figure 1-5: The trajectory of Functional Recovery. The blue line represents the trajectory of the patients' prehabilitation program. In the preoperative phase, functional capacity increases after exercise intervention. As a result of surgical stress, functional capacity decreases, but less than the non-prehabilitation patients (red line). After surgery, the prehabilitation patients recover faster and return to baseline earlier than the non-prehabilitation patients (206).

1.1.8. Multimodal Prehabilitation

Subgroup analysis of the study of Carli et al. showed that patients whose functional exercise capacity improved preoperatively recovered relatively well in the postoperative period (207). Despite the exercise intervention, one-third of patients deteriorated preoperatively and have a greater risk of prolonged recovery after surgery. It has been shown that poor preoperative physical function (fatigue, malnutrition, and physical performance), sleep difficulties (208), anxiety and depression symptoms were also significant confounding predictors of prolonged recovery (209-213). These results suggest that exercise training alone might not be sufficient to manage the stress response in all patients. It is also essential to address other factors, such as nutrition and coping behavior, that promote beneficial adaptation to training (32). Furthermore, after the diagnosis of CRC, there is a relatively short period of 4–5 weeks before the surgery (214).

The optimal approach to prehabilitation is still being debated. However, considering the relatively short window of opportunity for prehabilitation, supporting patients' physical and psychological needs is critical to prepare them best for surgery

and prompt recovery (72). This is possible only with robust, innovative multimodal interventions that include nutrition, psychological support, and exercise training. Subgroup analyses of Carli et al. (30, 215-217) showed meaningful changes in functional exercise capacity achieved with prehabilitation and reduced postoperative complications in patients scheduled for elective colorectal surgery for cancer compared to patients on rehabilitation (207, 217, 218). A randomized controlled trial of patients undergoing colorectal resection for cancer comparing rehabilitation to prehabilitation demonstrated meaningful changes in preoperative functional walking capacity and postoperative functional exercise capacity with a 4-week prehabilitation intervention (34). More specifically, patients in the prehabilitation period significantly improved while waiting for surgery by 25.2 m (SD, 50.2), while those in the rehabilitation group declined by 16.4 m (SD, 46.0); the mean difference between the two groups was 41.7 meters (95% CI, 19.8 to 63.5). These findings were consistent in colorectal cancer patients, demonstrating a clinically significant improvement in walking capacity measured using the 6-minute walk test by 48 meters between baseline and pre-surgery following a multimodal prehabilitation (219). Furthermore, several studies have shown that prehabilitation can reduce postoperative complications, hospital readmissions, length of hospital stay and care dependence by improving functional reserve (36, 220-222). Two randomized clinical trials describe a 50% reduction of complications after prehabilitation in high-risk patients undergoing major abdominal and colorectal surgery (223, 224). In a large RCT on multimodal prehabilitation for colorectal cancer surgery, severe complications (CCI score >20 considered clinically meaningful) dropped by almost 50% after prehabilitation (32, 35, 225).

Indeed, telemonitoring and community-based training are opportunities for monitoring home-based training and increasing adherence. The COVID-19 outbreak has hastened the shift towards providing remote interventions, and several ongoing trials mentioned engaging home-based prehabilitation models. Previous research indicates that a home-based multimodal prehabilitation program is feasible, effective, and may improve outcomes (226-229). Despite significant research focusing on the preoperative phase and prehabilitation interventions, limited knowledge is available on sleep behavior during this period. However, there is a need for further research to understand the impact

of preoperative sleep on patient outcomes and to develop interventions that can improve sleep behavior before surgery.

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Chapter 2 Association between physical activity, sedentary behaviors, and sleep-related outcomes among cancer survivors: a cross-sectional study

Prior research has shown a strong association between physical activity and sleep outcomes, but only limited epidemiological studies have examined this relationship in cancer survivors. Additionally, sedentary behavior plays a critical role in cancer. Most previous studies have focused on breast cancer and had small sample sizes. This chapter addresses these literature gaps by exploring the association between physical activity, sedentary behavior, and sleep-related outcomes using a large sample of US cancer survivors. We also aim to examine the potential effects of demographic and medical variables on these associations.

The article entitled 'Association between physical activity, sedentary behaviors, and sleep-related outcomes among cancer survivors: a cross-sectional study' has been submitted to the International Journal of Behavioral Medicine, which is currently under review—additional materials and outcomes in the Online Supplement following the main manuscript.

Association between physical activity, sedentary behaviors and sleep-related outcomes among cancer survivors: a cross-sectional study

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2.1 Abstract

Background: Limited research has examined the association between moderate to vigorous physical activity (MVPA), sedentary behavior (SB) and sleep-related outcomes in cancer survivors. Therefore, this study aimed to examine these associations using a nationally representative sample of U.S. adults. **Methods:** Data from the 2005-2018 National Health and Nutrition Examination Survey (NHANES) were analyzed. A total of 3229 adults with cancer histories were included. Physical activity was measured through accelerometry, and questions on daily activities, sedentary time and sleep were collected during the household interview. Weighted multivariable analyses were conducted after accounting for the complex sampling design of the NHANES dataset. **Results:** After adjustments, physical activity and SB outcomes were associated with several self-reported sleep-related parameters. Increases in minutes of self-reported MVPA and SB were associated with a decreased likelihood of reporting ≥ 8 hours of sleep (OR = 0.92, 95% CI = 0.86, 0.99 and OR = 0.88, 95% CI = 0.82, 0.95). Converse associations were found between device-measured MVPA and SB with the likelihood of reporting often/always feeling overly sleepy during the day (OR = 0.86, 95% CI = 0.75 and OR = 1.13, 95% CI = 1.05, respectively). However, an increased likelihood of waking up too early in the morning (OR = 1.22, 95% CI = 1.04) was observed with increases in minutes of device-measured MVPA. **Conclusions:** A sensible strategy to decrease the frequency of sedentary breaks and increase minutes of physical activity throughout the day may reduce sleep complaints reported in cancer survivors.

2.2 Introduction

Disturbed sleep, specifically insomnia, is one of the most prevalent cancer-related problems (1, 2). Sleep disturbances have been defined as problems with sleep initiation or maintenance, including a variety of clinical disorders (3) that may persist long after the end of cancer treatment (4, 5). The prevalence rates of sleep disturbance are consistently high, ranging from 23-87% (6, 7), of which insomnia symptoms are found in 30–50% of cancer patients (3, 8). In a recent cross-sectional survey including 5835 breast, prostate, and colorectal cancer survivors, more than 50% were identified as poor sleepers when subjectively determined (9). Poor sleep quality negatively affects the health condition of cancer patients, including increased fatigue symptoms, emotional distress, disturbing daily activity, and increased daily sedentary time life (8, 10), which is characterized by low energy expenditure activities (≤1.5 metabolic equivalents (MET)) (11, 12).

The American College of Sports Medicine (ACSM) (13) and The American Cancer Society (ACS) (14) guidelines for cancer survivors recommend at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic activity each week or an equivalent combination of MVPA per week. Despite the health benefits of physical activity, results of Loprinzi et al. suggest that most US cancer survivors are insufficiently active, and only 13% adhere to physical activity guidelines when physical activity was measured objectively using an accelerometer (15).

Research has shown that engaging in physical activity and reducing sedentary behavior can improve cancer outcomes (16). The benefits of regular physical activity (PA) in adults who have survived cancer are extensively documented (17-19) and there is evidence to suggest that it may also positively affect sleep outcomes (20, 21). Conversely, sedentary behavior is associated with adverse health outcomes. Previous studies have linked sedentary behavior with greater fatigue and pain, poorer mental well-being, and decreased quality of life (QoL) in cancer survivors (22-24). However, the influence of sedentary behaviors on sleep outcomes in cancer survivors has received little attention.

The limited epidemiological studies examining the association between physical activity and sleep outcomes in cancer survivors (25-29) showed inconsistent results. Moreover, methodological limitations of these studies (e.g., breast and gynecological cancer patients were the most represented subgroup, small sample size, single items measuring physical activity levels

and sleep outcomes) restrict the generalizability of these findings. To overcome some of these issues, we conducted a study aimed to examine the transversal associations between self-reported and device-measured MVPA, self-reported SB, and sleep-related outcomes using a nationally representative sample of U.S. cancer survivors aged 18 years and older from the NHANES 2005–2018. We also attempted to explore the potential effects of demographic and medical variables on these associations. We expected that more time spent on MVPA would be associated with better sleep-related outcomes, conversely to the daily minutes of SB.

2.3 Methods

2.3.1 Design and Participants

This study used data of adults aged 18 years and older from 2005–2018 National Health and Nutrition Examination Survey (NHANES), a cross-sectional survey of a representative sample of the U.S. civilian noninstitutionalized population selected with a complex, multistage probability design. Methods used in NHANES have been reported previously (30). Briefly, participants were interviewed in their homes and subsequently examined in mobile examination centers across numerous U.S. geographic locations. The study was approved by the National Center for Health Statistics ethics review board, with informed consent obtained from all participants prior to data collection (31). We extracted and aggregated data publicly available on sleep outcomes, sedentary behavior, physical activity and other characteristics from NHANES from cycles 2005-2018. Participants were asked about their personal health history, including cancer. If individuals report a history of cancer, they are further asked at what age they were diagnosed and what primary anatomical site was involved in the malignancy (Supplementary file, Table 2). Participants had to have sufficient accelerometry data, provide self-reported daily activities and sleeping data, and report having a cancer diagnosis to be included in the analyses.

2.3.2 Measurement of Physical Activity

Objective measured physical activity: The 2005-2006 NHANES cycle represents the objectively measured physical activity data. At the mobile examination centers, participants were asked to wear an ActiGraph 7164 accelerometer on the right hip for 7 consecutive days following their examination. The ActiGraph accelerometer measures accelerations in the vertical axis using a piezoelectric plate. The accelerometer output is digitized using an analog-to-digital converter,

and once digitized, the signal passes through a digital filter that detects accelerations ranging from 0.05 to 2.00 g in magnitude with frequency responses ranging from 0.25 to 2.5 Hz to filter motion outside the normal human movement. The filtered signal is then rectified and summed over a pre-determined epoch period. After the activity count is sorted into an epoch, it is stored in the internal memory, and then the integrator is reset to zero. For the present study, activity counts were summarized in 1-min time intervals. A weighted average of 4 accelerometer-derived intensity-related count cut-points classified moderate and vigorous physical activity intensity (32). The validated threshold for moderate-intensity was 2020 counts, and the threshold for vigorous-intensity was 5999 counts. Accelerometry data were reduced to the mean duration (min) of MVPA bouts accumulated over 1-min epoch lengths (time intervals). For the analyses described here, and as is recommended, only those participants with at least 4 days with 10 or more hours per day of monitoring data were included in the analyses (32).

Subjective measured physical activity: The NHANES 2007-2018 represent the self-reported physical activity data. Questions on daily activities were asked during the household interview using the Computer-Assisted Personal Interview (CAPI) system. Additionally, CAPI uses online help screens to assist interviewers in defining key terms. Interviewers learned about the daily duration of MVPA by asking five questions and one question identifying the daily duration of the sedentary behavior (Supplementary file, Table 1).

2.3.3 Measurement of Sleep Variables

During the NHANES cycle, various sleeping patterns, and outcomes, along with general productivity related to sleeping using the Functional Outcomes of Sleep Questionnaire (33), were examined in the present study. Questions on sleep were asked during the household interview using the CAPI system. Sleep outcomes include questions on hours of sleep per night, trouble sleeping, feeling sleepy during the day, waking up during the night, waking up too early in the morning, and trouble falling asleep. Response options were never, rarely, sometimes, often and almost always. The sleep-related outcomes used on each survey cycle are presented in Table 1.

2.3.4 Other Measurements

Information about age, race-ethnicity, marital status, type of cancer, income, education level, smoking status, anxiolytic, and hypnotic use were collected during the home interview.

Participants completed the Patient Health Questionnaire-9 (PHQ-9) (34) with values ranging from 0 to 27 (higher values indicate greater depression symptoms). The PHQ-9 depression scale consists of the actual 9 criteria upon which the diagnosis of DSM-IV depressive disorders is based.

2.4 Data Analysis

The NHANES data sets required for the current study were downloaded from https://www.cdc.gov/nchs/nhanes/index.htm and imported into SAS version 9.4 (SAS Institute Inc., Cary, NC) for data management and statistical analysis. All analyses were conducted using the *proc survey* commands to account for the complex survey design used in NHANES and to maintain the structure of the full NHANES sample when taking subsets of the NHANES data for analysis. The analyses included the use of appropriate sample weights, clustering variables, and primary sampling units to account for oversampling and non-response and to ensure the results were reflective of the United States civilian, non-institutionalized population. Descriptive data for patient demographics, outcome variables, predictor variables, and study covariates were obtained for each study sample (2007-2018 sample, and 2005-2006). Standard errors for all estimates were obtained using Taylor series linearization methods. Mean and standard deviation were reported for continuous variables, and frequency and percentage were reported for the categorical and binary variables. Linear regression models were used for the continuous sleep-related outcome, logistic regression was used for the binary sleep-related outcomes, and multinomial logistic regression was used for the categorical sleep-related outcomes. Appropriate model estimates were reported (β for linear regression and OR for logistic and multinomial logistic regression) along with their corresponding 95% confidence interval. A $p < 0.05$ was used to determine statistical significance. Table 1 summarizes the statistical models carried out of all survey cycles.

2.4.1 Outcome Variables

Six sleep-related outcomes were examined as the study endpoints. Hours of sleep per night was examined as both a continuous measure and categorical variables. There is evidence suggesting an association between sleep duration with survival in cancer patients. For instance, both short sleep duration (typically 5 or 6 h/night) and long sleep duration (typically 9 or 10 h/night) have

been found to significantly predict death in cancer patients and survivors (35-37). However, the mechanisms underlying these associations are not fully understood. Short sleep duration may not directly cause mortality in cancer survivors. Comorbid conditions, side effects, and immune system dysregulation may explain the association between short sleep duration and mortality (38, 39). Furthermore, long sleep duration has been previously associated with increased cause-specific mortality, possibly defined by residual confounding and comorbidities (40, 41). Based on prior research, sleep categories were <7 hours, 7-8 hours and ≥8 hours. Trouble sleeping was a binary (Yes/No) variable. The remaining endpoints were measured on a 5-point Likert scale with response options ranging from *never, rarely, sometimes, often and almost always*. Due to small event counts in some categories, the responses were combined into three categories as follows for analytic purposes: *Never, Rarely/Sometimes,* and *Often/Almost Always*.

2.4.2 Prediction Variables

Daily minutes spent on MVPA (self-reported and device-measured), daily duration of SB (self-reported).

2.4.3 Main Covariates

Age, race/ethnicity, sex, cigarette use, PHQ-9 depression score, self-reported health status, marital status, season, anxiolytic use, self-reported MVPA and SB, which are commonly linked to poor sleep or low level of physical activity in cancer patients (42-45). Accelerometer device wear time and hypnotic use were also included as a main covariate for the 2005-2006 NHANES survey cycle sample.

2.4.4 Primary Analyses

We tested two main models for the 2007-2018 NHANES survey cycle sample. In model 1, the prediction variable was daily minutes of self-reported MVPA. In model 2, the prediction variable was self-reported daily minutes spent in sedentary behavior. These two models tested, respectively, hypothesized that more time spent on MVPA positively affects sleep outcomes and more time spent on sedentary behavior negatively affects sleep outcomes, using self-reported variables. Similar models were conducted for the NHANES survey cycle samples from 2015 to 2018 to explore the potential effects of anxiolytic use on the associations between MVPA, SB,

and sleep-related outcomes. The supplementary file includes additional details on these analyses and a set of sensitivity analyses. One model was tested for the 2005-2006 NHANES survey cycle samples. In model 3, the prediction variable was device-measured MVPA, this model tested the hypothesis that more time spent on MVPA positively affects sleep outcomes. Models 1, 2, and 3 used the Akaike information criterion (AIC) fitting measure to determine whether the associations between PA and sleep-related outcomes were linear or curvilinear (46). To do this, the quadratic term for each prediction variable was to the models. The smaller AIC values indicated a better fitting regression model.

2.4.5 Sensitivity Analyses

For Models 1 and 2, a set of sensitivity analyses was performed by adding the NHANES sex and survey number as a covariate, and for model 3 only for sex. For the 2015-2018 NHANES survey cycle sample, models 1 and 2 were carried out by adding sex, survey number and anxiolytic use as a covariate (47, 48).

2.5 Results

Table 2 displays the sample demographics for each of the two study samples examined in the current study. A total of 3229 subjects (Figure 1), the mean (SE) age ranging from 61(1.25) - 62 (0.36) years old, participated in this study. More than half of the two study samples were female (57-64%), and reported good, very good, or excellent health (79-80%). Most participants had only 1 cancer diagnosis (>88%). More demographic information is available in the supplementary file (Table 3).

The data on anxiolytic use is available only for the 2015-2018 NHANES survey cycle, which includes 956 participants, accounting for 32.8% of the participants from the 2007-2018 survey cycle (supplementary file). Though the results of all survey cycles are reported and discussed in the manuscript, to simplify the visualization and interpretation of our results, the decision was made to present the main outputs of the survey cycle 2005-2006 and 2007-2018 in the tables of the manuscript. However, the supplementary file includes tables with the outcomes of all survey cycles (2005-2006, 2007-2018 and 2015-2018). The data on hypnotic use is available for the 2005-2006 cycle. The sleep-related outcomes, MVPA and SB characteristics of study participants are presented in Table 3. Mean sleep time ranged from 7.3 to 7.4 hours per

night, with 41% to 45% reporting 8 or more hours of sleep per night. About 1 in 3 participants (32-38%) reported having trouble sleeping. Among participants in the 2005-2006 NHANES, more than half reported having additional sleep issues at least once a month. The self-reported daily time spent in MVPA was 116.75 minutes (SE= 3.8) and the average daily minutes of SB was 397.24 minutes (SE= 5.0). Daily duration of the MVPA was collected for the 2005-2006 NHANES study participants. The device-measured daily minutes of MVPA was 22.5 minutes (SE = 8.2).

2.5.1 Association of Self-Reported MVPA, SB, and Sleep-Related Outcomes

Our linear regression analysis showed that the daily duration of MVPA was significantly associated with total hours of sleep per night and those who reported ≥ 8 hours of sleep. These associations were statistically significant only after adjusting for the daily time spent in SB, the anxiolytics use, sex and survey years (supplementary file, Table 7).

The multivariate linear regression analysis results indicated a negative association between the daily duration of moderate-to-vigorous physical activity (MVPA) and the total hours of sleep per night. Participants with a higher daily duration of MVPA tended to report fewer hours of sleep per night (β = -0.05, 95% CI = -0.08, -0.001, p = .01). However, the multinomial logistic regression analyses revealed that a longer daily duration of MVPA was associated with a lower likelihood of reporting 8 hours or more of sleep. For every 60 min increase of self-reported daily duration of MVPA, participants were 8% less likely to report ≥ 8 hours compared to those who report ≤ 7 hours of sleep (OR = 0.92, 95% CI = 0.86, 0.99, p = .02).

The linear regression analysis revealed significant associations between the daily time spent in sedentary behavior (SB) and the total hours of sleep per night, as well as reporting ≥ 8 hours of sleep and feeling overly sleepy during the day. Importantly, these associations remained significant even after adjusting for the daily time spent on moderate-to-vigorous physical activity (MVPA) (supplementary file, Table 6, 7). The multivariable linear regression analysis further confirmed that a higher daily time spent in SB was independently associated with fewer hours of sleep per night (β = -0.03, 95% CI = -0.05, -0.001, p = .02) (Table 4). These findings remained consistent when considering additional covariates such as sex, survey year, and anxiolytic use.

After adjusting for sex, survey year, and anxiolytics use the multinomial logistic regression analyses revealed that a longer daily time spent in SB is associated with a lower

likelihood of reporting 8 hours or more of sleep compared to those who reported sleeping for less than 7 hours. For every 60 min increase of self-reported SB, participants were 12% (OR = 0.88, 95% CI = 0.82, 0.95, p = .0005) less likely to report ≥ 8 hours of sleep than ≤ 7 hours (supplementary file, Table 6, 7). Additionally, the multinomial logistic regression analyses demonstrated that a longer daily time spent in sedentary behaviors is associated with an increased likelihood of often or always feeling overly sleepy during the day compared to those who never reported feeling overly sleepy. For every 60 min increased self-reported SB, participants were 13% more likely to feel *often\always* overly sleepy during the day (OR = 1.13, 95% CI = 1.05, 1.22, p = .0002) (Table 4). These associations remained consistent after adjusting for sex and survey year (supplementary file, Table 6) but became insignificant after further adjusting for the anxiolytics use (supplementary file, Table 7).

2.5.2 Association of Device-Measured MVPA and Sleep-Related Outcomes

Device-measured daily minutes of MVPA were not significantly associated with hours of sleep, trouble sleeping and falling asleep, wake up during the night (Table 4). However, the multivariate linear regression analysis showed that device-measured MVPA was associated with feeling overly sleepy during the day and waking up too early in the morning. Results were unchanged after adjusting the models for sex (Supplementary file, Table 8).

The multinomial logistic regression analyses revealed that a higher amount of device-measured MVPA was associated with a lower likelihood of rarely or sometimes feeling overly sleepy during the day compared to those who never reported feeling overly sleepy. For every 60 min increase of device-measured MVPA, participants were 14% less likely to feel *rarely\sometimes* overly sleepy during the day (OR = 0.86, 95% CI = 0.75, 0.99, p = .03). Furthermore, our analysis showed that a higher amount of device-measured MVPA was associated with an increased likelihood of rarely or sometimes waking up too early compared to those who never reported waking up early in the morning. For every 60 min increase of device-measured MVPA participants was 22% more likely to *rarely\sometimes* report waking up too early in the morning(OR = 1.22, 95% CI = 1.04, 1.44, p = .02).

2.5.3 Linear Versus Curvilinear Relationship

Tables 9-16 presented in the supplementary file display the secondary analyses' results

comparing the curvilinear and linear models. The study findings show that the linear models were preferred over the curvilinear models for the continuous sleep outcomes (hours of sleep per night and minutes to fall asleep). According to the AIC criteria, the curvilinear models were preferred over the linear models for all binary and categorical sleep outcome measures.

2.6 Discussion

Using a large US sample of adults, we attempted to examine the cross-sectional associations between self-reported and device-measured MVPA, self-reported SB, and sleep-related outcomes. Our analysis revealed that a higher daily duration of MVPA was associated with fewer hours of sleep per night. Additionally, for every 60 min increase of the self-reported daily duration of MVPA, participants were 8% less likely to report ≥ 8 hours of sleep than ≤ 7 hours. These findings were statistically significant only after adjusting for daily time spent in SB, survey year, sex, and anxiolytics use. Previous studies in the literature have shown inconsistent results when examining self-reported physical activity. For instance, a study with 359 ovarian cancer survivors found that those who met the public health physical activity guidelines reported significantly better sleep quality and efficiency subscale of the PSQI (27). The differences in results between these studies might be due to the difference in the populations studied. While our trial enrolled a mix of cancer types, the other explicitly focused on ovarian cancer survivors. Another factor is the differences in using questionnaires to evaluate sleep outcomes (49). The study by Stevinson et al. used the Pittsburgh Sleep Quality Index questionnaire; however, our study used single items of sleep.

Similarly, higher daily time spent in sedentary behaviors was associated with fewer hours of sleep. Additionally, for every 60 min increase of self-reported SB, participants were 12% less likely to report ≥ 8 hours of sleep than ≤ 7 hours. Our analyses did not find a significant association between sedentary behavior and trouble sleeping. However, we did observe that for every 60 min increase self-reported SB, participants were 13% more likely to feel *often\always* overly sleepy during the day compared to those who never reported feeling overly sleepy during the day. Our findings were independent of daily time spent on physical activity. This suggests that prolonged sedentary behavior may still affect sleep hours and perceptions of fatigue regardless of daily physical activity engagement. While several studies have documented the adverse effects of sedentary behaviors on physical and psychosocial functions in cancer

survivors (50-52), our findings contribute to confirming evidence. Our results indicated that both daily duration of physical activity and sedentary behavior impact sleep outcomes, in line with the Canadian 24-Hour Movement Guidelines for Adults (53). These guidelines underscore the importance of movement behaviors across the whole 24-h day, in contrast to the focus on a single movement behavior that identified physical activity guidelines for adults worldwide. Therefore, based on our findings, we encourage cancer survivors' adults to increase their frequency of sedentary breaks throughout the day.

To our knowledge, there is limited research exploring the relationship between sedentary behavior and sleep-related outcomes in cancer survivors. The existing literature presents conflicting findings on this topic. While some studies show negative associations between sedentary activities, insomnia symptoms (28, 54) and sleep disturbances, others have found no significant associations (29, 54). The conflicting results between self-reported and objectively estimated sedentary time warrant further investigation. Often, individuals are unaware of daily sedentary time spent and are more likely to underestimate sitting time (55). When physical activity was objectively measured, our results did not show associations between daily time spent on MVPA and hours of sleep. However, our findings revealed that for every 60 min increase of device-measured MVPA, participants were 14% less likely to feel *rarely\sometimes* overly sleepy during the day compared to those who never feel sleepy. Interestingly, individuals with higher levels of device-measured MVPA were 22% more likely to rarely or occasionally report waking up too early in the morning compared to those who never reported early morning awakening. The lack of significant associations between device-measured MVPA and sleep outcomes aligns with previous studies that used subjective measures of physical activity (26, 56). To our knowledge, no previous epidemiological studies have examined the association between MVPA objectively determined and sleep-related outcomes in cancer survivors. However, it is difficult to explain the null association between device-measured physical activity and sleep duration. It is possible that guided exercise interventions are more efficient and associated with better sleep-related outcomes. Other potential confounding variables relevant to the cancer population such as light exposure (57), as these variables were not measured in the 2005-2018 NHANES cycle.

Our findings showed inconsistent associations between the self-reported MVPA and the device-measured MVPA. While higher self-reported MVPA duration was negatively associated

with the hours of sleep and a lower likelihood of reporting 8 hours or more of sleep compared to those reporting less than 7 hours, device-measured MVPA did not show any associations with the hours of sleep. These inconsistent associations might be explained by the fact that self-reported MVPA estimates were higher (116.75 min/day) compared to device-measured MVPA (22.54 min/day). Similar discrepancies between self-reported and device-measured MVPA have been observed in previous studies involving Chinese (58) and Canadian (59) adult populations and a large international community sample (60). For example, data collected from 3865 adult participants in six countries shows that the weekly average MVPA estimated by the International Physical Activity Questionnaire - Long Form (IPAQ-LF) was 1185 min and accumulated 256 min of MVPA according to accelerometry (60). The level of agreement might be influenced by how accelerometry data were operationalized (e.g. data cut points (32, 61)). Some studies showed the MVPA reported with the IPAQ-LF showed a better concordance with the accelerometry-based variables that included light-intensity activities (<3 METs) as defined by the Freedson cut points (58, 62, 63). Another explanation is that the self-report measures of physical activity had generally higher results than objective measures (64), and self-reports overestimated physical activity to a greater extent in females than males (65) as respondents may be unable to provide valid estimates of PA intensity for each domain (60). Besides, whereas most activities are captured easily with the accelerometer (e.g., whole-body movement), others are complex (e.g., cycling, taking the bus) (66). This shows substantial discrepancies between self-reports and objective measures; consequently, the need to be carefully considered when interpreting the data collected of the PA, regardless of the measurement type used. Future studies should consider the limitations of each measurement method, and further efforts to improve measures are needed.

Cancer survivors might have high vulnerability to health risk factors and complications with increased daily sedentary time (55). For instance, cancer treatment and recovery phases may encourage subjects to be inactive and spend most of their waking time in sedentary activities (67), and result in further physical and psychological decline over time (55). While many advantages may result from increasing cancer survivors' MVPA, it may be equally important and potentially more feasible at a population level to increase lower-intensity activities and reduce minutes of SB. A multiple behavior approach to reduce daily minutes spent on sedentary behavior associated with disturbed sleep may provide the opportunity to understand these

behavioral patterns and identify intervention points in cancer survivors. Additionally, to provide adequate public health interventions, healthcare professionals must educate cancer survivors to engage in physical activity and reduce the time spent on sedentary behavior, which may help promote their overall health.

2.6.1 Strengths and Limitations

To the best of our knowledge, all epidemiological studies conducted to date have relied on self-report measures of physical activity and focused mainly on women with breast and gynecological cancer. Our study also has several important strengths. First, we used a nationally representative sample of all ages of cancer survivors. Second, we examined the association between physical activity, sedentary behavior and sleep using objectively measured physical activity. Third, we adjusted for several factors, including sex, cigarette use, depression score, self-reported health status, marital status, season, anxiolytic, and hypnotics use, and device wear time. Limitations to the present study include the cross-sectional study design, which prevents any causal inferences between variables. Additionally, the present study relies on self-reported sleep-related outcomes and sedentary behavior and the absence of additional objective measurements. Although the NHANES Actigraph data include the minutes of SB, the decision was made not to retain this data in the present study as the time of SB could be misinterpreted. When using a single accelerometer, distinguishing between SB and daytime sleep from each other and non-wear-times can be difficult, resulting in underestimation of SB (68, 69). Future studies may use accelerometry monitoring accompanied by activity and sleep diaries to identify unusual activities, naps, sleeping times, and non-wear time of accelerometers (70). Cancer-specific clinical details, including stage and prior treatment, are not reported. Other variables, including the type of cancer, number of cancer diagnoses, and years since diagnosis, were reported but were not included as covariables in our statistical models. However, it is important to note that these variables, along with specific cancer treatments (such as surgery, chemotherapy, and/or radiation therapy) and years since diagnosis may potentially influence individuals' likelihood of experiencing sleep problems (6, 71). Other factors related to the comorbidity conditions of cancer survivors that are not available here may have influenced the present study findings. Finally, specific outcomes like prescription of anxiolytic, and hypnotic are assessed within the past 30 days of the survey; use of these medications outside this window is not measured. The

availability of longitudinal data assessing these results over time would provide more robust evidence for this relationship.

2.7 Conclusion

Our findings showed that daily time spent in sedentary behavior and moderate-to-vigorous physical activity are both related to sleep outcomes. However, contradictory associations were found between self-reported and objectively measured physical activity. Our findings showed that independent of physical activity, sedentary behavior was associated with sleep duration and feeling overly sleepy and unrested throughout the day. However, the associations between physical activity and sleep outcomes are dependent on the daily time spent on sedentary behavior. To allow for causal inferences, future experimental studies must confirm that a daily balanced approach to physical activity and a reduction in the frequency of sedentary breaks may optimize sleep outcomes in cancer survivors.

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2.10 Declarations of Interest

The authors declare that they have no conflicts of interest.

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Figures and Tables

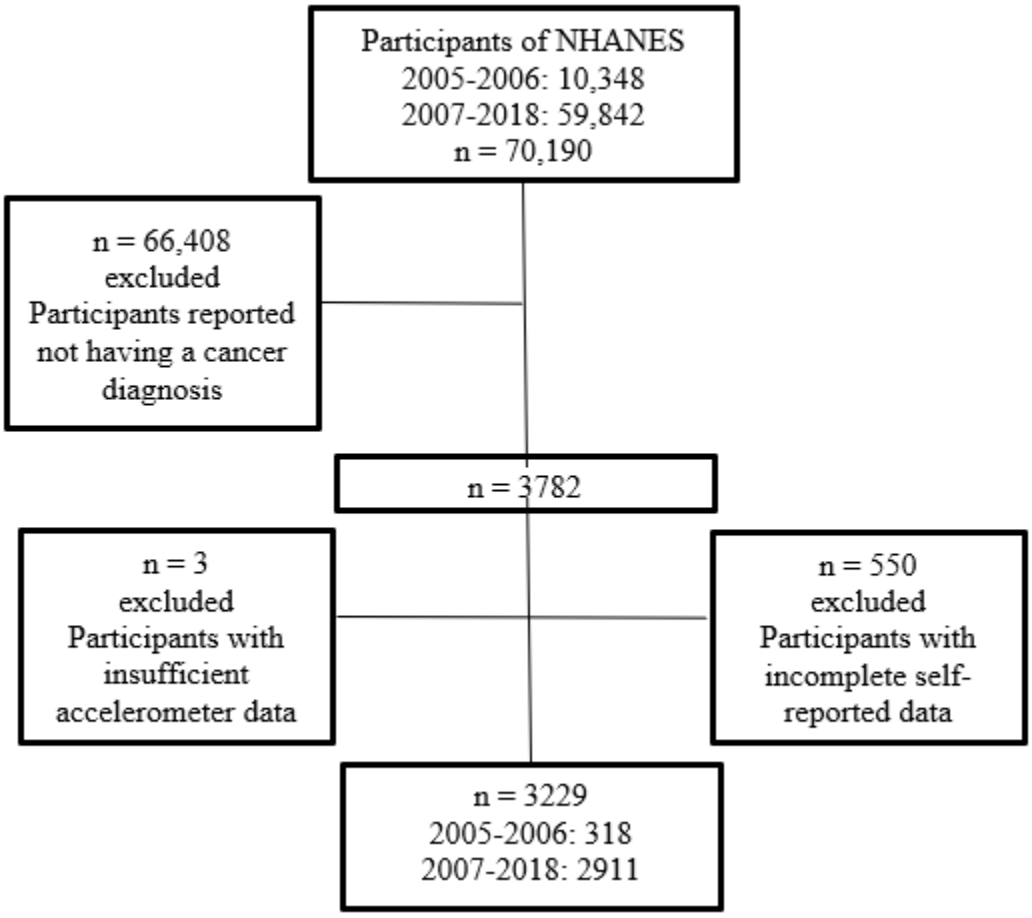

Figure 2-1: Flow chart of the screening process for the selection of eligible participants. NHANES, National Health and Nutrition Examination Survey.

Table 2-1: Summary of statistical Models for all survey cycles

NHANES Survey year / **Variables**		**2007-2018 self-reported PA and SB (model 1 and 2)**	**2005-2006 device-measured MVPA (model 3)**
Linear regression models			
Dependent variables		**Independent variables**	**Independent variables**
Sleep hour\night		1- MVPA 2- SB	MVPA
Logistic regression models			
Dependent variables		**Independent variables**	**Independent variables**
Trouble sleeping (yes/no)		1- MVPA 2- SB	MVPA
Multinomial logistic regression			
Dependent variables		**Independent variables**	**Independent variables**
1- **Sleep hour\night** <7 hours, 7-8 hours, ≥8 hours		1- MVPA 2- SB	MVPA
2- **Feeling overly sleepy**	Never, rarely/ sometimes, often/almost always	1- MVPA 2- SB	MVPA
3- **Waking up during the night**			MVPA
4- **Waking up too early in the morning**			MVPA
5- **Having trouble falling asleep**			MVPA
Sensitivity analysis			
Linear, logistic and multinomial logistic regression		1- Sex	1- Sex
		2- Survey cycle number	
		3- Anxiolytic medications (only for 2015-2018 NHANES survey)	

MVPA: moderate-to-vigorous physical activity
SB: Sedentary behavior

Table 2-2: Weighted means and percentages (standard error) for selected characteristics of the NHANES survey cycle sample.

Outcomes \ NHANES survey year	**2007-2018 self-reported MVPA and SB**	**2005-2006 device-measured MVPA**
No. patients in sample	2,911	318
Age, mean (SE)	62.76 (0.36)	61.27 (1.25)
Depression score	3.41 (0.13)	3.41 (0.23)
% Male	1386 (43.8)	139 (36.2)
Race/ethnicity		
%Hispanic	381 (5.0)	22 (3.3)
%Non-Hispanic, White	1943 (86.1)	248 (88.7)
%Non-Hispanic, Black	427 (5.2)	43 (5.0)
%Non-Hispanic, Other	160 (3.7)	5 (2.9)
Education		
%<High school	575 (11.2)	77 (16.6)
%High school graduate	648 (20.6)	76 (24.3)
%Some college	901 (32.1)	85 (29.7)
%College graduate	787 (36.0)	80 (29.4)
Marital status		
%Married/living with a partner	1741 (66.0)	208 (68.7)
%Widowed	497 (13.1)	43 (10.7)
%Divorced/separated	484 (14.8)	52 (15.8)
%Never married	189 (6.1)	15 (4.8)
Smoking status		
%Never smoked	1316 (46.5)	134 (41.7)
%Current smoker	454 (15.4)	49 (18.4)
%Former smoker	1141 (38.1)	135 (39.9)
Alcohol use		
%Never drinks	44 (1.1)	45 (12.8)
%Current drinker	284 (12.5)	217 (71.2)
%Former drinker	156 (4.5)	56 (16.0)
%Don’t know	2427 (81.9)	0 (0)
Current health status		
%Excellent/very good	947 (39.1)	115 (41.7)
%Good	1137 (39.5)	125 (37.3)
%Fair/Poor	827 (21.4)	78 (21.0)
Cancer diagnostic		
%Breast/cervix/ovary/uterus	845 (29.1)	105 (36.3)
%Colon/rectum/stomach	246 (6.2)	24 (5.2)
%Prostate/testis	502 (11.7)	46 (9.3)
%Other	1342 (51.7)	146 (49.7)

MVPA: moderate-to-vigorous physical activity, SB: Sedentary behavior

Table 2-3: Physical activity, sedentary behavior and sleep-related outcomes characteristics of study participants

NHANES survey year / Outcomes [1]	**2007-2018 self-reported MVPA and SB**	**2005-2006 device-measured MVPA**
Sleep related outcomes		
Sleep hours, mean (SE)	7.35 (0.04)	7.43 (0.27)
Sleep hours\night		
<7 hours	909 (27.64)	99 (26.64)
7-8 hours	706 (27.09)	87 (32.12)
≥8 hours	1296 (45.27)	132 (41.24)
Trouble sleeping	1050 (38.6%)	100 (32.9%)
Feel overly sleepy during the day		
Never	332 (20.0%)	120 (32.9%)
Rarely/sometimes	768 (55.2%)	124 (43.3%)
Often/almost always	379 (24.8%)	73 (23.8%)
Wake up during night		
Never		100 (30.5%)
Rarely/sometimes		138 (43.1%)
Often/almost always		80 (26.4%)
Wake up too early in the morning		
Never		130 (40.0%)
Rarely/sometimes		115 (38.0%)
Often/almost always		73 (22.0%)
Trouble falling asleep		
Never		119 (34.2%)
Rarely/sometimes		148 (49.5%)
Often/almost always		51 (16.3%)
Physical activity outcomes min\day		
MVPA	116.75 (3.87)	
SB	397.24 (5.09)	
MVPA		22.54 (8.24)
Device wear time [2]		1439.22 (0.37)

[1] Values are reported as frequency and weighted percent for categorical variables and weighted mean and standard error for continuous variables.

[2] Participants wore the accelerometer for at least 4 days with 10 or more hours per day of monitoring.

MVPA: moderate-to-vigorous physical activity, SB: sedentary behavior

Table 2-4: Multiple logistic regression models for the association between daily duration of MVPA, SB and sleep-related outcomes in the NHANES survey sample.

NHANES Survey year	**2007-2018 self-reported**		**2005-2006 device-measure**
Outcome Variable	**MVPA**	**SB**	**MVPA**
	β (95% CI)		
Hrs. sleep / night	-0.03 (-0.06, 0.01)	-0.03 (-0.05, -0.01) *	0.002 (-0.07, 0.08)
Time to fall asleep (min)			0.27 (-0.14, 0.68)
	OR (95% CI)		
Hrs. sleep / night			
<7 hours	1.0	1.0	1.0
7-8 hours	1.00 (0.95, 1.05)	0.99 (0.94, 1.04)	1.00 (0.66, 1.54)
≥8 hours	0.96 (0.92, 1.01)	0.96 (0.93, 1.00)	1.16 (0.86, 1.56)
Trouble sleeping	0.99 (0.95, 1.04)	0.99 (0.96, 1.03)	0.25 (0.04, 1.48)
Feel overly sleepy			
Never	1.0	1.0	1.0
Rarely/sometimes	0.99 (0.94, 1.06)	1.05 (0.97, 1.12)	0.86 (0.75, 0.99) *
Often/almost always	1.02 (0.95, 1.09)	1.13 (1.05, 1.22) **	0.20 (0.02, 2.16)
Trouble falling asleep			
Never			1.0
Rarely/sometimes			1.32 (<0.001, >999.99)
Often/almost always			0.47 (<0.001, >999.99)
Wake up during night			
Never			1.0
Rarely/sometimes			1.23 (<0.001, >999.99)
Often/almost always			1.06 (<0.001, >999.99)
Wake up too early in the morning			
Never			1.0
Rarely/sometimes			1.22 (1.04, 1.44) *
Often/almost always			1.18 (0.96, 1.45)

[1] Effect size reported as a 60-minute change in device-measured and self-reported activity level
MVPA: moderate-to-vigorous physical activity. SB: Sedentary behavior. * p<0.05, ** p<0.005

Online Supplement

2.12 Additional Tables

Table 2-1: Items identifying the daily duration of MVPA and sedentary behavior among the analyzed sample 2007-20018

Moderate-to-vigorous physical activity (MVPA)
"How much time -do you/does SP- spend doing vigorous-intensity activities at work on a typical day?"
"How much time -do you/does SP- spend doing moderate-intensity activities at work on a typical day?
"How much time -do you/does SP- spend walking or bicycling for travel on a typical day?
'How much time -do you/does SP- spend doing vigorous-intensity sports, fitness or recreational activities on a typical day?
"How much time -do you/does SP- spend doing moderate-intensity sports, fitness or recreational activities on a typical day?
Sedentary behavior (SB)
"The following question is about sitting at school, at home, getting to and from places, or with friends including time spent sitting at a desk, traveling in a car or bus, reading, playing cards, watching television, or using a computer. Do not include time spent sleeping. How much time -do you/does SP- usually spend sitting on a typical day?".

Table 2-2: Questionnaires defined adults with cancer.

1. Have you/Has SP- ever been told by a doctor or other health professional that - you/s/he- had cancer or a malignancy of any kind?
2. Have you/Has SP- ever been told by a doctor or other health professional that - you/s/he- had cancer or a malignancy of any kind?
3. What kind of cancer was it?
4. 1st cancer - what kind was it?
5. 2nd cancer - what kind was it?
6. 3rd cancer - what kind was it?
7. More than 3 kinds of cancer?
8. How old -were you/was SP- when cancer was first diagnosed?
9. How old -were you/was SP- when some other type of cancer was first diagnosed?
10. How long (have/has) -you/SP- had cancer (# of days)?
11. Cancer antigen 15.3 (mU/mL)
12. Cancer antigen 125 (U/mL)

Table 2-3: Weighted means and percentages (standard error) for selected characteristics of the NHANES survey cycle sample

	Sample 1	Sample 2	Sample 3
No. patients in sample	2,911	956	318
Age, mean (SE)	62.76 (0.36)	63.83 (0.58)	61.27 (1.25)
Age diagnosed, mean (SE)	51.45 (0.41)	52.40 (0.72)	49.92 (1.22)
Years since diagnosis, mean (SE)	11.30 (0.29)	11.44 (0.49)	11.36 (1.04)
Depression score	3.41 (0.13)	3.18 (0.17)	3.41 (0.23)
No. cancer diagnoses			
1	2605 (89.6%)	850 (88.3%)	283 (88.5%)
2	269 (9.2%)	89 (9.9%)	31 (10.2%)
3	32 (1.1%)	16 (1.7%)	4 (1.3%)
>3	5 (0.1%)	1 (0.02%)	0 (0%)
Male	1386 (43.8%)	463 (44.3%)	139 (36.2%)
Race/ethnicity			
Hispanic	381 (5.0%)	150 (5.7%)	22 (3.3%)
Non-Hispanic, White	1943 (86.1%)	582 (84.0%)	248 (88.7%)
Non-Hispanic, Black	427 (5.2%)	140 (5.0%)	43 (5.0%)
Non-Hispanic, Other	160 (3.7%)	84 (5.3%)	5 (2.9%)
Education			
<High school	575 (11.2%)	148 (8.0%)	77 (16.6%)
High school graduate/GED	648 (20.6%)	213 (21.2%)	76 (24.3%)
Some college	901 (32.1%)	339 (33.2%)	85 (29.7%)
College graduate	787 (36.0%)	256 (37.7%)	80 (29.4%)
Income			
<$25,000	878 (19.7%)	284 (18.3%)	102 (68.7%)
$25,000-44,999	639 (18.3%)	190 (14.8%)	43 (10.7%)
$45,000-74,999	522 (20.6%)	172 (22.3%)	52 (15.8%)
$75,000-99,999	222 (10.4%)	73 (10.6%)	15 (4.8%)[2]
>$100,000	437 (23.8%)	153 (25.7%)	N/A
Don't know	213 (7.1%)	84 (8.4%)	0 (0%)
Marital status			
Married/living with a partner	1741 (66.0%)	535 (64.0%)	208 (68.7%)
Widowed	497 (13.1%)	161 (13.1%)	43 (10.7%)
Divorced/separated	484 (14.8%)	190 (16.6%)	52 (15.8%)
Never married	189 (6.1%)	70 (6.3%)	15 (4.8%)
Time of year participated in NHANES survey			
Nov 1 – Apr 30	1220 (41.2%)	450 (46.4%)	124 (37.9%)
May 1 – Oct 31	1691 (58.8%)	506 (53.6%)	194 (62.1%)
Smoking status			
Never smoked	1316 (46.5%)	444 (47.8%)	134 (41.7%)
Current smoker	454 (15.4%)	145 (13.9%)	49 (18.4%)

Former smoker	1141 (38.1%)	367 (38.3%)	135 (39.9%)
Alcohol use			
Never drinks	44 (1.1%)	44 (3.1%)	45 (12.8%)
Current drinker	284 (12.5%)	281 (33.9%)	217 (71.2%)
Former drinker	156 (4.5%)	151 (12.0%)	56 (16.0%)
Don't know	2427 (81.9%)	480 (51.1%)	0 (0%)
Anxiolytic use	N/A	160 (17.7%)	N/A
Antidepressant use	N/A	146 (17.3%)	N/A
Current health status			
Excellent/very good	947 (39.1%)	300 (40.4%)	115 (41.7%)
Good	1137 (39.5%)	394 (39.3%)	125 (37.3%)
Fair/Poor	827 (21.4%)	262 (20.3%)	78 (21.0%)
Cancer of the:			
Breast/cervix/ovary/uterus	845 (29.1%)	265 (29.7%)	105 (36.3%)
Colon/rectum/stomach	246 (6.2%)	76 (5.0%)	24 (5.2%)
Prostate/testis	502 (11.7%)	181 (13.6%)	46 (9.3%)
Bladder/gall bladder/larynx/kidney/pancreas/liver	187 (4.8%)	69 (5.4%)	12 (3.5%)
Bone/brain/nervous system	34 (0.9%)	7 (0.6%)	3 (0.6%)
Esophagus	19 (0.4%)	7 (0.4%)	2 (0.7%)
Leukemia/blood	46 (1.7%)	19 (2.3%)	3 (0.7%)
Lung	77 (2.1%)	28 (1.7%)	8 (2.5%)
Lymphoma/Hodgkin's disease/thyroid/skin/mouth/tongue/lip	871 (37.6%)	270 (34.5%)	107 (36.8%)
Other	163 (6.4%)	58 (7.3%)	15 (5.9%)
Take pills to sleep			
Never	N/A	N/A	231 (71.6%)
Rarely (1 time a month)	N/A	N/A	18 (6.4%)
Sometimes (2-4 times a month)	N/A	N/A	21 (6.2%)
Often (5-15 times a month)	N/A	N/A	11 (4.7%)
Almost always (16-30 times a month)	N/A	N/A	37 (11.1%)
Year			
2005-2006	N/A	N/A	318 (100%)
2007-2008	513 (13.8%)	N/A	N/A
2009-2010	538 (15.5%)	N/A	N/A
2011-2012	404 (14.9%)	N/A	N/A
2013-2014	487 (18.7%)	N/A	N/A
2015-2016	484 (18.8%)	479 (51.1%)	N/A
2017-2018	485 (18.2%)	477 (48.9%)	N/A

[1] Values are reported as frequency and weighted percent for categorical variables and weighted mean and standard error for continuous variables

[2] Due to changes in the way NHANES assessed income in the 2005-2006 survey cycle, this category is >$75,000

Sample 1: Contains data from NHANES 2007-2018 to study the cross-sectional association between self-reported physical activity and sleep measures

Sample 2: Contains data from NHANES 2015-2018 to study cross-sectional association between self-reported physical activity and sleep measures; this sample contains information on anxiolytic use, allowing us to control for these variables in the regression models

Sample 3: Contains data from the NHANES 2005-2006 to study the effect of accelerometer measures of physical activity on sleep

Table 2-4: Sleep-related outcomes characteristics of study participants of the NHANES survey cycle sample

	Sample 1	Sample 2	Sample 3
Sleep Duration			
Sleep hours, mean (SE)	7.35 (0.04)	7.80 (0.04)	7.43 (0.27)
Sleep hours			
<7 hours	909 (27.64)	198 (17.38)	99 (26.64)
7 hours	706 (27.09)	229 (27.36)	87 (32.12)
≥8 hours	1296 (45.27)	529 (55.25)	132 (41.24)
Sleep Quality			
Trouble sleeping	1050 (38.6%)	365 (41.1%)	100 (32.9%)
Feel overly sleepy during the day			
Never	332 (20.0%)	141 (15.4%)	120 (32.9%)
Rarely/sometimes (1-4 times/month)	768 (55.2%)	541 (58.1%)	124 (43.3%)
Often/almost always (5-30 times/month)	379 (24.8%)	272 (26.5%)	73 (23.8%)
Wake up during night			
Never	N/A	N/A	100 (30.5%)
Rarely/sometimes (1-4 times/month)	N/A	N/A	138 (43.1%)
Often/almost always (5-30 times/month)	N/A	N/A	80 (26.4%)
Wake up too early in the morning			
Never	N/A	N/A	130 (40.0%)
Rarely/sometimes (1-4 times/month)	N/A	N/A	115 (38.0%)
Often/almost always (5-30 times/month)	N/A	N/A	73 (22.0%)
Trouble falling asleep			
Never	N/A	N/A	119 (34.2%)
Rarely/sometimes (1-4 times/month)	N/A	N/A	148 (49.5%)
Often/almost always (5-30 times/month)	N/A	N/A	51 (16.3%)

[1] Values are reported as frequency and weighted percent for categorical variables and weighted mean and standard error for continuous variables

Sample 1: Contains data from NHANES 2007-2018 self-reported MVPA and SB

Sample 2: Contains data from NHANES 2015-2018 self-reported MVPA and SB. This sample contains information on anxiolytic use, allowing us to control for these variables in the regression models

Sample 3: Contains data from the NHANES 2005-2006 device-measured MVPA

Table 2-5: MVPA and SB of study participants of the NHANES survey cycle sample

	Sample 1	Sample 2	Sample 3
Self-reported MVPA	116.75 (3.87)	136.05 (6.84)	98.35 (8.14)
Self-reported SB	397.24 (5.09)	389.69 (7.15)	195.78 (9.29)
Device-measured MVPA	N/A	N/A	22.54 (8.24)
Device wear time or compliance to wear the accelerometer	N/A	N/A	1439.22 (0.37)

[1] Values are reported as weighted mean and standard error for continuous variables
Sample 1: Contains data from NHANES 2007-2018 self-reported MVPA and SB
Sample 2: Contains data from NHANES 2015-2018 self-reported MVPA and SB. This sample contains information on anxiolytic use, allowing us to control for these variables in the regression models
Sample 3: Contains data from the NHANES 2005-2006 device-measured MVPA

Table 2-6: Regression model examining the association between self-reported MVPA, SB and sleep-related outcomes among the NHANES 2007-2018 sample

Outcome Variable	Primary Model[0]				With Survey Year[0]				Excluding sex[0]			
	Moderate to vigorous activity[1,2,5]		Sedentary activity[1, 2,5]		Moderate to vigorous activity[1,3,5]		Sedentary activity[1, 3,5]		Moderate to vigorous activity[1,4,5]		Sedentary activity[1, 4,5]	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Hrs. sleep / night	-0.03 (-0.06, 0.01)	0.10	-0.03 (-0.05, -0.01)	0.02	-0.04 (-0.07, -0.01)	0.01	-0.03 (-0.05, -0.01)	0.02	-0.03 (-0.06, 0.01)	0.07	-0.03 (-0.06, -0.01)	0.02
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Hours of sleep per night												
<7 hours	1.0		1.0		1.0		1.0		1.0		1.0	
7 hours	1.00 (0.95, 1.05)	0.99	0.99 (0.94, 1.04)	0.65	0.99 (0.95, 1.04)	0.65	0.98 (0.93, 1.03)	0.49	0.99 (0.95, 1.05)	0.87	0.99 (0.94, 1.04)	0.61
≥8 hours	0.96 (0.92, 1.01)	0.07	0.96 (0.93, 1.00)	0.05	0.94 (0.90, 0.99)	0.009	0.96 (0.92, 0.99)	0.04	0.95 (0.92, 0.99)	0.02	0.96 (0.92, 0.99)	0.03
Trouble sleeping	0.99 (0.95, 1.04)	0.80	0.99 (0.96, 1.03)	0.80	0.99 (0.95, 1.04)	0.67	0.99 (0.96, 1.03)	0.62	0.99 (0.95, 1.03)	0.57	0.99 (0.96, 1.03)	0.65
Feel overly sleepy												
Never	1.0		1.0		1.0		1.0		1.0		1.0	
Rarely/sometimes	0.99 (0.94, 1.06)	0.98	1.05 (0.97, 1.12)	0.22	0.99 (0.93, 1.05)	0.73	1.03 (0.96, 1.12)	0.40	0.99 (0.94, 1.06)	0.92	1.04 (0.97, 1.12)	0.23
Often/almost always	1.02 (0.95, 1.09)	0.65	1.13 (1.05, 1.22)	0.002	1.00 (0.93, 1.08)	0.96	1.11 (1.02, 1.21)	0.01	1.02 (0.95, 1.09)	0.60	1.13 (1.05, 1.23)	0.002

[0] Model include both moderate to vigorous activity and sedentary activity as key independent variables; this was done so that the independent effect of each variable on the sleep outcomes could be assessed

[1] Effect size reported as a 60 minute change in self-reported activity levels

[2] Model control for age, race/ethnicity, sex, cigarette use, PHQ-9 depression score, self-reported health status, in a partnered relationship, and season

[3] Model control for age, race/ethnicity, sex, cigarette use, PHQ-9 depression score, self-reported health status, in a partnered relationship, season, and survey cycle

[4] Model control for age, race/ethnicity, cigarette use, PHQ-9 depression score, self-reported health status, in a partnered relationship, season, and survey cycle

[5] Estimates based on a linear regression model for hours of sleep per night (continuous variable), multinomial regression model for hours of sleep per night (categorical variable), and feeling overly sleepy during the day, and a logistic regression model for trouble sleeping. All regression models take into account the complex survey design of the NHANES database and are weighted to be nationally representative of the US population

Table 2-7: Regression model examining the association between self-reported MVPA, SB and sleep-related outcomes among the NHANES 2015-2018 sample (with information on anxiety and antidepressant medication usage)

Outcome Variable	Primary Model[0]				With Survey Year[0]			
	Moderate to vigorous activity[1,2,6]		Sedentary activity[1, 2,6]		Moderate to vigorous activity[1,3,6]		Sedentary activity[1, 3,6]	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Hrs. sleep / night	-0.05 (-0.08, -0.01)	0.01	-0.06 (-0.10, -0.02)	0.01	-0.05 (-0.08, -0.01)	0.01	-0.06 (-0.11, -0.02)	0.009
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Hours of sleep per night								
<7 hours	1.0		1.0		1.0		1.0	
7 hours	1.02 (0.94, 1.10)	0.71	0.91 (0.82, 0.99)	0.047	1.02 (0.94, 1.10)	0.66	0.91 (0.82, 0.99)	0.04
≥8 hours	0.92 (0.86, 0.99)	0.02	0.88 (0.82, 0.95)	0.0005	0.92 (0.86, 0.99)	0.02	0.88 (0.92, 0.94)	0.0003
Trouble sleeping	1.00 (0.94, 1.07)	0.88	0.99 (0.92, 1.08)	0.91	0.99 (0.92, 1.08)	0.88	1.00 (0.94, 1.07)	0.98
Feel overly sleepy								
Never	1.0		1.0		1.0		1.0	
Rarely/sometimes	1.01 (0.93, 1.11)	0.80	1.01 (0.91, 1.12)	0.87	1.01 (0.93, 1.11)	0.80	1.01 (0.91, 1.12)	0.87
Often/almost always	1.03 (0.94, 1.12)	0.55	1.09 (0.98, 1.21)	0.11	1.03 (0.94, 1.12)	0.55	1.09 (0.98, 1.21)	0.11
	Excluding sex[0]				With Anxiety and Depression Medication Usage[0]			
	Moderate to vigorous activity[1,4,6]		Sedentary activity[1, 4,6]		Moderate to vigorous activity[1,5,6]		Sedentary activity[1, 5,6]	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Hrs. sleep / night[‡]	-0.05 (-0.09, -0.01)	0.007	-0.06 (-0.11, -0.02)	0.007	-0.04 (-0.08, -0.01)	0.02	-0.06 (-0.10, -0.01)	0.01

	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Hours of sleep per night‡								
<7 hours	1.0		1.0		1.0		1.0	
7 hours	0.99 (0.93, 1.08)	0.99	0.90 (0.81, 0.99)	0.03	1.02 (0.94, 1.10)	0.66	0.91 (0.82, 1.00)	0.06
≥8 hours	0.91 (0.85, 0.97)	0.006	0.88 (0.81, 0.94)	0.0004	0.92 (0.86, 0.99)	0.03	0.88 (0.82, 0.95)	0.001
Trouble sleeping‡	0.99 (0.92, 1.08)	0.89	1.01 (0.94, 1.08)	0.91	0.99 (0.92, 1.08)	0.91	1.00 (0.94, 1.07)	0.99
Feel overly sleepy								
Never	1.0		1.0		1.0		1.0	
Rarely/sometimes	1.01 (0.93, 1.10)	0.86	1.01 (0.91, 1.12)	0.91	1.01 (0.93, 1.11)	0.78	1.01 (0.91, 1.12)	0.87
Often/almost always	1.03 (0.95, 1.12)	0.51	1.09 (0.98, 1.21)	0.10	1.03 (0.94, 1.13)	0.51	1.09 (0.98, 1.21)	0.11

[0] Model include both moderate to vigorous activity and sedentary activity as key independent variables; this was done so that the independent effect of each variable on the sleep outcomes could be assessed

[1] Effect size reported as a 60 minute change in self-reported activity levels

[2] Models control for age, race/ethnicity, sex, cigarette use, PHQ-9 depression score, self-reported health status, in a partnered relationship, and season.

[3] Models control for age, race/ethnicity, sex, cigarette use, PHQ-9 depression score, self-reported health status, in a partnered relationship, season, and survey cycle

[4] Models control for age, race/ethnicity, cigarette use, PHQ-9 depression score, self-reported health status, in a partnered relationship, and season

[5] Models control for age, race/ethnicity, sex, cigarette use, PHQ-9 depression score, self-reported health status, in a partnered relationship,, season, and anxiolytic use.

[6] Estimates based on a linear regression model for hours of sleep per night (continuous variable), multinomial regression model for hours of sleep per night (categorical variable), and feeling overly sleepy during the day, and a logistic regression model for trouble sleeping. All regression models take into account the complex survey design of the NHANES database and are weighted to be nationally representative of the US population

† anxiety medications use is statistically significant ‡ anti-depressant medications usage is statistically significant

Table 2-8: Regression model examining the association between device measured MVPA and sleep related outcomes among the NHANES 2005-2006 sample

	Primary Model		Excludes sex as a Covariate	
Outcome Variable	MVPA[1,2]		MVPA[1,3]	
	β (95% CI)	*P*	β (95% CI)	*P*
Hrs. sleep / night	0.002 (-0.07, 0.08)	0.95	0.01 (-0.05, 0.07)	0.73
Time to fall asleep (minutes)	0.27 (-0.14, 0.68)	0.18	0.26 (-0.11, 0.63)	0.15
	OR (95% CI)	*P*	OR (95% CI)	*P*
Hours of sleep / night				
<7 hours	1.0		1.0	
7 hours	1.00 (0.66, 1.54)	0.99	1.07 (0.55, 2.10)	0.84
≥8 hours	1.16 (0.86, 1.56)	0.33	1.22 (0.66, 2.24)	0.51
Trouble sleeping	0.25 (0.04, 1.48)	0.13	0.22 (0.04, 1.38)	0.11
Feel overly sleepy				
Never	1.0		1.0	
Rarely/sometimes	0.86 (0.75, 0.99)	0.03	0.86 (0.74, 1.00)	0.04
Often/almost always	0.20 (0.02, 2.16)	0.18	0.24 (0.03, 2.40)	0.23
Trouble falling asleep				
Never	1.0		1.0	
Rarely/sometimes	1.32 (<0.001, >999.99)	0.99	1.24 (<0.001, >999.99)	0.99
Often/almost always	0.47 (<0.001, >999.99)	0.99	0.35 (<0.001, >999.99)	0.99
Wake up during night				
Never	1.0		1.0	
Rarely/sometimes	1.23 (<0.001, >999.99)	0.99	1.20 (<0.001, >999.99)	0.99
Often/almost always	1.06 (<0.001, >999.99)	0.99	1.04 (<0.001, >999.99)	0.99

Wake up too early in the morning				
Never	1.0		1.0	
Rarely/sometimes	1.22 (1.04, 1.44)	0.02	1.22 (1.03, 1.44)	0.02
Often/almost always	1.18 (0.96, 1.45)	0.13	1.17 (0.96, 1.43)	0.13

[1] Effect size reported as a 60 minute change in accelerometer activity levels

[2] Models control for age, race/ethnicity, sex, cigarette use, PHQ-9 depression score, self-reported health status, in a partnered relationship, season, using pills to sleep, device wear time [3] Models control for age, race/ethnicity, cigarette use, PHQ-9 depression score, self-reported health status, in a partnered relationship, season, using pills to sleep, and device wear time [4] Estimates based on a linear regression model for hours of sleep per night and time to fall asleep, a logistic regression model for trouble sleeping, and a multinomial logistic regression model for all other outcomes. All regression models take into account the complex survey design of the NHANES database and are weighted to be nationally representative of the US population. MVPA: moderate-to-vigorous physical activity

Table 2-9: Comparison of linear and curvilinear primary models for the self-reported MVPA, SB and sleep-related outcomes of the 2007-2018 NHANES Sample

	Linear Model			Curvilinear Model				
	Mod-Vig Activity		AIC	Mod-Vig Activity		Mod-Vig Activity^2		AIC
	B (95% CI)	P		B (95% CI)	P	B (95% CI)	P	
Total Sleep Hours	-0.03 (-0.06, 0.01)	0.10	13671.51	-0.01 (-0.08, 0.06)	0.72	-0.001 (-0.007, 0.004)	0.64	13681.08
	OR (95% CI)	*P*	AIC	OR (95% CI)	*P*	OR (95% CI)	*P*	AIC
Hours of sleep per night			127212891					127125238
<7 hours	1.0			1.0		1.0		
7 hours	1.00 (0.95, 1.05)	0.99		1.09 (0.98, 1.21)	0.13	0.99 (0.98, 1.00)	0.054	
≥8 hours	0.96 (0.92, 1.01)	0.07		1.00 (0.91, 1.10)	0.98	1.00 (0.99, 1.01)	0.39	
Trouble sleeping	0.99 (0.95, 1.04)	0.80	75512832	1.12 (1.01, 1.24)	0.03	0.988 (0.978, 0.997)	0.01	75257995
Feel overly sleepy			57469507					57302898
Never	1.0			1.0		1.0		
Rarely/sometimes	0.99 (0.94, 1.06)	0.98		1.15 (1.03, 1.30)	0.02	0.99 (0.98, 0.995)	0.002	
Often/almost always	1.02 (0.95, 1.09)	0.65		1.09 (0.92, 1.29)	0.31	0.99 (0.98, 1.01)	0.29	
	Sedentary Activity		AIC	Sedentary Activity		Sedentary Activity^2		AIC
	B (95% CI)	P		B (95% CI)	P	B (95% CI)	P	
Total Sleep Hours	-0.03 (-0.05, -0.01)	0.02	13671.51	0.03 (-0.06, 0.12)	0.52	-0.004 (-0.009, 0.002)	0.18	13681.64
	OR (95% CI)	*P*	AIC	OR (95% CI)	*P*	OR (95% CI)	*P*	AIC
Hours of sleep per night			127212891					126985833

<7 hours	1.0			1.0		1.0		
7 hours	0.99 (0.94, 1.04)	0.65		1.06 (0.90, 1.25)	0.49	1.00 (0.99, 1.01)	0.42	
≥8 hours	0.96 (0.93, 1.00)	0.05		1.14 (1.004, 1.28)	0.04	0.99 (0.982, 0.997)	0.01	
Trouble sleeping	0.99 (0.96, 1.03)	0.80	75512832	0.99 (0.86, 1.15)	0.92	1.00 (0.99, 1.01)	0.97	75512731
Feel overly sleepy			57469507					57154921
Never	1.0			1.0		1.0		
Rarely/sometimes	1.05 (0.97, 1.12)	0.22		1.37 (1.11, 1.69)	0.003	0.98 (0.968, 0.996)	0.01	
Often/almost always	1.13 (1.05, 1.22)	0.002		1.49 (1.24, 1.79)	<0.0001	0.98 (0.97, 0.99)	0.005	

[1] Effect size reported as a 60 minute change in self-reported activity levels

[2] Models control for age, race/ethnicity, sex, cigarette use, PHQ-9 depression score, self-reported health status, in a partnered relationship, and season

[3] Estimates based on a linear regression model for hours of sleep per night (continuous variable), multinomial regression model for hours of sleep per night (categorical variable), and feeling overly sleepy during the day, and a logistic regression model for trouble sleeping. All regression models take into account the complex survey design of the NHANES database and are weighted to be nationally representative of the US population. MVPA: moderate-to-vigorous physical activity, SB: Sedentary behavior

Table 2-10: Comparison of linear and curvilinear models for the self-reported MVPA, SB and sleep-related outcomes of the 2007-2018 NHANES Sample- Including cohort effects

	Linear Model			Curvilinear Model				
	Mod-Vig Activity		AIC	Mod-Vig Activity		Mod-Vig Activity^2		AIC
	B (95% CI)	P		B (95% CI)	P	B (95% CI)	P	
Total Sleep Hours	-0.04 (-0.07, -0.01)	0.01	13602.33	-0.04 (-0.11, 0.03)	0.22	0.00 (-0.01, 0.01)	0.94	13612.13
	OR (95% CI)	*P*	AIC	OR (95% CI)	*P*	OR (95% CI)	*P*	AIC
Hours of sleep per night			124603744					124540689
<7 hours	1.0			1.0		1.0		
7 hours	0.99 (0.95, 1.04)	0.65		1.06 (0.96, 1.18)	0.28	0.99 (0.986, 1.001)	0.10	
≥8 hours	0.94 (0.90, 0.99)	0.009		0.96 (0.87, 1.06)	0.43	1.00 (0.99, 1.01)	0.71	
Trouble sleeping	0.99 (0.95, 1.04)	0.67	75016897	0.99 (0.978, 0.998)	0.02	1.11 (1.001, 1.24)	0.047	74785917
Feel overly sleepy			56058439					55929309
Never	1.0			1.0		1.0		
Rarely/sometimes	0.99 (0.93, 1.05)	0.73		1.12 (0.99, 1.27)	0.07	0.99 (0.979, 0.998)	0.01	
Often/almost always	1.00 (0.93, 1.08)	0.96		1.05 (0.88, 1.25)	0.60	1.00 (0.98, 1.01)	0.55	
	Sedentary Activity		AIC	Sedentary Activity		Sedentary Activity^2		AIC
	B (95% CI)	P		B (95% CI)	P	B (95% CI)	P	
Total Sleep Hours	-0.03 (-0.05, -0.01)	0.02	13602.33	0.05 (-0.04, 0.14)	0.30	-0.005 (-0.01, 0.001)	0.08	13609.21
	OR (95% CI)	*P*	AIC	OR (95% CI)	*P*	OR (95% CI)	*P*	AIC
Hours of sleep per night			124603744					124319164
<7 hours	1.0			1.0		1.0		

7 hours	0.98 (0.93, 1.03)	0.49		1.06 (0.90, 1.25)	0.48	1.00 (0.99, 1.01)	0.36	
≥8 hours	0.96 (0.92, 0.99)	0.04		1.16 (1.01, 1.32)	0.03	0.99 (0.98, 0.997)	0.01	
Trouble sleeping	0.99 (0.96, 1.03)	0.62	75016897	0.98 (0.85, 1.14)	0.80	1.00 (0.99, 1.01)	0.90	75015898
Feel overly sleepy			56058439					55782352
Never	1.0			1.0		1.0		
Rarely/sometimes	1.03 (0.96, 1.12)	0.40		1.35 (1.08, 1.68)	0.01	0.982 (0.967, 0.998)	0.02	
Often/almost always	1.11 (1.02, 1.21)	0.01		1.46 (1.18, 1.79)	0.0004	0.983 (0.968, 0.997)	0.02	

[1] Effect size reported as a 60 minute change in self-reported activity levels

[2] Models control for age, race/ethnicity, sex, cigarette use, PHQ-9 depression score, self-reported health status, in a partnered relationship, season, and survey cycle year

[3] Estimates based on a linear regression model for hours of sleep per night (continuous variable), multinomial regression model for hours of sleep per night (categorical variable), and feeling overly sleepy during the day, and a logistic regression model for trouble sleeping. All regression models take into account the complex survey design of the NHANES database and are weighted to be nationally representative of the US population, MVPA: moderate-to-vigorous physical activity. SB: Sedentary behavior

Table 2-11: Comparison of linear and curvilinear models for the self-reported MVPA, SB and sleep-related outcomes of the 2007-2018 NHANES Sample- Excluding sex

	Linear Model			Curvilinear Model				
	Mod-Vig Activity		AIC	Mod-Vig Activity		Mod-Vig Activity^2		AIC
	B (95% CI)	P		B (95% CI)	P	B (95% CI)	P	
Total Sleep Hours	-0.03 (-0.06, 0.01)	0.07	13669.16	-0.02 (-0.08, 0.05)	0.64	-0.001 (-0.007, 0.005)	0.68	13680.78
	OR (95% CI)	*P*	AIC	OR (95% CI)	*P*	OR (95% CI)	*P*	AIC
Hours of sleep per night			127428414					127349385
<7 hours	1.0			1.0		1.0		
7 hours	0.99 (0.95, 1.05)	0.87		1.08 (0.97, 1.20)	0.18	0.99 (0.985, 1.001)	0.07	
≥8 hours	0.95 (0.92, 0.99)	0.02		0.99 (0.90, 1.08)	0.76	1.00 (0.99, 1.01)	0.48	
Trouble sleeping	0.99 (0.95, 1.03)	0.57	75686192	1.11 (1.00, 1.23)	0.01	0.99 (0.979, 0.998)	0.0503	75453853
Feel overly sleepy			57520006					57361338
Never	1.0			1.0		1.0		
Rarely/sometimes	0.99 (0.94, 1.06)	0.92		1.15 (1.03, 1.28)	0.02	0.99 (0.979, 0.995)	0.002	
Often/almost always	1.02 (0.95, 1.09)	0.60		1.10 (0.93, 1.29)	0.28	0.99 (0.98, 1.01)	0.28	
	Sedentary Activity		AIC	Sedentary Activity		Sedentary Activity^2		AIC
	B (95% CI)	P		B (95% CI)	P	B (95% CI)	P	
Total Sleep Hours	-0.03 (-0.06, -0.01)	0.02	13669.16	0.03 (-0.06, 0.12)	0.53	-0.004 (-0.009, 0.002)	0.18	13677.28
	OR (95% CI)	*P*	AIC	OR (95% CI)	*P*	OR (95% CI)	*P*	AIC

Hours of sleep per night			127428414					127200932
<7 hours	1.0			1.0		1.0		
7 hours	0.99 (0.94, 1.04)	0.61		1.06 (0.90, 1.24)	0.52	1.00 (0.99, 1.01)	0.43	
≥8 hours	0.96 (0.92, 0.99)	0.03		1.13 (0.998, 1.28)	0.054	0.99 (0.982, 0.998)	0.01	
Trouble sleeping	0.99 (0.96, 1.03)	0.65	75686192	0.99 (0.86, 1.14)	0.88	1.00 (0.99, 1.01)	0.97	75686093
Feel overly sleepy			57520006					57202609
Never	1.0			1.0		1.0		
Rarely/sometimes	1.04 (0.97, 1.12)	0.23		1.37 (1.11, 1.69)	0.003	0.98 (0.968, 0.996)	0.01	
Often/almost always	1.13 (1.05, 1.23)	0.002		1.50 (1.25, 1.80)	<0.0001	0.98 (0.97, 0.99)	0.004	

[1] Effect size reported as a 60 minute change in self-reported activity levels. [2] Models control for age, race/ethnicity, cigarette use, PHQ-9 depression score, self-reported health status, in a partnered relationship, season, and survey cycle year. [3] Estimates based on a linear regression model for hours of sleep per night (continuous variable), multinomial regression model for hours of sleep per night (categorical variable), and feeling overly sleepy during the day, and a logistic regression model for trouble sleeping. All regression models take into account the complex survey design of the NHANES database and are weighted to be nationally representative of the US population. MVPA: moderate-to vigorous physical activity. SB: Sedentary behavior

Table 2-12: Comparison of linear and curvilinear primary models for the self-reported MVPA, SB and sleep-related outcomes of the 2015-2018 NHANES Sample

	Linear Model			Curvilinear Model				
	Mod-Vig Activity		AIC	Mod-Vig Activity		Mod-Vig Activity^2		AIC
	B (95% CI)	P		B (95% CI)	P	B (95% CI)	P	
Total Sleep Hours	-0.05 (-0.08, -0.01)	0.01	3731.76	-0.11 (-0.19, -0.04)	0.004	0.01 (-0.0003, 0.01)	0.06	3737.65
	OR (95% CI)	*P*	AIC	OR (95% CI)	*P*	OR (95% CI)	*P*	AIC
Hours of sleep per night			42688903					42597011
<7 hours	1.0			1.0		1.0		
7 hours	1.02 (0.94, 1.10)	0.71		0.91 (0.69, 1.20)	0.48	1.01 (0.98, 1.04)	0.41	
≥8 hours	0.92 (0.86, 0.99)	0.02		0.79 (0.62, 1.01)	0.055	1.02 (0.99, 1.05)	0.23	
Trouble sleeping	1.00 (0.94, 1.07)	0.88	27639222	0.98 (0.96, 0.99)	0.008	1.26 (1.02, 1.55)	0.03	27312113
Feel overly sleepy			39160946					39102467
Never	1.0			1.0		1.0		
Rarely/sometimes	1.01 (0.93, 1.11)	0.80		1.10 (0.92, 1.32)	0.28	0.99 (0.98, 1.01)	0.19	
Often/almost always	1.03 (0.94, 1.12)	0.55		1.03 (0.80, 1.33)	0.82	1.00 (0.98, 1.02)	0.99	
	Sedentary Activity		AIC	Sedentary Activity		Sedentary Activity^2		AIC
	B (95% CI)	P		B (95% CI)	P	B (95% CI)	P	
Total Sleep Hours	-0.06 (-0.10, -0.02)	0.01	3731.76	0.06 (-0.04, 0.15)	0.24	-0.01 (-0.01, -0.002)	0.01	3733.35
	OR (95% CI)	*P*	AIC	OR (95% CI)	*P*	OR (95% CI)	*P*	AIC
Hours of sleep per night			42688903					42560650
<7 hours	1.0			1.0		1.0		

7 hours	0.91 (0.82, 0.99)	0.047		0.98 (0.72, 1.33)	0.90	1.00 (0.98, 1.01)	0.65	
≥8 hours	0.88 (0.82, 0.95)	0.0005		1.09 (0.86, 1.37)	0.49	0.99 (0.97, 1.00)	0.09	
Trouble sleeping	0.99 (0.92, 1.08)	0.91	27639222					
Feel overly sleepy			39160946					38814534
Never	1.0			1.0		1.0		
Rarely/sometimes	1.01 (0.91, 1.12)	0.87		1.43 (1.08, 1.88)	0.01	0.98 (0.961, 0.996)	0.02	
Often/almost always	1.09 (0.98, 1.21)	0.11		1.62 (1.28, 2.05)	<0.0001	0.98 (0.96, 0.99)	0.002	

[1] Effect size reported as a 60 minute change in self-reported activity levels. [2] Models control for age, race/ethnicity, cigarette use, PHQ-9 depression score, self-reported health status, in a partnered relationship, season, and survey cycle year [3] Estimates based on a linear regression model for hours of sleep per night (continuous variable), multinomial regression model for hours of sleep per night (categorical variable), and feeling overly sleepy during the day, and a logistic regression model for trouble sleeping. All regression models take into account the complex survey design of the NHANES database and are weighted to be nationally representative of the US population. MVPA: moderate-to-vigorous physical activity. SB: Sedentary behavior.

Table 2-13: Comparison of linear and curvilinear models for the self-reported MVPA, SB and sleep-related outcomes of the 2015-2018 NHANES Sample- Including cohort effects

	Linear Model			Curvilinear Model				
	Mod-Vig Activity		AIC	Mod-Vig Activity		Mod-Vig Activity^2		AIC
	B (95% CI)	P		B (95% CI)	P	B (95% CI)	P	
Total Sleep Hours	-0.05 (-0.08, -0.01)	0.01	3730.43	-0.11 (-0.19, -0.04)	0.004	0.01 (-0.0002, 0.01)	0.056	3736.16
	OR (95% CI)	*P*	AIC	OR (95% CI)	*P*	OR (95% CI)	*P*	AIC
Hours of sleep per night			42523184					42430646
<7 hours	1.0			1.0		1.0		
7 hours	1.02 (0.94, 1.10)	0.66		0.91 (0.69, 1.20)	0.49	1.01 (0.98, 1.04)	0.42	
≥8 hours	0.92 (0.86, 0.99)	0.02		0.79 (0.61, 1.01)	0.059	1.02 (0.99, 1.05)	0.24	
Trouble sleeping	0.99 (0.92, 1.08)	0.88	27555804	0.98 (0.96, 0.99)	0.04	1.25 (1.01, 1.54)	0.01	27239377
Feel overly sleepy			39147767					39090306
Never	1.0			1.0		1.0		
Rarely/sometimes	1.01 (0.93, 1.11)	0.80		1.10 (0.92, 1.32)	0.28	0.99 (0.98, 1.01)	0.21	
Often/almost always	1.03 (0.94, 1.12)	0.55		1.03 (0.80, 1.33)	0.82	1.00 (0.98, 1.02)	0.99	
	Sedentary Activity		AIC	Sedentary Activity		Sedentary Activity^2		AIC
	B (95% CI)	P		B (95% CI)	P	B (95% CI)	P	
Total Sleep Hours	-0.06 (-0.11, -0.02)	0.009	3730.43	0.05 (-0.05, 0.15)	0.32	-0.01 (-0.01, -0.001)	0.02	3734.80
	OR (95% CI)	*P*	AIC	OR (95% CI)	*P*	OR (95% CI)	*P*	AIC
Hours of sleep per night			42523184					42425419

<7 hours	1.0			1.0		1.0		
7 hours	0.91 (0.82, 0.99)	0.04		0.95 (0.70, 1.29)	0.74	1.00 (0.98, 1.01)	0.79	
≥8 hours	0.88 (0.92, 0.94)	0.0003		1.05 (0.83, 1.33)	0.70	0.99 (0.976, 1.004)	0.14	
Trouble sleeping	1.00 (0.94, 1.07)	0.98	27555804	1.03 (0.81, 1.31)	0.84	1.00 (0.98, 1.02)	0.86	27553539
Feel overly sleepy			39147767					38806136
Never	1.0			1.0		1.0		
Rarely/sometimes	1.01 (0.91, 1.12)	0.87		1.43 (1.10, 1.86)	0.008	0.98 (0.962, 0.995)	0.01	
Often/almost always	1.09 (0.98, 1.21)	0.11		1.61 (1.27, 2.05)	<0.0001	0.98 (0.96, 0.99)	0.003	

[1] Effect size reported as a 60 minute change in self-reported activity levels

[2] Models control for age, race/ethnicity, sex, cigarette use, PHQ-9 depression score, self-reported health status, in a partnered relationship, season, and survey cycle year

[3] Estimates based on a linear regression model for hours of sleep per night (continuous variable), multinomial regression model for hours of sleep per night (categorical variable), and feeling overly sleepy during the day, and a logistic regression model for trouble sleeping. All regression models take into account the complex survey design of the NHANES database and are weighted to be nationally representative of the US population. MVPA: moderate-to-vigorous physical activity. SB: Sedentary behavior

Table 2-14: Comparison of linear and curvilinear models for the self-reported MVPA, SB and sleep-related outcomes of the 2015-2018 NHANES Sample- Excluding sex

	Linear Model			Curvilinear Model				
	Mod-Vig Activity		AIC	Mod-Vig Activity		Mod-Vig Activity^2		AIC
	B (95% CI)	P		B (95% CI)	P	B (95% CI)	P	
Total Sleep Hours	-0.05 (-0.09, -0.01)	0.007	3733.61	-0.12 (-0.20, -0.04)	0.002	0.01 (0.00, 0.014)	0.052	3737.21
	OR (95% CI)	*P*	AIC	OR (95% CI)	*P*	OR (95% CI)	*P*	AIC
Hours of sleep per night			43151985					43048863
<7 hours	1.0			1.0		1.0		
7 hours	0.99 (0.93, 1.08)	0.99		0.88 (0.67, 1.17)	0.38	1.01 (0.98, 1.04)	0.38	
≥8 hours	0.91 (0.85, 0.97)	0.006		0.77 (0.61, 0.99)	0.04	1.02 (0.99, 1.05)	0.21	
Trouble sleeping	0.99 (0.92, 1.08)	0.89	27641936	1.26 (1.02, 1.55)	0.03	0.98 (0.96, 0.99)	0.008	27313417
Feel overly sleepy			39221068					39166956
Never	1.0			1.0		1.0		
Rarely/sometimes	1.01 (0.93, 1.10)	0.86		1.10 (0.92, 1.31)	0.29	0.99 (0.98, 1.01)	0.20	
Often/almost always	1.03 (0.95, 1.12)	0.51		1.03 (0.80, 1.33)	0.80	1.00 (0.98, 1.02)	0.98	
	Sedentary Activity		AIC	Sedentary Activity		Sedentary Activity^2		AIC
	B (95% CI)	P		B (95% CI)	P	B (95% CI)	P	
Total Sleep Hours	-0.06 (-0.11, -0.02)	0.007	3733.61	0.05 (-0.04, 0.15)	0.28	-0.007 (-0.01, -0.002)	0.01	3735.30
	OR (95% CI)	*P*	AIC	OR (95% CI)	*P*	OR (95% CI)	*P*	AIC
Hours of sleep per night			43151985					43034494

<7 hours	1.0			1.0		1.0		
7 hours	0.90 (0.81, 0.99)	0.03		0.96 (0.69, 1.32)	0.79	1.00 (0.98, 1.02)	0.72	
≥8 hours	0.88 (0.81, 0.94)	0.0004		1.07 (0.83, 1.37)	0.62	0.99 (0.97, 1.004)	0.14	
Trouble sleeping	1.01 (0.94, 1.08)	0.91	27641936	1.04 (0.83, 1.32)	0.72	1.00 (0.98, 1.01)	0.76	27635859
Feel overly sleepy			39221068					38869180
Never	1.0			1.0		1.0		
Rarely/sometimes	1.01 (0.91, 1.12)	0.91		1.43 (1.08, 1.88)	0.01	0.98 (0.96, 0.996)	0.02	
Often/almost always	1.09 (0.98, 1.21)	0.10		1.63 (1.29, 2.06)	<0.0001	0.98 (0.96, 0.99)	0.002	

[1] Effect size reported as a 60 minute change in self-reported activity levels

[2] Models control for age, race/ethnicity, sex, cigarette use, PHQ-9 depression score, self-reported health status, in a partnered relationship, season, and survey cycle year

[3] Estimates based on a linear regression model for hours of sleep per night (continuous variable), multinomial regression model for hours of sleep per night (categorical variable), and feeling overly sleepy during the day, and a logistic regression model for trouble sleeping. All regression models take into account the complex survey design of the NHANES database and are weighted to be nationally representative of the US population. MVPA: moderate-to-vigorous physical activity. SB: Sedentary behavior

Table 2-15: Comparison of linear and curvilinear models for the 2015-2018 NHANES Sample- Including anxiolytic use

	Linear Model			Curvilinear Model				
	Mod-Vig Activity		AIC	Mod-Vig Activity		Mod-Vig Activity^2		AIC
	B (95% CI)	P		B (95% CI)	P	B (95% CI)	P	
Total Sleep Hours	-0.04 (-0.08, -0.01)	0.02	3720.94	-0.12 (-0.20, -0.04)	0.002	0.01 (0.001, 0.02)	0.03	3725.58
	OR (95% CI)	*P*	AIC	OR (95% CI)	*P*	OR (95% CI)	*P*	AIC
Hours of sleep per night			41755618					41611178
<7 hours	1.0			1.0		1.0		
7 hours	1.02 (0.94, 1.10)	0.66		0.89 (0.68, 1.17)	0.40	1.01 (0.99, 1.04)	0.32	
≥8 hours	0.92 (0.86, 0.99)	0.03		0.76 (0.59, 0.97)	0.03	1.02 (0.99, 1.05)	0.13	
Trouble sleeping	0.99 (0.92, 1.08)	0.91	26665908	1.23 (0.99, 1.52)	0.06	0.98 (0.96, 0.997)	0.02	26413150
Feel overly sleepy			39067260					39003482
Never	1.0			1.0		1.0		
Rarely/sometimes	1.01 (0.93, 1.11)	0.78		1.10 (0.92, 1.32)	0.28	0.99 (0.98, 1.004)	0.19	
Often/almost always	1.03 (0.94, 1.13)	0.51		1.02 (0.80, 1.30)	0.85	1.00 (0.98, 1.02)	0.94	
	Sedentary Activity		AIC	Sedentary Activity		Sedentary Activity^2		AIC
	B (95% CI)	P		B (95% CI)	P	B (95% CI)	P	
Total Sleep Hours	-0.06 (-0.10, -0.01)	0.01	3720.94	0.05 (-0.04, 0.15)	0.27	-0.006 (-0.013, -0.001)	0.01	3726.83
	OR (95% CI)	*P*	AIC	OR (95% CI)	*P*	OR (95% CI)	*P*	AIC
Hours of sleep per night			41755618					41635421
<7 hours	1.0			1.0		1.0		

7 hours	0.91 (0.82, 1.00)	0.06		0.98 (0.72, 1.33)	0.87	1.00 (0.98, 1.01)	0.68	
≥8 hours	0.88 (0.82, 0.95)	0.001		1.08 (0.96, 1.36)	0.52	0.99 (0.97, 1.002)	0.10	
Trouble sleeping	1.00 (0.94, 1.07)	0.99	26665908	1.05 (0.83, 1.33)	0.71	1.00 (0.98, 1.01)	0.71	26657841
Feel overly sleepy			39067260					38706029
Never	1.0			1.0		1.0		
Rarely/sometimes	1.01 (0.91, 1.12)	0.87		1.44 (1.09, 1.90)	0.009	0.98 (0.96, 0.995)	0.01	
Often/almost always	1.09 (0.98, 1.21)	0.11		1.64 (1.31, 2.05)	<0.0001	0.98 (0.96, 0.99)	0.001	

[1] Effect size reported as a 60 minute change in self-reported activity levels

[2] Models control for age, race/ethnicity, sex, cigarette use, PHQ-9 depression score, self-reported health status, in a partnered relationship, season, and survey cycle year

[3] Estimates based on a linear regression model for hours of sleep per night (continuous variable), multinomial regression model for hours of sleep per night (categorical variable), and feeling overly sleepy during the day, and a logistic regression model for trouble sleeping. All regression models take into account the complex survey design of the NHANES database and are weighted to be nationally representative of the US population

MVPA: moderate-to-vigorous physical activity. SB: Sedentary behavior

Table 2-16: Comparison of linear and curvilinear primary models for the device-measured MVPA and sleep-related outcomes for the 2005-2006 NHANES Sample

	Linear Model			Curvilinear Model				
	Accelerometer Mod-Vig Activity		AIC	Accelerometer Mod-Vig Activity		Accelerometer Mod-Vig Activity^2		AIC
	B (95% CI)	P		B (95% CI)	P	B (95% CI)	P	
Hrs. sleep / night	0.002 (-0.07, 0.08)	0.95	2041.05	0.26 (-2.24, 2.76)	0.84	-0.01 (-0.13, 0.11)	0.84	2044.76
Time to fall asleep (minutes)	0.27 (-0.14, 0.68)	0.18	2691.42	-0.02 (-7.97, 7.92)	0.99	0.01 (-0.37, 0.40)	0.94	2692.85
	OR (95% CI)	*P*	AIC	OR (95% CI)	*P*	OR (95% CI)	*P*	AIC
Hours of sleep / night			25747530					25714663
<7 hours	1.0			1.0		1.0		
7 hours	1.00 (0.66, 1.54)	0.99		0.58 (0.03, 13.29)	0.73	1.70 (0.14, 20.18)	0.68	
≥8 hours	1.16 (0.86, 1.56)	0.33		0.47 (0.02, 12.24)	0.65	1.74 (0.15, 20.85)	0.66	
Trouble sleeping	0.25 (0.04, 1.48)	0.13	11567618	1.54 (0.02, 125.99)	0.85	0.13 (0.003, 5.37)	0.28	11519080
Feel overly sleepy			23318877					22942322
Never	1.0			1.0		1.0		
Rarely/sometimes	0.86 (0.75, 0.99)	0.03		35.87 (1.64, 781.39)	0.02	0.09 (0.01, 0.82)	0.03	
Often/almost always	0.20 (0.02, 2.16)	0.18		0.47 (0.06, 3.90)	0.48	1.01 (0.84, 1.23)	0.89	
Trouble falling asleep			24136521					23950670
Never	1.0			1.0		1.0		
Rarely/sometimes	1.32 (<0.001, >999.99)	0.99		1.24 (<0.001, >999.99)	0.99	1.01 (<0.001, >999.99)	0.99	
Often/almost always	0.47 (<0.001, >999.99)	0.99		50.90 (<0.001, >999.99)	0.99	0.004 (<0.001, >999.99)	0.99	
Wake up during night			26184504					26177904
Never	1.0			1.0		1.0		
Rarely/sometimes	1.23 (<0.001, >999.99)	0.99		1.06 (<0.001, >999.99)	0.99	1.01 (<0.001, >999.99)	0.99	
Often/almost always	1.06 (<0.001, >999.99)	0.99		1.09 (<0.001, >999.99)	0.99	1.00 (<0.001, >999.99)	0.99	

Wake up too early in the morning			25471185		25298353			
Never	1.0			1.0		1.0		
Rarely/sometimes	1.22 (1.04, 1.44)	0.02		0.66 (0.23, 1.93)	0.45	1.04 (0.98, 1.09)	0.17	
Often/almost always	1.18 (0.96, 1.45)	0.13		2.23 (0.72, 6.90)	0.16	0.97 (0.92, 1.02)	0.23	

[1] Effect size reported as a 60 minute change in accelerometer activity levels

[2] Models control for age, race/ethnicity, sex, cigarette use, PHQ-9 depression score, self-reported health status, in a partnered relationship, season, using pills to sleep, device wear time

[3] Estimates based on a linear regression model for hours of sleep per night and time to fall asleep, a logistic regression model for trouble sleeping, and a multinomial logistic regression model for all other outcomes. All regression models take into account the complex survey design of the NHANES database and are weighted to be nationally representative of the US population

MVPA: moderate-to-vigorous physical activity

Preface to Chapter 3: Literature Review

The relationship between physical activity and sleep is complex. The previous chapter's findings suggest that more physical activity is associated with better sleep in some aspects but not all. For instance, participants with a higher daily duration of MVPA reported fewer hours of sleep per night. Despite sleeping less, they were less likely to feel overly sleepy during the day. The results showed that for every 60 minutes increase of device-measured MVPA, participants were 14% less likely to feel rarely/sometimes overly sleepy during the day. This finding suggests that participants who engage in more physical activity may be experiencing a more restorative sleep, allowing them to feel more refreshed and alert during the day despite sleeping fewer hours.

Emphasizing the importance of physical activity for improving sleep outcomes in cancer survivors, it is crucial to identify the most suitable time to intervene during the cancer treatment process. One such critical period is the preoperative phase, which may serve as a window of opportunity to enhance patients' overall condition and facilitate long-lasting lifestyle changes. The importance of intervening during the preoperative period lies in its potential to address various physical and psychological factors, ultimately enhancing patients' recovery, quality of life, and long-term health outcomes.

This chapter provides context and summarizes the most current evidence on the impact of preoperative exercise training alone or as part of multimodal prehabilitation on sleep disturbances and sleep quality in cancer patients. Previous articles provide evidence for the effects of exercise on sleep disturbances in cancer patients. Still, this systematic review presented a more comprehensive approach to investigating this research question in cancer patients during the preoperative period. The article discusses clinical trial outcomes (RCTs and non-RCTs) and suggests inconsistent conclusions and limited effects of exercise interventions on sleep disturbances. This systematic review is essential for further research and developing targeted interventions to optimize sleep outcomes in cancer patients during this critical phase.

The review article entitled: ‘Exercise intervention in cancer patients with sleep disturbances scheduled for elective surgery: Systematic review’ was published in the August 2021 issue of the International Journal of Surgery.

Chapter 3 : Literature Review

Exercise intervention in cancer patients with sleep disturbances scheduled for elective surgery: Systematic Review

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Keywords: sleep quality, sleep disturbances, structured exercise, exercise prehabilitation, cancer patient, pre-operative

3.1 Abstract

Background & Objectives: Sleep disturbance is one of the patients' major complaints after major surgery and can impair postoperative recovery. Pre-operative exercise has been shown to increase functional capacity and resilience in cancer patients; scarce knowledge is available on the effects of pre-operative exercise on sleep disturbances. This systematic review aims to determine the impact of pre-operative exercise training alone or as part of multimodal prehabilitation on sleep disturbances and sleep quality in cancer patients. **Methods**: A systematic search including MEDLINE, Cochrane Library and CENTRAL, EMBASE, and clinical trial registries (clinicaltrials.gov, International Clinical Trials Registry Platform and Google Scholar) was performed to identify studies involving a pre-operative exercise intervention in cancer patients awaiting surgery. Trials had to contain at least one sleep measure, assessed subjectively and objectively were included in the systematic review. The quality of the included trials was assessed using the RoB 2 tool for evaluating the risk of bias in randomized trials and the ROBINS-I tool for evaluating the risk of bias in non-randomized studies. **Results**: Six studies were included (1 RCT, 2 non-RCTs and 3 single-arm designs). Due to substantial heterogeneity in the interventions across studies, a meta-analysis was not conducted. The available empirical evidence on the presurgical effect of exercise on sleep outcomes is scarcer and, overall, suggests that it has a limited effect. Besides, non-significant improvement of the pre-operative exercise on sleep was unique to the studies that used a single item to assess sleep disturbances changes during cancer treatment**. Conclusion**: There are conflicting results and a lack of quality data proving the pre-operative exercise on sleep quality and disturbances. More research is needed in the pre-operative period using clinical sleep disturbances such as insomnia as an inclusion criterion, subjectively and objectively assessed.

3.2 Highlights

- Sleep disturbance is commonly seen before surgery, limited studies on this topic.
- Preoperative exercise increases functional capacity and resilience in cancer patients.
- Preoperative exercise may have beneficial effects on sleep quality in cancer patients.
- Lack of quality data proving the benefit of preoperative exercise on patient-sleep outcomes.

3.3 Introduction

Sleep disturbances such as insomnia, hypersomnolence and restless leg syndrome disorder affect between 30% to 60% of patients with cancer, of which insomnia syndrome contributes approximately 20 % (1, 2). Forty-eight percent to 60% of cancer patients have poor sleep quality, defined as “subjective perceptions about one's sleep” (3-5). Sleep disturbances are considered a stress factor for cancer patients undergoing surgery (6, 7) and can contribute to delayed postoperative recovery (8, 9). In the pre-operative period, disturbed sleep may be related to anxiety, pain and environmental factors (10). Furthermore, sleep may be affected by surgery-related factors such as type and duration of the procedure, the severity of disease (malignant vs. benign), associated pain (8), and other factors leading to the patient’s discomfort. In a large-scale longitudinal study by Savard et al., over 1000 patients with different cancer types were followed from the decision to operate during the perioperative period and up to 18 months. Before surgery, 59% of patients reported insomnia symptoms (28% with insomnia disorder), and at 18 months after surgery, 36% still suffered from insomnia symptoms (21% with insomnia disorder) (1, 11). The results indicate that sleep disturbances may occur before and may persist long after the cancer treatment and, therefore, must become a priority to health care providers, who should provide effective interventions.

Although the most common treatment for sleep disturbances is pharmacotherapy, long term use of these medications is not recommended. Their adverse effects include rebound insomnia, depression and anxiety, cognitive impairment and an increased risk of falls, cancer, and overall mortality (12, 13). Several studies have shown that exercise intervention during and after cancer treatment significantly improves health-related quality of life (14), physical fitness (15), lean body mass (16), fatigue (17, 18), depressive symptoms (19), and anxiety (20). There are some inconsistent results concerning exercise's effects on sleep disturbances in cancer patients (21-24). Two recent meta-analyses suggested that aerobic exercise interventions significantly improved sleep disturbances in cancer patients (21, 22), but no significant improvement was obtained for sleep quality (22). Recently, the results of Fang and colleagues' meta-analyses showed a slight improvement in self-reported sleep quality (23). Besides, no significant improvement of self-reported sleep quality and objectively assessed sleep parameters in cancer patients of Mercier's meta-analysis (24). These reviews were generally not planned a priori to the presurgical exercise training in cancer patients.

Although pre-operative exercise alone or as part of a multimodal prehabilitation program has been shown to increase functional capacity and resilience in cancer patients (25-28), scarce knowledge is available on the effects of pre-operative exercise on sleep disturbances. The purpose of this systematic review is to determine if pre-operative exercise training alone or as part of multimodal prehabilitation has an impact on sleep disturbances and sleep quality in cancer patients before and after surgery.

3.4 Methods

The work been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (29) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines (30). It was conducted following the registered protocol on Prospero (Registration number CRD42020207369).

3.4.1 Search Strategy

The following databases were searched for relevant studies on November 23, 2020: Biosis (via ClarivateAnalytics); The Cochrane CENTRAL Register of Controlled Trials & Cochrane Database of Systematic Reviews (via Wiley Issue 11 of 12, November 2020); Embase Classic +Embase (via Ovid 1947 to 2020 November 20); MEDLINE (via Ovid 1946 to November 20, 2020; and PsycINFO (via Ovid 1987 to November Week 3 2020). The search strategies designed by a librarian (IM) used text words and relevant indexing to identify studies on the exercise intervention in cancer patients with sleep disturbances scheduled for elective surgery. The MEDLINE strategy was applied to all databases, with modifications to search terms, as necessary. No language limits were applied. Search strategies were peer-reviewed by two librarians. In addition, clinical trials registries [clinicaltrials.gov], and Google Scholar were searched. The Medline strategy will be rerun before submission.

3.4.2 Study Selection

Randomized control trials (RCT), as well as non-randomized trials, were included. This decision was made a priori to appraise all available evidence. Adult patients (18 years and older) with any cancer type or stage that were surgical candidates (during or after neoadjuvant treatment) and reported sleep disturbances at the baseline were included. Trials had to contain at least one

validated measure of sleep disturbances or sleep quality. Studies had to examine sleep as the outcome and post-intervention measurement of the exercise program's effect. Since this review focuses only on pre-operative exercise, studies that started the exercise intervention after the surgery were excluded. Various forms of exercise interventions were considered eligible, including aerobics, resistance or a combination of both. Exercise interventions could be combined with flexibility exercises or other types of intervention (e.g., counselling). However, yoga interventions were excluded, given the large heterogeneity of yoga types, being physically demanding. No restriction was made regarding the frequency, intensity, or duration of the program. Interventions could be home-based or supervised. Control arms could be usual care (no exercise intervention) or an alternative intervention (e.g., relaxation).

3.4.3 Data Extraction

One reviewer (SA) performed the searches. The same reviewer exported all references in EndNote X9 (Thomson Reuters, Thomson Corporation, USA) and removed duplicates. Results were then imported to the Rayyan platform (31) (Screening platform), and a PRISMA flow diagram of the selection process was created. After removing duplicates and non-relevant records, two independent reviewers (SA and MCM) completed the full-text analyses of those deemed eligible and determined suitability for inclusion based on the established selection criteria. A consensus between the two reviewers was used to resolve any disagreement. Full-text analyses and data extraction of those deemed eligible were conducted by one reviewer (SA). All relevant studies were examined to extract data on participants' characteristics, study design, exercise interventions and results following the PICO (Population, Intervention, Comparison, Outcomes) framework (29) by one independent reviewer (SA). The following baseline characteristics were recorded if the data were available: patient age, patient sex, number of patients, cancer site and stage, and treatment status of the patients (Table 1). Intervention characteristics were collected, including exercise prescription (frequency, intensity, session length, and deliverance mode), following-up, duration of intervention, and intervention compliance (Table 2). A description of the following results was collected, including pre-and postoperative changes in sleep score, type of measure sleep outcomes, effect, and significance on sleep outcomes (Table 3). We attempted to contact the authors of the included studies to provide any missing data detected during the process.

3.4.4 Quality Assessment

The quality of the included trials was assessed using the by the Cochrane Risk of Bias Tool for assessing the risk of bias in randomized trials (32). Each domain of the risk of bias tool (i.e., random sequence generation; allocation concealment; selective reporting; other bias; blinding of participant and personnel; blinding of outcome assessment; incomplete outcome data) was classified as low, high, or unclear of bias. The ROBINS-I tool for assessing the risk of bias in non-randomized studies (33) where seven main factors were assessed (Confounding, Selection of participants, Bias in classification of interventions, Deviation from intended intervention, Missing data, Outcome measurement, Selective outcome reporting) was classified as low, moderate, serious, and critical risk. The risk of bias for the selected publications is summarized in Table 4.

3.4.5 Data Items

Studies that reported a validated sleep disturbance or sleep quality tools and meaningful cut off points were included in the systematic review. Trials had to contain at least one sleep measure objectively or subjectively assessed. The subjective sleep quality was most commonly self-reported in response to a structured questionnaire such as a single sleep-related symptom item in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) or the Pittsburgh Sleep Quality Index (PSQI). The EORTC QLQ-C30 (34) is a single item that measured sleep disturbances in the past week: "During the past week, have you had trouble sleeping?". This item is rated on a 1 to 4 scale: "not at all" (coded as 1), a little, quite a bit, and very much" (coded as 4). A higher score is indicative of greater symptoms problems of sleep disturbances. The PSQI (35) is a 24-item scale that measures sleep disturbances during the past month along seven dimensions: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, sleep medication use, and daytime dysfunction. In this study, participants were considered eligible to obtain a total score of greater than 5 on the PSQI. The objective sleep quality was measured by Actigraphy Brands (36, 37). The Actigraph monitoring period should be at least 3 days. Sleep disturbance is indicated by a total sleep time (TST) of <6.5 h (38), sleep efficiency (SE) of <85% (39), sleep onset latency (SOL) of >30 min (40) or wake after sleep onset (WASO) of >30 min (41).

3.5 Results

3.5.1 Study Selection

The initial electronic searches identified 3676 references, 2726 of which were duplicates. After reviewing titles and abstracts, 2706 were excluded because they did not meet all inclusion criteria. After screening on title and abstract, 23 studies were found relevant and underwent full review, resulting in 16 exclusions. Reasons for exclusion were the following: postoperative exercise intervention: 9 studies (42-50), unfinished studies: 2 studies, publications reporting non-relevant outcomes: 3 studies (51-53), unspecified exercise intervention: one study (54) and one observational study (55). We noticed that the studies by Brunet et al. (56), and Loughney et al. (57), provide results from the same trial with an identical sample and intervention but with different sleep outcomes, a subjective one in the first and an objective one in the second. Seven manuscripts (56-62) satisfied the inclusion criteria and were included in this systematic review. Figure 1 summarizes the search results. A meta-analysis was not conducted due to heterogeneity in interventions and lack of systematic reporting of outcome measures.

3.5.2 Studies' Characteristics

Table 1 summarizes the characteristics of the six studies. Studies were separated according to the study design. Table 1 summarizes the characteristics of the seven studies. Studies were separated according to the study design. One of the seven included studies was a RCT (abstract) (60), two were non-randomized studies (same trial) (56, 57), and four were single-arm design (58, 59, 61, 62). The total number of patients studied was 134 cancer patients, with a sample size ranging from 10 to 49 per study. Women accounted for 62.6 % (n: 84) of the total patients. The seven studies included one study with breast cancer patients (60); the other studies were rectal cancer patients. Five out of the seven studies specified cancer stage, ranging from stage I to stage IV (56-60). In four studies, patients undertook exercise during cancer treatment (e.g., Neoadjuvant Chemoradiation Treatment) (58, 59, 61, 62). On the other hand, in the two non-randomized studies, exercise intervention was conducting after finishing neoadjuvant cancer treatment (56, 57). The RCT study of Ligibel et al. (60) compared exercise with the mind-body intervention for women with newly diagnosed breast cancer.

3.5.3 Intervention Characteristics

Table 2 summarizes the presurgical exercise program interventions. The length of the intervention programs ranged from 4 (60) to 16 weeks (62). The exercise frequency varied from 1 (58) to 3 (56, 57, 59) times per week, and the duration ranged from 40 (56, 57) to 60 (58, 61, 62) min per day. All studies performed supervised exercise programs for an intensity varied from moderate to moderate-vigorous physical activity, except three of them combined supervised and home-based exercise programs (60-62). One study did not report the duration and intensity of the exercise intervention (60).

3.5.4 Sleep Outcomes

Table 3 summarizes sleep outcomes and the main results obtained for each study. Six studies used patient-reported outcome (PRO) questionnaires, and only one study has assessed sleep quality objectively using an accelerometer. Loughney et al. (57) continuously used an accelerometer worn on the upper right arm for three consecutive weekdays. The device records and reports daily movement, such as sleep duration and efficiency. At the baseline, SE was 75%, and TST was 260 min/day. Five studies have used a single item of the EORTC QLQ-C30 (56, 58, 60-62) with a baseline score between 16 (58) and 35.9 (60) of insomnia score. One study used the PSQI questionnaire (59). Seven sleep components were assessed during the month of follow-up (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction). The baseline score was 6.1, indicated poor sleep quality.

3.5.4.1 Pre- and Post-intervention Sleep Outcomes Changes

Ligibel et al. RCT: No significant effect for the exercise intervention on self-reported sleep disturbance (60) in breast cancer patients who performed supervised and home-based aerobic and strength training compared to those who performed mind-body relaxation training ($p = .52$). No information was reported for the difference in the change scores between the exercise intervention and the mind-body relaxation training group.

Non-randomized trials: Brunet et al. results showed no significant change from pre- to post-exercise intervention for the insomnia score between ($p = .89$) and within ($ps \geq .26$) the exercise group and the control group (56). However, the difference in the change scores between the intervention and the control group was not reported. For the same trial, Loughney et al., showed

a significant improvement in sleep efficiency (%) (78 (13) vs. 80 (15) compared to 69 (24) vs. 76 (20); p = .022) and sleep duration group (190 (269) vs. 369 (81) compared to (265 (315) vs. 299 (39); p = .028) between week 0 and week 6 in the exercise group compared to the usual care control group (57). The exercise program in both studies was conducted after cancer treatment.

Single-arm studies: Two single-arm studies in rectal cancer patients who performed supervised aerobic exercise did not show statistically significant self-improvement before surgery in the sleep quality score (PSQI) (95% CI: -1.6 - 1.7; M: 0.1) (59), either in the insomnia score reported using the single item of EORTC QLQ C-30 (95% CI: −17 - 10; M: −3.0), p = .56) (58). Similarly, two other studies that performed supervised exercise training combined with home-based did not improve the insomnia score reported by EORTC QLQ C-30 after 10 (61) (95% CI: −2.8 - 12.1; M: 4.7, p =141) and 16 (95% CI: −34.9 - 26.6; M: -4.2, p = 1.000) weeks (62). In these studies, exercise programs were conducted during the cancer treatment (e.g. neoadjuvant chemoradiotherapy).

3.5.5 Summary of the Qualitative Synthesis

All six studies reported no evidence of changes in insomnia, and sleep quality scores observed from pre- to post-exercise intervention differed significantly. To note, all six studies used subjective measures to assess sleep disturbances. However, only the study by Loughney et al. (57) found a significant difference between the exercise group compared to the usual care group whereby sleep efficiency (%) 78 (13) vs. 80 (15) compared to 69 (24) vs. 76 (20) (p = .022), and sleep duration (min) (190 (269) vs. 369 (81) compared to (265 (315) vs. 299 (39); p = .028). The result suggests that people who participated in the 6-week in-hospital exercise training program significantly benefit from better sleep duration and efficiency compared with people in the usual care control group.

3.5.6 Exercise Adherence

Three studies recorded total exercise volume weekly, two studies using an accelerometer (57, 58) and one using exercise diaries (59). Six studies reported exercise adherence rates ranging from 74% (59) to 96% (56, 57). However, one study did not report the adherence rate to the program (60).

3.5.7 Risk of Bias Within Studies

The risk of bias of studies was deemed to be moderate, as determined by the Cochrane Risk of Bias Tool (63) and the ROBINS-I tool (33) (Table 4). The randomized controlled trial by Ligibel et al., (60) considered a high risk of bias given the missing reported information. Specifically, with exercise and mind-body interventions, the blinding from results, patient allocation, and counselling were not reported in this randomized controlled trial. However, non-randomized control trials by Loughney et al. (57), and Brunet et al. (56) (same trial), Loughney et al., reported blinding the outcome assessors from knowing which intervention the participant received. Besides, Loughney et al. was the only study that used objective measures to assess sleep disturbances. The overall methodology and outcome assessment performed in this study was considered low risk of bias. Most studies used a single item of EORTC QLQ C-30 to assess sleep disturbances that considered a low quality of outcome measurement and therefore present a high risk of bias. Important covariables were generally missing in tested models, although they were directly associated with sleep quality and physical activity such as weekday, season (64), psychotropic use (65), and baseline fitness level. The overall methodology and outcome assessment performed in all included studies was considered a moderate risk of bias.

3.6 Discussion

This systematic review summarizes the most current evidence on the effects of pre-operative exercise training on sleep outcomes in cancer patients who experienced sleep disturbance. Given that the pre-operative effect of exercise interventions on sleep outcomes in cancer patients has been scarcely studied, both RCTs and non-RCTs were included, and only seven studies met the inclusion criteria for this review. The included studies detailed seven trials, one RCT design of breast cancer patients, two non-randomized trials (proceed from the same trial) and four single-arm study designs of rectal cancer patients. We found one non-RCT that compared exercise to the usual care using an accelerometer to assess sleep and physical activity outcomes (57) that significantly improved sleep duration and efficiency, favouring the exercise group over the usual care group, after six weeks of supervised exercise training programme in rectal cancer patients following neoadjuvant chemoradiotherapy. All other studies that used subjective measures to assess sleep outcomes did not show any significant improvement.

To our knowledge, this is the first systematic review to address the pre-operative effect

of exercise on sleep among cancer patients and only includes studies with participants for various sleep parameters. The interventions, the reported outcomes, and the methodology used in the included studies varied greatly, making it difficult to determine the presurgical effect of exercise training on sleep disturbances and sleep quality. A meta-analysis was not conducted due to heterogeneity in interventions and lack of systematic reporting of outcome measures.

Exercise training programs showed contrasting results; among the seven studies, only one study by Loughney et al. showed significant improvement in objective sleep parameters between the exercise and the usual care control group (57). Thus, for the same trial of Brunet et al., subjective sleep measures did not significantly improve sleep between groups (56). Among studies reviewed in the current systematic review, five out of seven studies used the single sleep item from the EORTC QLQ C-30 questionnaire to assess sleep disturbances. The EORTC QLQ-C30 (34) is widely used in cancer research. However, as there is no official cut-off point for poor sleep, the EORTC QLQ-C30 is an unspecific questionnaire to detect sleep problems (66). Besides, subjective measures are critical for assessing sleep disturbance. Thus, objective assessment offers an unbiased measure of sleep parameters and increased precision. Therefore, objective and subjective measures of both sleep and exercise should be included in future studies (67). Thus, self-reported repeated measures that elicit data over shorter periods (weekly or daily) may reduce recall bias and improve subjective sleep data reliability. Subjective sleep complaints are strongly associated with perturbation emotional processes and are necessary for diagnosing insomnia (68). Evidence showed that even when the objective amount of sleep was sufficient, the subjective negative sleep duration experience can influence mood and behavior (24). Nevertheless, the complex relationship between sleep and emotions seems to be bidirectional (69), and future research should investigate this relationship in line with exercise.

In Loughney et al. study, positive outcomes were obtained after the cancer treatment phase than in patients still receiving treatment. Although exercise may be less effective during this period, exercise could prevent sleep difficulties while patients are receiving treatment (70), as radiation and chemotherapy are both known to develop sleep disturbances (2, 71). However, more research is needed on this topic. Only one RCT was included, and they did not use a placebo when exercise intervention was tested, increasing the risk of bias. On the other hand, cognitive-behavioral therapy for insomnia (CBT-I) has been recommended as the first-line intervention for cancer-related insomnia (72, 73). Future research on sleep disturbances in patients with cancer

must compare pre-operative exercise programs' efficacy to another sleep intervention such as CBT-I (50).

It is unclear whether the type and intensity of exercise training such as walking could explain discordances results. The effect of walking on sleep disturbances has been studied by Fang et al. (23), Mercier et al. (24), and Langford et al. (74), who showed a positive association with sleep outcomes, and more impactful than any other aerobic exercise. The exercise dose-effect required to improve sleep is uncertain because none of the included studies compared aerobic exercise doses. Two RCTs compared a post-surgical higher dose of aerobic exercise to a standard dose (46, 75). Results suggest that a high dose of aerobic exercise may be needed to improve sleep quality among cancer patients. These results need to be proved preoperatively in cancer patients (75).

Psychological and physiological mechanisms could explain inconsistent conclusions from the included studies through which exercise could improve sleep open to further study (76). On the psychological level, the interaction between insomnia, mood and anxiety has been well-studied in cancer patients (77-79). Recently, in a large survey of 294 different types of cancer patients of the Irish population, Harrold et al. (73) found that higher score of the Hospital Anxiety and Depression Scale-Depression/Anxiety (HADS>11), female sex, age <65 years, cancer subtype, and alcohol consumption were associated with statistically significant higher odds ratios of insomnia syndrome. Similar to the findings of a cross-sectional study in 434 Chinese cancer patients, pain and anxiety were positively associated with preoperative insomnia (80), which was in line with previous studies reporting that psychological disorders in cancer patients (77-79, 81) were strongly associated with sleep difficulties. In cancer, exercise training has the potential to improve the patients' mood (82) and self-esteem (83), to decrease symptoms of depression (84-86), anxiety, chronic pain (87). On the physiological level, Sprod et al. (88) observed an association between increasing levels of IL-6 and reduced sleep efficiency and duration, which suggested that exercise could improve sleep through regulating pro-inflammatory cytokines. Other potential mechanisms that are relevant to the cancer population should be involved, such as light exposure. Evidence suggests that exercise could have a beneficial effect on sleep through increased exposure to natural daylight, a powerful zeitgeber that helps resynchronize circadian rhythms and may improve nocturnal sleep (89, 90). Recently, Chen et al. (44) results indicate that exercising with exposure to daylight is significantly related to improved subjective sleep

quality in lung cancer patients. In the non-daylight exposure group, worsened SOL was observed from baseline to 3-month follow-up. Insufficient exposure to sunlight has been shown to disrupt work and sleep cycles (91). Nevertheless, future research involving an experimental design should examine the bidirectional relationship between exercise and cancer-related outcomes and identify the underlying mechanisms.

3.7 Future Directions

Sleep disturbance is commonly seen before surgery, but there are limited studies on this topic and no guidelines to manage this condition. Therefore, more research is needed in the pre-operative period. Large RCTs evaluate the effects of the pre-operative exercise alone or as part of a multimodal rehabilitation program on sleep quality. Include various subjective and objective sleep measures administered and follow-up assessments to assess the sustainment improvement over time. Mechanisms linking exercise with sleep and optimal dosage of exercise needed to affect sleep positively also warrant investigation.

3.8 Strengths and Study Limitations

This study is the first to review the literature systematically and specifically on the effects of pre-operative exercise alone or as part of a multimodal rehabilitation program on sleep quality. Although we performed a comprehensive search of the literature, it is still possible that relevant studies were missing. Because sleep has often been a secondary outcome, other studies not reviewed may have examined this outcome without reporting the results. This is especially likely if the effect on sleep was not significant. The literature on pre-operative exercise intervention effects on sleep in cancer patients is relatively scarce, such that this systematic review contains a minimal number of studies (n=7) with a small sample size, including patients with only colorectal and breast cancer thus limiting the generalization of findings. Besides, the psychotropic/sleep medication use (65), baseline fitness level, the season and day of the week (64) are important confounders that could not be tested and may have introduced a bias because they are seen as a factor influencing sleep quality and the amount of physical activity. There is substantial heterogeneity between the eligible studies in this review, making a comparison between them difficult. The length of interventions ranged from 4.2 (60) weeks to (62) weeks with various frequencies and intervention intensity. All the included studies subjectively

assessed sleep on a questionnaire (five out of the seven studies using a single item). These factors make it difficult to draw any conclusions on the effects of a pre-operative exercise intervention on cancer patients' sleep quality and impossible to conduct a meta-analysis.

3.9 Conclusions

A large body of evidence supports the numerous benefits of exercise in the cancer context (e.g., improved physical functioning, decreased fatigue). The available empirical evidence on the presurgical effect of exercise on sleep outcomes is scarce and, overall, suggests that it can have a limited effect. However, the studies analyzed were characterized by many methodological limitations. Future studies need to be conducted using clinical sleep disturbances (e.g., insomnia) as an inclusion criterion, subjectively and objectively assessed.

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3.11 Declarations of Interest

None.

3.12 References

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Figures and Tables

Table 3-1: Studies' characteristics

Authors (years)	N	Sex (m:f)	Mean age (SD)	Treatment status	Cancer Site	Cancer Stage
RCT						
Ligibel et al., 2017 (60) USA	49 MB: 22 EG: 27	0:49	NR	NR	Breast	I-III
Non-randomized trials						
Brunet et al., 2017 (56) Canada	35 CG:11 EG: 24	23:12	68	After neoadjuvant chemoradiation therapy	Rectal	≥ stage T2/N+
Loughney et al., (57) 2017 Canada	33 CG:10 EG: 23					
Single-arm						
Alejo et al., 2019 (58) Spain	12	3:9	61 (7.0)	During neoadjuvant chemoradiotherapy	Rectal	II–III
Singh et al., 2018 (61) Australia	10	7:3	54.6 (14.1)	During neoadjuvant chemoradiotherapy	Rectal	NR
Singh et al. 2017 (62) Australia	10	5:5	54.4 (12.9)	During neoadjuvant chemoradiotherapy	Rectal	NR
Morelli et al., 2016 (59) Canada	18	12:6	57.5 (10.4)	During and after neoadjuvant chemoradiotherapy	Rectal	II: 11.1% III: 77.7% IV: 5.5% N/A:5.5%

MB: mind-body intervention, Ex: exercise intervention group, CG: control group, NR: not reported. Data are presented as mean (SD)

Table 3-2: Summary of exercise program interventions

Authors (years)	Type of exercise	Delivery mode	Following up	Intensity	Frequency / Week	Session length	Duration/ week	Adherence rate %
RCT								
Ligibel et al., 2017	Aerobic and strength-training	Supervised + Home-based	Baseline (before intervention) & 4.2 weeks prior to surgery	NR	2 days	NR	4.2	NR
Non-randomized trials								
Brunet et al., 2017 Loughney et al., 2017	Aerobic and strength-training	Supervised	Baseline, 3 and 6 weeks	50-80% of HR_{max}	3 days	40 min	6	96
Single-arm								
Alejo et al., 2019	Aerobic, resistance, flexibility exercises	Supervised	Pre-NACRT, post-NACRT, and pre-surgery	MVPA	1 days	60 min	5	89
Singh et al., 2018	Aerobic, resistance	Supervised + home-based	Pre and post-intervention	60-80% of HR_{max}	2 days	60 min	10	77
Singh et al., 2017	Aerobic, resistance	Supervised + home-based	Pre and post-intervention	60-80% of HR_{max}	2 days	60 min	16	80
Morelli et al., 2016	Aerobic (treadmill, bike, elliptical, and rower)	Supervised	Pre-NACRT, post-NACRT, and pre-surgery	Moderate	3 days	50 min	6	74

PSQI: Pittsburgh Sleep Quality Index, A total score >5 suggests the presence of significant sleep difficulties

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Core 30 questionnaire. A higher score is indicative of higher symptoms problems of sleep disturbances.
SE: sleep efficiency; TST: total sleep time; Sleep disturbance is indicated by a TST of <6.5 h, and SE <85%
NR: not reported, MVPA: moderate to vigorous physical activity, HR_{max}: maximal heart rate, NACRT: neoadjuvant chemoradiotherapy treatment, MB: mind-body intervention, Ex: exercise intervention group, CG: control group

Table 3-3: Summary of sleep outcomes and main results

Authors (years)	**Sleep outcomes**	**Baseline sleep measure and score (Mean ± SD)**	**Effect on sleep outcomes**	**Significance**
RCT				
Ligibel et al., 2017	Subjective: Sleep disturbances EORTC QLQ C-30 (0–100)	MB: 34.9 (35.7) EG: 35.9 (32.6)	MB: -8.3 (21.3), $p = 0.06$ EG: -16.7 (32.6), $p = 0.03$	No significant changes for the insomnia score between groups ($p = 0.52$)
Non-randomized trials				
Brunet et al., 2017	Subjective: Sleep disturbances EORTC QLQ C-30 (0–100)	CG:33 (0, 42.5) EG:33 (33, 67)	CG:0 (0, 49.8) EG:33 (0, 67)	No significant changes for the insomnia score between ($p = 0.89$), and within groups ($ps \geq 0.26$)
Loughney et al., 2017	Objective: Accelerometer SE % TST (min/day)	**median (IQR)** **SE**: CG: 69 (24) EG:78 (13) **TST**: CG: 265 (315) EG:190 (265)	**median (IQR) \ Change, % change** **SE ($p = 0.022$):** CG: 76 (20) / 6 (11), 7 (17) EG:80 (15) / 6 (28), 6 (39) **TST ($p = 0.028$):** CG: 299 (39) / 143 (235), 3 (112) EG:369 (81) / 0 (141), 1 (52)	EG showed significant improvements in SE (%) and TST compared to CG
Single-arm				
Alejo et al., 2019	Subjective: Sleep disturbances EORTC QLQ C-30 (0–100)	16.0 (23.0)	13.0 (17.0)	No significant change for the insomnia score (95% CI: −17 - 10; M: −3.0), $p = 0.56$)
Singh et al., 2018	Subjective: Sleep disturbances	23.3 (16.1)	28.0(21.7)	No significant change for the insomnia score (95% CI: −2.8 - 12.1; M: 4.7, $p = 141$)

	EORTC QLQ C-30 (0–100)			
Singh et al., 2017	Subjective: Sleep disturbances EORTC QLQ C-30 (0–100)	33.3 (25.2)	29.2 (33.0)	No significant change for the insomnia score (95% CI: −34.9 - 26.6; M: -4.2, p = 1.000)
Morelli et al., 2016	Subjective: Global sleep quality PSQI (0–21)	5.6 (2.9)	5.6 (3.2)	No significant improvement for the PSQI: (95% CI: −1.6 - 1.7; M: 0.1)

PSQI: Pittsburgh Sleep Quality Index, A total score >5 suggests the presence of significant sleep difficulties
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Core 30 questionnaire. A higher score is indicative of higher symptoms problems of sleep disturbances.
SE: sleep efficiency; TST: total sleep time; Sleep disturbance is indicated by a TST of <6.5 h, and SE <85%
NR: not reported, MVPA: moderate to vigorous physical activity, HR_{max}: maximal heart rate, NACRT: neoadjuvant chemoradiotherapy treatment, MB: mind-body intervention, Ex: exercise intervention group, CG: control group

Table 3-4: Risk of bias of RCT and non-randomized controlled trials***

*Each criterion has been evaluated as being "high," "low," or "some concerns" regarding the risk of bias following the Cochrane Risk of Bias Tool for assessing the risk of bias in randomized trials **Each criterion has been evaluated as being "low risk," "moderate risk," "serious risk", "critical risk", and "no information" regarding the risk of bias following the ROBINS-I tool for assessing the risk of bias.

RCTs							
Study	**Random sequence generation**	**Allocation concealment**	**Selective reporting**	**Other bias**	**Blinding participants**	**Blinding outcome**	**Attrition description**
Ligibel et al., 2017	unclear	Low	unclear	unclear	unclear	Low	Low
Non-randomized controlled trials							
Study	**Confounding**	**Selection of participants**	**Bias in classification of interventions**	**Deviation from intended intervention**	**Missing data**	**Outcome measurement**	**Selective outcome reporting**
Brunet et al., 2017	critical risk	critical risk	critical risk	no information	low risk	serious risk	moderate risk
Loughney et al., 2017						low risk	

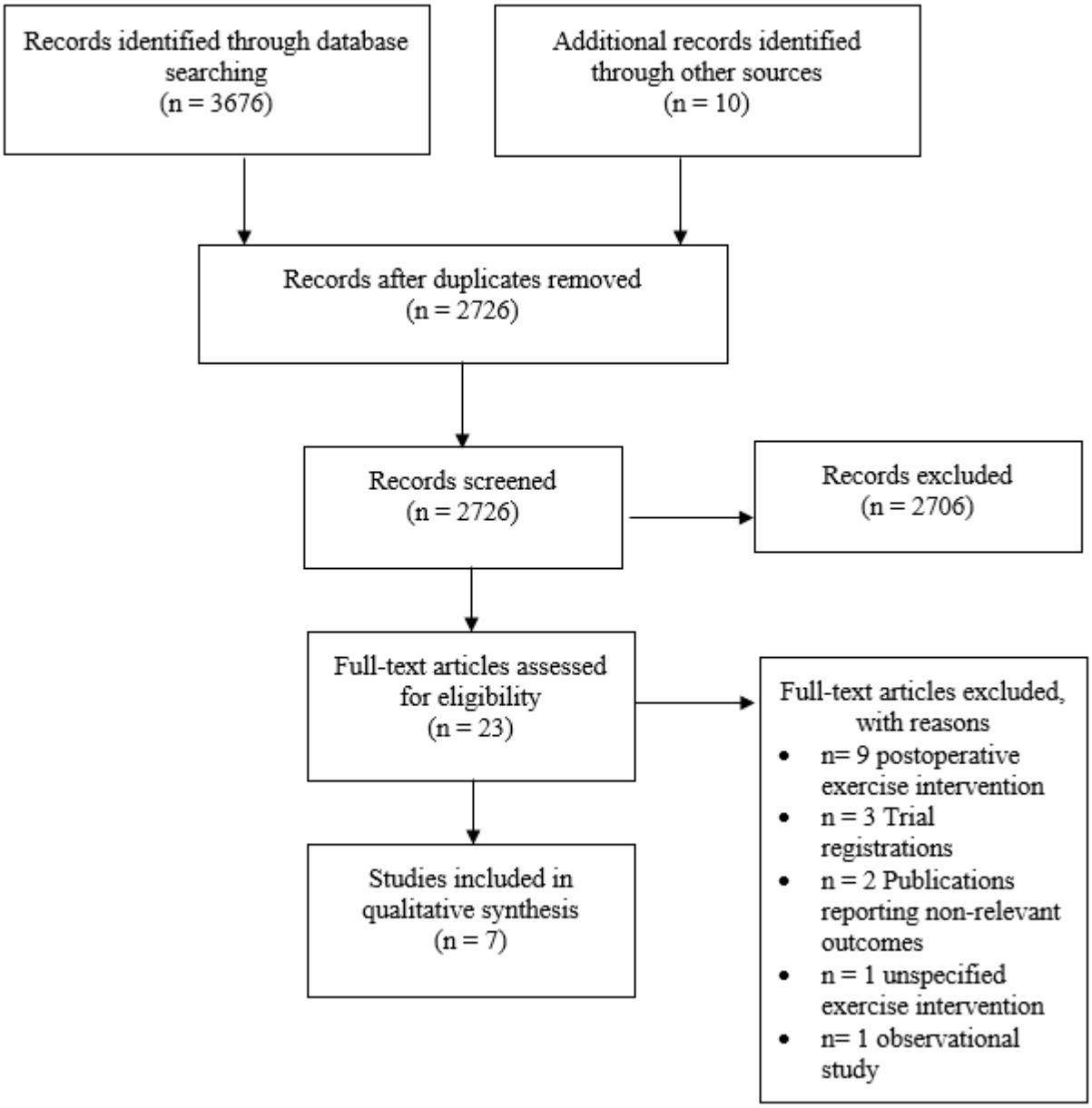

Figure 3-1: PRISMA flow diagram describing systematic review search results, abstract screening, and article selection.

3.13 Detailed Methods

3.13.1 Targets

(24649148 or 32502851 or 32897907 or 32505970 or 31353674).ui

Effects of systematic rehabilitation programs on quality of life in patients undergoing lung resection.Li XH, Zhu JL, Hong C, Zeng L, Deng LM, Jin LY.Mol Clin Oncol. 2013 Jan;1(1):200-208. doi: 10.3892/mco.2012.31. Epub 2012 Oct 2. PMID: 24649148
Sleep problems in cancer patients: a comparison between the Jenkins Sleep Scale and the single-item sleep scale of the EORTC QLQ-C30.Hofmeister D, Schulte T, Hinz A.Sleep Med. 2020 Jul;71:59-65. doi: 10.1016/j.sleep.2019.12.033. Epub 2020 Apr 3. PMID: 32502851
Level of Exercise Influences the Severity of Fatigue, Energy Levels, and Sleep Disturbance in Oncology Outpatients Receiving Chemotherapy. Moy S, Kober KM, Viele C, Paul SM, Hammer M, Melisko M, Wright F, Conley YP, Levine JD, Miaskowski C.Cancer Nurs. 2020 Sep 4. doi: 10.1097/NCC.0000000000000875. Online ahead of print. PMID: 32897907
Effectiveness of aerobic exercise and mind-body exercise in cancer patients with poor sleep quality: A systematic review and meta-analysis of randomized controlled trials.Takemura N, Cheung DST, Smith R, Deng W, Ho KY, Lin J, Kwok JYY, Lam TC, Lin CC.Sleep Med Rev. 2020 Oct;53:101334. doi: 10.1016/j.smrv.2020.101334. Epub 2020 May 13. PMID: 32505970 Review.
Meta-analysis: Exercise intervention for sleep problems in cancer patients. Fang YY, Hung CT, Chan JC, Huang SM, Lee YH.Eur J Cancer Care (Engl). 2019 Sep;28(5):e13131. doi: 10.1111/ecc.13131. Epub 2019 Jul 28. PMID: 31353674 Review.

3.13.2 Methodology

The following databases were searched for relevant studies on November 23 2020: Biosis (via ClarivateAnalytics); The Cochrane CENTRAL Register of Controlled Trials & Cochrane Database of Systematic Reviews (via Wiley Issue 11 of 12, November 2020); Embase Classic +Embase (via Ovid 1947 to 2020 November 20); MEDLINE (via Ovid 1946 to November 20, 2020; and PsycINFO (via Ovid 1987 to November Week 3 2020).

The search strategies designed by a librarian used text words and relevant indexing to identify the exercise intervention in cancer patients with sleep disturbances scheduled for elective surgery.

The MEDLINE strategy (Appendix 1) was applied to all databases, with modifications to search terms as necessary. No language limits were applied. Search strategies were peer-reviewed by two librarians. In addition, clinical trials registries [clinicaltrials.gov], and Google Scholar were searched. The Medline strategy will rerun before submission to indicate whether relevant studies are found.

3.13.3 Databases Searched

BIOSIS (Clarivate Analytics) (November 23, 2020)

Indexes=BCI Timespan=All years

#	Results	Searches
#1	416,282	TS= (exercise* or rehab* or re-hab*)
#2	27,509	TS= ((activit* Near/3 (life* or living)) or (ADL or IADL))
#3	83,058	TS= (((resistanc* or strength* or enduranc*) Near/3 train*) or stretch*)
#4	9,356	TS=((multimodal* or multi-modal*) Near/3 (Therap* or Treat* or approach*))
#5	79,887	TS= (physical* Near/2 (activ* or train*))
#6	182	TS= (prehab* or pre-hab*)
#7	539,885	#6 or #5 or #4 or #3 or #2 or #1
#8	2,946,479	TS= (cancer* or tumo?r* or neo?plas* or carcinom* or oncolog* or sarcom*)
#9	25,133	#7 and #8
#10	82,511	TS= ((sleep* Near/4 (disorder* or disturb* or disease* or poor* or problem* or quality or difficult* or onset* or efficien* or latent* or time* or lack* or restful* or duration* or length* or pattern* or initiat* or maintain* or maintenance* or score* or scale*)) or insomni* or dyssomni*)
#11	163,788	TS= sleep*
#12	163,392	TS=(quality-of-life or life-quality or QALY or QoL or hrqol or hrql or SF36 or short-form-36 or short-form-12 or SF12 or SF8 or EQ5D or EUROQOL or EURO-QOL or WHO-QOL-BREF or MD-Anderson-Symptom-Inventory or MDASI or PedsQL or EORTC-QLQ* or qlq*)
#13	6,317	#11 and #12
#14	83,864	#10 or #13
#15	279	#9 and #14
#16	907,414	TI= (newborn* or new-born* or neonat* or neo-nat* or infan* or child* or adolesc* or paediatr* or pediatr* or baby* or babies* or toddler* or kid or kids or boy* or girl* or juvenile* or teen* or youth* or pubescen*)
#17	272	#15 not #16
#18	2,760,271	TI=((animals or animal or canine* or cat or cats or dog or dogs or feline or goat* or hamster* or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep*) not (human* or patient*))
#19	269	#17 not #18

Cochrane CENTRAL Register of Controlled Trials (Wiley) (November 23, 2020)

Cochrane Database of Systematic Reviews & Cochrane Central Register of Controlled Trials Issue 11 of 12, November 2020

ID	Search	Hits
#1	(exercise* or rehab* or re-hab*):ti,ab,kw	136780
#2	((activit* Near/3 (life* or living)) or (ADL or IADL)):ti,ab,kw	17724
#3	(((resistanc* or strength* or enduranc*) Near/3 train*) or stretch*):ti,ab,kw	21360
#4	((multimodal* or multi-modal*) Near/3 (Therap* or Treat* or approach*)):ti,ab,kw	3550
#5	(physical* Near/2 (activ* or train*)):ti,ab,kw	35189
#6	(prehab* or pre-hab*):ti,ab,kw	368
#7	#1 or #2 or #3 or #4 or #5 or #6	169334
#8	(cancer* or tumo?r* or neo?plas* or carcinom* or oncolog* or sarcom*):ti,ab,kw	213757
#9	#7 and #8	12505
#10	((sleep* Near/4 (disorder* or disturb* or disease* or poor* or problem* or quality or difficult* or onset* or efficien* or latent* or time* or lack* or restful* or duration* or length* or pattern* or initiat* or maintain* or maintenance* or score* or scale*)) or insomni* or dyssomni*):ti,ab,kw	31914
#11	sleep*:ti,ab,kw	39135
#12	(quality-of-life or life-quality or QALY or QoL or hrqol or hrql or SF36 or short-form-36 or short-form-12 or SF12 or SF8 or EQ5D or EUROQOL or EURO-QOL or WHO-QOL-BREF or MD-Anderson-Symptom-Inventory or MDASI or PedsQL or EORTC-QLQ* or qlq*):ti,ab,kw	118559
#13	#11 and #12	7025
#14	#10 or #13	33298
#15	#9 and #14	659
#16	(newborn* or new-born* or neonat* or neo-nat* or infan* or child* or adolesc* or paediatr* or pediatr* or baby* or babies* or toddler* or kid or kids or boy* or girl* or juvenile* or teen* or youth* or pubescen*):ti	132430
#17	#15 NOT #16	647
#18	((animal or animals or canine* or cat or cats or dog or dogs or feline or hamster* or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep*) not (human* or patient*)):ti,kw	2559
#19	#17 NOT #18	647
#20	(Pubmed):an OR (Embase):an	1042155
#21	#19 not #20	248

Embase [Ovid] (November 23, 2020)

Embase Classic+Embase 1947 to 2020 November 20

#	Searches	Results
1	exp exercise/	379476
2	(exercise* or rehab* or re-hab*).tw,kw.	674439
3	rehabilitation/ or exp kinesiotherapy/ or daily life activity/ or heart rehabilitation/	278340
4	((activit* adj3 (life* or living)) or (ADL or IADL)).tw,kw.	72576
5	(((resistanc* or strength* or enduranc*) adj3 train*) or stretch*).tw,kw.	119333
6	((multimodal* or multi-modal*) adj3 (Therap* or Treat* or approach*)).tw,kw.	31271
7	(physical* adj2 (activ* or train*)).tw,kw.	183842
8	(prehab* or pre-hab*).tw,kw.	1266
9	1 or 3 or 4 or 5 or 6 or 7 or 8	866179
10	exp neoplasms/	5024310
11	(cancer* or tumo?r* or neo?plas* or carcinom* or oncolog* or sarcom*).tw,kw.	4716031
12	10 or 11	6096700
13	9 and 12	77970
14	sleep deprivation/ or sleep latency/ or insomnia/ or sleep disorder/	145616
15	((sleep* adj4 (disorder* or disturb* or disease* or poor* or problem* or quality or difficult* or onset* or efficien* or latent* or time* or lack* or restful* or duration* or length* or pattern* or initiat* or maintain* or maintenance* or score* or scale*)) or insomni* or dyssomni*).tw,kw.	176088
16	14 or 15	242018
17	sleep/	109953
18	sleep*.tw,kw.	297644
19	17 or 18	310852
20	"quality of life"/	487517
21	(quality-of-life or life-quality or QALY or QoL or hrqol or hrql or SF36 or short-form-36 or short-form-12 or SF12 or SF8 or EQ5D or EUROQOL or EURO-QOL or WHO-QOL-BREF or MD-Anderson-Symptom-Inventory or MDASI or PedsQL or EORTC-QLQ* or qlq*).tw,kw.	499148
22	20 or 21	630863
23	19 and 22	27518
24	16 or 23	248976

25	13 and 24	2247
26	(exp child/ or exp adolescent/) not exp adult/	2521440
27	(newborn* or new-born* or neonat* or neo-nat* or infan* or child* or adolesc* or paediatr* or pediatr* or baby* or babies* or toddler* or kid or kids or boy* or girl* or juvenile* or teen* or youth* or pubescen*).ti.	1966295
28	(pediatr* or paediatr*).jx.	762084
29	26 or 27 or 28	3281385
30	25 not 29	2124
31	(exp animal/ or exp juvenile animal/ or adult animal/ or animal cell/ or animal tissue/ or nonhuman/ or animal experiment/ or animal model/) not human/	7587378
32	(animal or animals or canine* or cat or cats or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*).ti,kw,dq,jx. not (human* or patient*).mp.	2497132
33	31 or 32	7701457
34	30 not 33	2114
35	remove duplicates from 34	2077

Medline [Ovid] (November 23, 2020)

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily** 1946 to November 20, 2020

#	Searches	Results
1	exp Exercise/	200275
2	Exertion/ or Physical Fitness/	27581
3	limit 2 to yr="1966 - 1988"	5043
4	(exercise* or rehab* or re-hab*).tw,kf.	464581
5	Rehabilitation/ or exp Exercise Therapy/ or Activities of Daily Living/ or Cardiac Rehabilitation/	134218
6	((activit* adj3 (life* or living)) or (ADL or IADL)).tw,kf.	48140
7	(((resistanc* or strength* or enduranc*) adj3 train*) or stretch*).tw,kf.	99975
8	((multimodal* or multi-modal*) adj3 (Therap* or Treat* or approach*)).tw,kf.	20389
9	(physical* adj2 (activ* or train*)).tw,kf.	131347
10	(prehab* or pre-hab*).tw,kf.	795
11	1 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	809629
12	exp Neoplasms/	3384417
13	(cancer* or tumo?r* or neo?plas* or carcinom* or oncolog* or sarcom*).tw,kf.	3346414
14	12 or 13	4380258
15	11 and 14	57321
16	sleep deprivation/ or sleep latency/	9870
17	"Sleep Initiation and Maintenance Disorders"/	13475
18	Sleep Wake Disorders/	22755
19	((sleep* adj4 (disorder* or disturb* or disease* or poor* or problem* or quality or difficult* or onset* or efficien* or latent* or time* or lack* or restful* or duration* or length* or pattern* or initiat* or maintain* or maintenance* or score* or scale*)) or insomni* or dyssomni*).tw,kf.	105570
20	16 or 17 or 18 or 19	119699
21	sleep/	53935
22	sleep*.tw,kf.	188462
23	21 or 22	197461
24	"Quality of Life"/	200093
25	(quality-of-life or life-quality or QALY or QoL or hrqol or hrql or SF36 or short-form-36 or short-form-12 or SF12 or SF8 or EQ5D or EUROQOL or EURO-QOL or WHO-QOL-BREF or MD-Anderson-Symptom-Inventory or MDASI or PedsQL or EORTC-QLQ* or qlq*).tw,kf.	306589
26	24 or 25	363083
27	23 and 26	14733
28	20 or 27	123301
29	15 and 28	939
30	(exp Child/ or exp Infant/ or Adolescent/) not exp Adult/	1898226

31	(newborn* or new-born* or neonat* or neo-nat* or infan* or child* or adolesc* or paediatr* or pediatr* or baby* or babies* or toddler* or kid or kids or boy* or girl* or juvenile* or teen* or youth* or pubescen*).ti.	1524324
32	(pediatr* or paediatr*).jw.	579592
33	30 or 31 or 32	2488955
34	29 not 33	891
35	(Animals/ or Models, animal/ or Disease models, animal/) not Humans/	4725281
36	((animals or animal or canine* or cat or cats or dog or dogs or feline or hamster* or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*) not (human* or patient*)).ti,kf,jw.	2397643
37	35 or 36	5147315
38	34 not 37	888
39	remove duplicates from 38	885

APA PscyInfo [Ovid] (November 23, 2020)

APA PsycInfo 1806 to November Week 3 2020

#	Searches	Results
1	(exercise* or rehab* or re-hab*).tw.	129749
2	((activit* adj3 (life* or living)) or (ADL or IADL)).tw.	17143
3	(((resistanc* or strength* or enduranc*) adj3 train*) or stretch*).tw.	8011
4	((multimodal* or multi-modal*) adj3 (Therap* or Treat* or approach*)).tw.	3258
5	(physical* adj2 (activ* or train*)).tw.	39774
6	(prehab* or pre-hab*).tw.	53
7	1 or 2 or 3 or 4 or 5 or 6	180846
8	(cancer* or tumo?r* or neo?plas* or carcinom* or oncolog* or sarcom*).tw.	81438
9	7 and 8	4891
10	((sleep* adj4 (disorder* or disturb* or disease* or poor* or problem* or quality or difficult* or onset* or efficien* or latent* or time* or lack* or restful* or duration* or length* or pattern* or initiat* or maintain* or maintenance* or score* or scale*)) or insomni* or dyssomni*).tw.	49017
11	sleep*.tw.	80859
12	(quality-of-life or life-quality or QALY or QoL or hrqol or hrql or SF36 or short-form-36 or short-form-12 or SF12 or SF8 or EQ5D or EUROQOL or EURO-QOL or WHO-QOL-BREF or MD-Anderson-Symptom-Inventory or MDASI or PedsQL or EORTC-QLQ* or qlq*).tw.	74890
13	11 and 12	3763
14	10 or 13	49733
15	9 and 14	248
16	(newborn* or new-born* or neonat* or neo-nat* or infan* or child* or adolesc* or paediatr* or pediatr* or baby* or babies* or toddler* or kid or kids or boy* or girl* or juvenile* or teen* or youth* or pubescen*).ti.	570650
17	(pediatr* or paediatr*).jx.	18722

18	16 or 17	575565
19	15 not 18	231
20	(animal or animals or canine* or cat or cats or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*).ti,tw,jx. not (human* or patient*).mp.	289776
21	19 not 20	229
22	remove duplicates from 21	229

3.13.4 Duplication & Removal of Records

Duplicates were removed by using EndNote's Author/Title/Year duplicate checker, followed by a manual verification of duplicates.

Database	Before Duplicate Removal	After Duplicate Removal	% Retained
Biosis (Web of Science)	237	87	37%
Cochrane	248	231	93%
Embase	2077	1433	69%
Medline	885	881	100%
PsycINFO	229	94	41%
Totals	*3676*	*2726*	*74%*

3.13.5 Other Sources

Clinical Trials.gov
Google Scholar

3.13.6 Additional Details

Limits:

Adults

Human

Legends:

Legend for Databases

Legends for Medline (Ovid), Embase (Ovid) & CINAHL are available on our website:

http://www.muhclibraries.ca/Documents/Database_Legends.pdf

Chapter 4 Does a Multimodal Prehabilitation Program Improve Sleep Quality and Duration in Patients Undergoing Colorectal Resection for Cancer? Pilot Randomized Control Trial

The systematic review emphasizes the limited available knowledge concerning the influence of preoperative exercise interventions on sleep outcomes, with only modest improvements in sleep disturbances observed. Physical activity alone may not be effective enough to significantly improve sleep during a limited preoperative period, further underscoring the need to investigate the effects of multimodal approaches. Given the brief window of opportunity for intervention before surgery, typically around 4 weeks, it is essential to explore more comprehensive strategies that combine various methods, such as exercise, psychological support, and nutrition, to maximize the potential benefits for patients' sleep and overall well-being.

Considering these findings, we propose a pilot randomized controlled trial (RCT) to investigate the effects of multimodal interventions on sleep outcomes. By combining exercise with nutrition and psychosocial interventions, we aim to enhance the efficacy of preoperative interventions and improve sleep quality for patients during this critical period before surgery. We were particularly interested in assessing sleep quality and parameters using subjective and objective methods during the preoperative period and up to 8 weeks after surgery. We aimed to determine the effect of multimodal prehabilitation on sleep quality and parameters by comparing a multimodal program with a standard-of-care group (no formal intervention) in colorectal cancer adults during the preoperative period using a single-blind pilot randomized controlled trial (RCT). The impact on sleep quality and parameters will be assessed preoperatively and up to 8 weeks after surgery, which had not previously been documented in the context of prehabilitation and surgery. Finally, as sleep contributes to mental and physical dysfunction, our goal was also extended to explore potential moderators of these associations.

This study showed a limited improvement in the perceived sleep quality for the prehabilitation group only at the preoperative time point. In addition, the associations were moderated by the baseline walking capacity and the anxiety symptoms. This study highlighted that prehabilitation intervention might significantly improve sleep of specific patients'

subgroups.

The article entitled ‘Does a Multimodal Prehabilitation Program Improve Sleep Quality and Duration in Patients Undergoing Colorectal Resection for Cancer? Pilot Randomized Control Trial’ was accepted for publication in the Journal of Behavioral Medicine on July 10th, 2023. The main manuscript is followed by the online supplement, which includes the expanded materials and outcomes.

Does a Multimodal Prehabilitation Program Improve Sleep Quality and Duration in Patients Undergoing Colorectal Resection for Cancer? Pilot Randomized Control Trial

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Keywords: Prehabilitation, Multimodal intervention, Colorectal surgery, Cancer, Sleep quality, Sleep parameters.

4.1 Abstract

Sleep difficulties are a common symptom in cancer patients at different stages of treatment trajectory and may lead to numerous negative consequences for which management is required. This pilot Randomized Controlled Trial (RCT) aims to assess the potential effectiveness of home-based prehabilitation intervention (prehab) on sleep quality and parameters compared to standard care (SOC) in colorectal cancer patients during the preoperative period and up to 8 weeks after the surgery. One hundred two participants (48.3% female, mean age 65 years) scheduled for elective resection of colorectal cancer were randomized to the prehab (n = 50) or the SOC (n = 52) groups. Recruitment and retention rates were 54% and 72%, respectively. Measures were completed at the baseline and preoperative, 4- and 8-week after-surgery follow-ups. Our mixed models' analyses revealed no significant differences between groups observed over time for all subjective and objective sleep parameters. A small positive change was observed in the perceived sleep quality only at the preoperative time point for the prehabilitation group compared to the SOC group, with an effect size d = 0.11 and a confidence interval (CI) between -2.1 and -0.1, p = .048. Prehab group patients with high anxiety showed a significant improvement in the rate of change of sleep duration over time compared to the SOC group, with a difference of 110 minutes between baseline and 8 weeks after surgery (d = .51, 95% CI: 92.3 to 127.7, p = .02). Multimodal prehabilitation intervention is feasible in colorectal cancer patients and may improve sleep duration for patients with high anxiety symptoms. Future large-scale RCTs are needed to confirm our results.

4.2 Introduction

In Canada, colorectal cancer is the third most commonly diagnosed cancer, and surgical resection remains the primary treatment (1). Although cancer treatments can prolong survival, treatment side effects significantly contribute to the development and persistence of various complications that are invasive to the patient's physical, emotional, and social life (2, 3). Surgical resection is the primary treatment for most CRC diagnoses; however, it has been associated with a complication rate of up to 30.2% (4).

Sleep disorders are common and significant complaints of cancer patients (5). Specifically, cancer surgery is recognized as one of the related risk factors for sleep disturbances (6). Sleep disturbances, defined as nighttime or wakefulness disruptions, include various clinical disorders (e.g., insomnia, hypersomnolence, restless leg syndrome disorder) (7). Patients undergoing surgery experience perioperative sleep disturbances (8-10). Up to 79% of patients complain of sleep disorders (11-13), and it may persist for six months or more after surgery in many patients (14, 15). In addition to the physical (16-19) and psychological side effects (20-23), sleep disorders can adversely affect patient recovery, increase morbidity, and decrease hospitalization satisfaction (24, 25). Therefore, perioperative sleep management of patients may directly improve outcomes after surgery and the effectiveness of the prehabilitation intervention by addressing the patient's needs.

Intervening in the factors contributing to the physical and mental recovery and managing the emotional distress related to anticipating surgery and recovery may be more effective during the preoperative period (26-29). Prehabilitation refers to improving an individual's functional capacity with interventions during the preoperative period so the stress of upcoming surgery can be handled better (30). While a large part of any multimodal prehabilitation program is physical strength and exercise training, nutritional counselling and psychological support may promote beneficial adaptation to training (31, 32). Multimodal prehabilitation program has been shown to increase functional capacity and reduced postoperative complications in patients scheduled for elective colorectal surgery for cancer compared to patients on rehabilitation (33-36).

No study has investigated the effect of a multimodal prehabilitation intervention on sleep quality in cancer patients, despite the well-established associations linking exercise, mental health, and diet with sleep outcomes. A recent systematic review (37) highlights the inconsistent findings and the lack of firm conclusions regarding the impact of exercise interventions on sleep

disturbances during the preoperative period. Mainly due to inadequate sleep assessment measures, such as one-item scales and significant methodological limitations (e.g., no intention-to-treat analyses and lack of control for potential confounders such as sleep medication usage). Furthermore, multiple studies have consistently emphasized the bidirectional comorbidity between sleep disturbances and psychiatric disorders, particularly depression and anxiety symptoms (38, 39). In cancer patients, cognitive-behavioral therapy for insomnia (CBT-I) has improved sleep quality and reduced anxiety, depression, and fatigue symptoms (40-43). Diet composition may also affect sleep. A diet higher in complex carbohydrates (e.g., fiber), healthier fats (e.g., unsaturated), and higher protein were associated with better sleep quality (44, 45).
Building upon the existing evidence, this pilot Randomized Controlled Trial (RCT) aims to assess the potential effectiveness of a multimodal prehabilitation intervention (prehab) on sleep quality and parameters compared to standard care (SOC) in colorectal cancer patients during the preoperative period and up to 8 weeks after surgery. It was hypothesized that patients participating in the multimodal prehabilitation group would lead to significant improvement in sleep quality and duration before and after surgery.

4.3 Methods

4.3.1 Subjects

The study was approved by the McGill University Health Centre Research Ethics Board, Montreal, Quebec, Canada, and the protocol was registered at http://clinicaltrials.gov (NCT04270500). In response to the COVID-19 pandemic, organizational and safety issues required a change in the original protocol. Therefore, we have adapted our pre-existing face-to-face prehabilitation program to a telehealth-delivered home-based format, and cardiopulmonary Exercise Testing (CPET) was not performed. Patient enrollment was initiated in November 2020 and completed in November 2022 at a single university-affiliated tertiary center in Montreal, Canada. The inclusion criteria for this study were all adult patients who were scheduled for elective resection of colorectal cancer and were approached at their first appointment following their surgeon's office visit. These patients were required to provide written informed consent to participate in the study. On the other hand, there were specific exclusion criteria applied. Subjects were not eligible if they did not speak English or French or had comorbid conditions that contraindicated exercise. Patients with sleep disorders other than insomnia (e.g., sleep-

disordered breathing) or who received psychotherapy specifically for insomnia and night-shift workers were deemed ineligible (46).

4.3.2 Perioperative Care

Perioperative care was guided by a standardized multielement evidence-based, comprehensive enhanced recovery after surgery (ERAS) pathway following the consensus review on the best care for patients undergoing colorectal surgery (47). A pilot study was conducted in 2008 by our multidisciplinary team on the feasibility of implementing the enhanced recovery after surgery pathway at our institution (48). Thereafter, the enhanced recovery after surgery pathway was applied to all patients scheduled for elective colorectal resection.

4.3.3 Study Design

The study was designed as a single-blind two parallel-arm RCT: multimodal prehabilitation intervention (n = 50) and standard care (n = 52) group. Approximately four weeks before each patient's scheduled operation, a medical examination was conducted, and participants completed baseline questionnaires and biochemical, functional, and anthropometric measurements. All measurements were repeated and collected by a research assistant preoperatively (~one month after the baseline), 4- and 8-weeks after the operation. All participants were provided with an actigraph monitor (Actigraph wGT3X-BT) to be worn continuously on their non-dominant arm for four weeks. The same procedure was repeated one month after surgery. Upon completing the initial steps, participants were randomly assigned by the same research assistant on a 1:1 ratio by computer-generated random numbers to receive either multimodal prehabilitation intervention (Prehab) or standard of care (SOC). No group stratifications were performed. Group allocation was concealed by using sequentially numbered sealed envelopes. All collected data were entered and managed in Redcap, a secure clinical trials management system.

4.3.4 Procedure

The scheduling of surgery was not affected by the study group. At the baseline visit, a kinesiologist, a dietitian, and a psychologist saw participants in the Prehab group. They were instructed to begin the prehabilitation program at home while waiting for surgery, typically around 4 weeks. In contrast, the SOC group were encouraged to maintain a healthy lifestyle

without specific tips on precise types and duration of exercises. To facilitate adherence to the program, participants received an instruction manual, written in an easily comprehensible language with instructions and figures demonstrating all program elements and a Borg scale to determine appropriate exercise intensity at home. The booklet also contained a diary where the patients were asked to document all activities related to the program. To encourage and measure adherence, prehab patients' group were contacted weekly by telephone and assessed with a standardized set of open-ended questions to uncover issues related to maintaining adherence to the frequency, intensity, or duration of exercise, the amount of whey protein ingested, and whether the participants experienced any adverse effects. Based on the information obtained through telephone and the patient diary, a percentage for adherence was tabulated for each element of the program and equally accounted for in the total adherence value calculated.

4.3.4.1 Exercise Intervention

A certified kinesiologist assessed and trained each participant following the American College of Sports Medicine guidelines (49). The total-body exercise prescription consisted of up to 50 min of home-based, unsupervised exercise for at least three days per week, alternating between aerobic and resistance training. Aerobic exercise intensity was prescribed based on the rate of perceived exertion (Borg scale) from the 6-min walk test (6MWT). The Karvonen formula [220 − age) − (resting heart rate × % intensity) + resting heart rate] was used to determine the heart rate to be maintained to achieve the desired, prescribed intensity. Participants were free to choose the type of aerobic exercise to engage in and adhere to their exercise program, including brisk walking, jogging, or using an aerobic exercise machine at a moderate intensity corresponding to 12-15 on a scale of 6 to 20 (Borg scale (50)). Each session included a 5-min warm-up, 20 min of aerobic exercise (starting at 40% of heart rate reserve), 20min of resistance training (eight exercises targeting major muscle groups performed at an intensity of 8 to 12 repetitions maximum), and a 5-min cool down. Progression of training intensity occurred when the participant could complete the aerobic exercise with mild exertion (Borg 12) and/or when the participant could complete 15 repetitions of a given resistance exercise. To complete the exercises at home, each participant was given three resistance bands (light, moderate, and/or vigorous). Participants were asked to document, for each day, the type of exercise performed and the duration and intensity (perceived effort according to the modified Borg scale). This allowed

us to calculate the frequency and the total duration of the exercise performed per week and assess patients' adherence to the exercise program. After hospital discharge, participants were encouraged to maintain a home-based prehabilitation program but were not asked to document the duration and intensity of the exercise performed each day. Due to the nature of the surgery, participants were asked to avoid upper body exercises such as shoulder lateral raises and wall push-ups. Exercise regimen-related issues were discussed over the telephone.

4.3.4.2 Nutrition Intervention

A registered dietitian assessed and provided individualized care to each patient based on the 3-day food diary completed at the time of enrollment. Dietary protein and energy intake were estimated from the food records provided using food exchange lists and a food composition database (51). Dietary intake was then evaluated based on individually calculated energy and protein requirements (determined using indirect calorimetry), and food choices were compared with Eating Well with Canada's Food Guide recommendations (52). Individualized nutrition care plans focus on meeting energy and protein requirements with appropriate food choices, management of cancer-related symptoms (such as diarrhea and constipation), blood glucose control, optimization of body composition (i.e., weight loss or gain if necessary), and nutrient intake by using practical suggestions based on actual intake. Individual protein requirements were calculated as 1.2g of protein per kilogram of body weight (adjusted body weight was used for obese patients), as per European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines for surgical patients (53). All participants were given a whey protein supplement to guarantee adequate daily protein intake (Immunocal®; Immunotec Inc., Vaudreuil, Quebec, Canada) at a quantity that matched the estimated dietary deficit. Participants were asked to consume the protein supplement within one h of their exercise regimen to capitalize on postexercise muscle protein synthesis (54). After hospital discharge, participants were encouraged to adhere to the nutrition program. Nutrition-related issues were discussed over the telephone to adjust or modify the program if necessary.

4.3.4.3 Psychosocial Intervention

Only participants who scored more than 6 points in the HADS-Anxiety or more than 8 in the HADS-Depression (55) received up to a 60-min visit with a trained psychologist who provided techniques to reduce anxiety, such as relaxation exercises based on imagery and visualization,

together with breathing exercises. Participants practiced these exercises with the psychologist and were then provided with a compact disc to perform these exercises at home two to three times per week.

4.3.5 Follow-up Assessments

All patients in both groups were asked to attend the clinic to fill up questionnaires and perform functional measurements at 4 weeks following the baseline assessment (preoperative). During this assessment, the actigraph was also returned. All measurements and questionnaires were collected one month following the surgery again. At this point, participants were asked to wear the actigraph for four continuous weeks (from 4 weeks until 8 weeks post-surgery).

4.3.6 Outcomes and Measures

4.3.6.1 Subjective Sleep Quality

Pittsburgh Sleep Quality Index (56). This questionnaire was developed to assess the subjective sleep quality of the previous month on seven components: sleep latency, sleep duration, daytime dysfunction, sleep disorders, use of sleep medication, habitual sleep efficiency and subjective sleep quality. The questionnaire consists of 19 items using a Likert scale ranging from 0 (“no difficulty”) to 3 (“severe difficulties”). The total score ranges from 0 to 21 with a higher score indicating a poorer sleep. A total score >5 suggests the presence of significant sleep difficulties with a sensitivity of 89.6% and a specificity of 86.5% for distinguishing between good and poor sleepers (kappa = .75, $p < .001$). The internal consistency ($\alpha = .83$) and the test-retest reliability (on average 29 days later, $r = .83$) of the scale were supported in the general population. The PSQI has been validated in many populations including surgical ones (57, 58), predicting recovery after colorectal surgery and has a reliability of 0.81 (59).

4.3.6.2 Objective Measurement

Actigraphy (ActiGraph wGT3X-BT) is a small, waterproof, non-intrusive device worn on the wrist. Participants were instructed to wear the actigraphic recorder on their non dominant hand for four consecutive weeks, 24-hour periods at each time assessment (before and after surgery). By calculating orientation and movement, the Actigraph estimates sleep-wake activity and provides an objective measure of the same sleep parameters as the sleep diary. In the current

study, actigraphic data was also used to objectively measure the participants' physical activity levels before and after surgery. The validity of actigraphy has been demonstrated for evaluating sleep quality and duration (60) in cancer patients. The following variables were derived from the actigraph: sleep onset latency (SOL; time from lights out to sleep onset), wake after sleep onset (WASO; time spent awake after initial sleep onset), total sleep time (TST; the sum of all sleep periods from initial sleep onset until the last awakening) and sleep efficiency (SE; TST divided by total time in bed [TIB]) (61, 62). For sleep assessment, the Standards of Practice Committee of the American Academy of Sleep Medicine recommends that at least 3 consecutive 24-hour periods of accelerometry recording time are needed to obtain reliable sleep estimates.

4.3.6.3 Exercise diary

During the exercise counselling session, the kinesiologist gives participants instructions to complete the exercise diary daily during the 4-week intervention phase. Specifically, they were asked to document, for each day, the type of exercise they performed, its duration and intensity (perceived effort according to the Borg scale). This allowed us to calculate the frequency and the total duration of the exercise performed per week and assess patients' adherence to the exercise program.

4.3.6.4 The Community Health Activities Model Program for Seniors (CHAMPS)

CHAMPS questionnaire is a self-reported measure of physical activity (63), comprising 41 activities evaluated according to the total number of hours done during an average week. The CHAMPS has been validated as a measure of increasing physical activity levels and recovery after elective abdominal surgery (64).

4.3.6.5 The Hospital Anxiety and Depression Scale (HADS)

HADS questionnaire (65) contains seven items, each scored from 0 to 3 points for anxiety and depression. It provides summary measures on a scale of 0–21, with scores exceeding 6 points in anxiety or more than 8 in depression, suggesting the presence of a disorder (66).

4.3.6.6 The Functional capacity as measured with the six-minute walk test (6MWT)

6MWT is validated in the colorectal surgical population (67) evaluates the ability of an individual to maintain a moderate level of physical endurance. Moderate to strong correlations have been

found between the 6MWT and maximum oxygen consumption values obtained with other methods of exercise testing (68). The 6MWT was created to test exercise tolerance but is now used clinically and in research to test functional exercise capacity, defined as "the ability to undertake physically demanding activities of daily living" (67). Participants were instructed to walk back and forth a 20-m stretch of the hallway for 6min at a pace that would make them tired by the end of the walk. The total distance covered in 6min was recorded in meters. Participants were allowed to rest, although any time spent resting was accounted for in the total distance covered in 6min. Standard motivational messages were given each minute per American Thoracic Society guidelines (69). A change in 6MWT of 20 m was considered clinically meaningful as this is the estimated measurement error in community-dwelling elderly (70). A baseline walking distance of 6MWT less than 400 m is a cut-off for unfit populations. In older adults, the inability to walk 400 meters has been associated with a higher risk of mortality, cardiovascular disease, limitation in mobility, and disability (71-73).

4.3.6.7 Muscle strength

Handgrip strength was measured with the Jamar® hydraulic dynamometer in kg. Three tests will be done to measure strength at maximal contraction on both sides in alternation (74, 75). Maximal strength will be recorded, according to standardized procedures. Isokinetic leg strength will be measured with a Biodex on the dominant side.

4.3.6.8 Insomnia Severity Index (ISI)

ISI questionnaire (76) includes seven items which evaluate, for the previous 2 weeks, the perceived severity of difficulties falling asleep, difficulties maintaining sleep and early morning awakenings, as well as the degree of dissatisfaction with current sleep, the degree to which sleep difficulties interfere with daytime functioning, the degree to which the deterioration of functioning related to the sleep problem is noticeable by others, and the level of distress or worry caused by the sleep difficulties (rated on a scale from 0 ["not at all"] to 4 ["very much"]). The ISI has been empirically validated among cancer patients and a score of 8 or greater is used to detect clinically significant insomnia symptoms (95% sensitivity), while a score of 15 or greater suggests the presence of an insomnia syndrome (77).

4.3.6.9 The generic health-related quality of life questionnaire

The 36-Item Short Form Survey from the RAND Medical Outcomes Study [SF-36]) (78). A reliable and valid generic index of perceived health status for cancer patients and used on the previous study for patients undergoing scheduled colorectal surgery (78-80). It includes eight subscales: physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health; each subscale is scored on a 0 to 100 scale. (78). Two summary scores have been developed: The Physical Component Summary and the Mental Component Summary have been standardized to have a mean of 50 and a standard deviation of 10 (78). A greater score on the SF-36 subscales or component summary measures indicates a better quality of life.

4.3.6.10 The World Health Organization Disability Assessment Schedule (WHODAS 2.0)

12 items used to measure disability due to health conditions including diseases, illnesses, injuries, mental or emotional problems, and problems with alcohol or drugs. The WHODAS 2.0 was introduced to measure disability in the aged and for disease-related states (81). It has been evaluated in surgical populations and has been found to have construct validity, clinical reliability, and responsiveness. Disability-free survival (DFS) is calculated as the percentage of patients who have a WHODAS score of <25% (82).

4.3.6.11 The patient-generated subjective global assessment (PG-SGA)

A validated nutritional assessment tool for cancer patients. It was used at baseline to globally classify patients as (A) well nourished, (B) moderate or suspected undernutrition, and (C) severely undernourished, based on weight loss, functional limitations, dietary intake, and presence of symptoms that affect intake (83, 84). Due to the lack of dietitians, the PG-SGA form was performed only for the prehabilitation intervention group.

4.3.6.12 Postoperative complications

Rates were graded by severity using the Dindo–Clavien classification, in which grade I complications require bedside management, grade II complications require pharmacologic treatment, grade III complications require surgical, endoscopic, or radiologic intervention, and grade IV complications require intensive care treatment (85).

4.3.7 Statistical Analysis and Sample Size Calculation

Sample size was calculated based on findings from a previously conducted pilot study (86). According to the results of that study, the mean [standard deviation (SD)] PSQI scores of the exercise and usual-care groups were 7.25 (4.99) and 8.50 (4.51), respectively, after a 12-week home-based exercise program. The sample size estimate of 40 participants per group focused on the study's primary parameters of total sleep time (TST) and Pittsburgh Sleep Quality Index (PSQI). To achieve a power level of .80, 40 participants per group were needed with a significant level of .05, an effect size of .26, and a correlation of .8. Based on an assumed dropout rate of 30%, the enrollment of 100 patients was considered adequate. Analyses were performed using an intent-to-treat approach. Analysis began by obtaining descriptive statistics for the study baseline variables, overall and by study condition. Mean, and standard deviation were reported for the normally distributed continuous variables, the median and interquartile range was reported for the non-normally distributed continuous variables, and frequency and percentage were reported for the categorical variables. The next step in the analysis was to assess whether or not randomization was successful. To do this, baseline participant characteristics were compared between the prehabilitation intervention and SOC groups. Independent samples t-tests were used to compare the normally distributed continuous variables between study conditions, Mann-Whitney U tests were used to compare the non-normally distributed continuous variables between study conditions, and chi-square tests were used to compare the categorical variables between study conditions. Randomization was assumed to be successful for the baseline characteristics that did not significantly differ between study conditions ($p > .05$). Randomization was deemed unsuccessful for those variables that significantly differed between study conditions ($p < .05$). The variables where randomization was deemed unsuccessful were flagged and included as covariables in all subsequent analyses.

Subjective sleep measurement. Linear mixed models were used to test the effect of the prehabilitiation intervention on subjective measures of sleep (PSQI). The model contained fixed effects for study condition, time, and a study condition x time interaction and random intercepts and slopes for subject and time respectively. Smoking status was included as a model covariable due to differences at baseline between the study conditions. The distribution of the outcome measure as well as the model residuals were used to specify the model distribution and link function. Classical sandwich estimation was used to protect against model misspecification. Post hoc pairwise comparisons were conducted within the mixed model via orthogonal contrasts

(using the lsmeans statement). These pairwise comparisons included comparing PSQI scores between study groups at each time period, comparing PSQI scores between data collection time points within study condition, and comparing the rates of change between study conditions. The Holm test was used to correct for multiple comparisons and maintain a two-tailed familywise alpha value of .05. Estimated marginal means, along with 95% confidence intervals were reported, and $p < .05$ was used to determine statistical significance. After this primary analysis was completed, a secondary analysis was conducted to test whether the prehabilitation intervention effects were moderated by baseline fitness level as measured by the 6MWT, baseline anxiety as measured by the HADS-A, and baseline depression as measured by the HADS-D. To do this, a three-way interaction term (study condition x time x fitness level/anxiety/depression) was added to the above linear mixed models. If this three-way interaction term was statistically significant ($p < .05$), moderation was deemed to occur. When significant moderation effects were found, results were presented stratified by appropriate subgroups.

Objective sleep measurement. Objective measures of sleep were collected daily 4 weeks before and 4 weeks after the surgery. Participants were considered to have usable objective measurement data for a study week if they had actigraph measurements for three or more consecutive days with at least 20 hours each. Mixed models were used to test the effect of the prehabilitiation intervention on objective measures of sleep (SOL, WASO, TST, and SE). Only measurements from weeks with 3 or more consecutive days with at least 20 hours each were used. The daily measures were used in the mixed model estimation and were averaged to the weekly level. The mixed models contained fixed effects for the study condition, time, and a study condition x time interaction and random intercepts and slopes for subject and time, respectively. Smoking status was included as a model covariable due to differences at baseline between the study conditions. Season and day of the week were included in the models as covariates only when examining the impact of the intervention on objective sleep quality and duration because they are seen as a factor of influence on sleep quality and the amount of physical activity (87-89). The distribution of the outcome measure and the model residuals were used to specify the distribution and link function for each model. The Gaussian distribution and identity link were used for SOL, WASO, TST, and SE, while the Poisson distribution and log link were used for SOL. The Poisson distribution was used for SOL due to a large number of zero observations. Although the Poisson distribution is also commonly used for the other actigraph measures

(WASO, TST, SE), the Gaussian distribution was used in this instance due to its better fit statistics and the presence of overdispersion that alternative approaches, including the use of a negative binomial distribution, could not correct. Classical sandwich estimation was used to protect the model against possible misspecification. Post hoc pairwise comparisons were conducted within the mixed model via orthogonal contrasts. These pairwise comparisons included comparing SOL, WASO, TST, and SE between study groups at each time period, comparing SOL, WASO, TST, and SE between data collection time points within the study condition, and comparing the rates of change in SOL, WASO, TST, and SE between study conditions. The Holm test was used to correct for multiple comparisons and maintain a two-tailed familywise alpha value of .05. Estimated marginal means and 95% confidence intervals were reported, and $p < .05$ was used to determine statistical significance.

After this primary analysis was completed, we also attempted to explore whether the baseline walking capacity and the levels of anxiety and depression moderated the intervention effects. This last aim was posed because high rates of anxiety and depression in the cancer population at baseline may influence functional capacity during the pre-and postoperative periods (80, 90, 91) and are essential factors for developing sleep problems (92). In addition, the inability to walk 400 meters in older adults has been associated with several limitations in mobility and disability (71, 72), which may affect adherence to the intervention (93). A secondary analysis was conducted to test whether the prehabilitation intervention effects were moderated by baseline fitness level as measured by the 6MWT, baseline anxiety as measured by the HADS-A, and baseline depression as measured by the HADS-D. A three-way interaction term (study condition x time x fitness level/anxiety/depression) was added to the above linear mixed models. If this three-way interaction term was statistically significant ($p < .05$), moderation was deemed to occur. When significant moderation effects were found, results were presented stratified by appropriate subgroups. Analyses were completed using R version 4.1.2 with the dplyr, lsmeans, and lme4 packages (94-96). Effect sizes (Cohen's d) for time effects were calculated to provide a standardized measure of effect size. The reported d values are determined by dividing the mean difference between the two groups by the pooled standard deviation.

4.4 Results

The baseline participants' demographic and medical characteristics were presented in Table 1. Among the clinical variables, the laparoscopic approach was used in eighty-one (91%) of the participants studied. Eleven out of the 89 participants (12.35%) also received Neoadjuvant chemotherapy. The median duration between the baseline assessment and surgery was 42 days [IQR, 35 to 58] in the Prehab group and 45 days [IQR, 33 to 65] in the SOC group (p = 0.53). Finally, 13.48% (12/89) of the sample were hypnotic/anxiolytic users at least once a week in the preceding month. No significant differences between-group were found on any demographic and medical variable at baseline except for the smoking status, which was six vs 1 participant reported smoking in the SOC group.

4.4.1 Feasibility Evaluation

4.4.1.1 Recruitment and Retention

Out of the 259 screened patients, 189 (73%) were eligible for the study, and 102 (54%) were recruited. The overall participation rate was 39.3% (102/259 of eligible patients). The main reasons for exclusion were either inability to commute because of transport issues (n=39), not being a surgical candidate (n=30) or participating in another research program (n=32) (n = 101, representing 38.9% of all exclusions). Fifteen participants (28.5%) were assigned to the Prehab group, and fourteen (25%) were assigned to the SOC group and dropped out during the study, for a total dropout rate of 28.4%. Among all participants, 13 were excluded after randomization (12.7%). Most reasons for exclusions before surgery were not being a surgical candidate or changing the treatment plan (n= 11). After surgery, 8 participants in each group (17.9%) stopped the study primarily because of reasons related to the surgery itself (complications, not feeling well) (n= 5) or unable to commute (n= 6). Figure 1 shows the participants' flowchart and detailed reasons for exclusions.

4.4.1.2 Exercise and Nutrition Prescription and Adherence to the Program

Participants in the prehab group reported commitment to the exercise prescription of 85.6% (18.69) and 96.9% (7.78) adherence to the nutrition program. Reasons for not being committed included losing interest (n= 3), adverse events (n= 3) or being busy (n= 3). Nine out of the 43 participants received psychosocial intervention; however, no adherence rate was recorded.

4.4.1.3 Perioperative Outcomes

No differences between the two groups were seen in the incidence of Clavien classification for postoperative complication severity or emergency department visits and readmission, as well as no difference in median length of stay (Table 2). However, two participants in the prehab group required intensive care unit (ICU) after major pulmonary complications that caused death.

4.4.1.4 Adverse Events

During the study period, three participants in the prehab group reported difficulties performing the exercise program at home due to a frozen shoulder, a herniated back disk and a shingles infection caused by varicella zoster virus (VZV). Therefore, the exercise prescription was modified and adjusted to their needs. In addition, one participant in the SOC group was hospitalised for an altered state of consciousness due to a brain infection that caused death.

4.4.2 Feasibility of Clinical Outcome Assessments

4.4.2.1 Self- Reported Outcomes and Functional Measurements

Of the 89 participants, 73 completed measurements for all four-time points (82%). Among those who did not complete or withdrew from the study, 6/16 submitted measurements at only one time (6.7%), 7/16 submitted measurements at two collection time points (7.8%), and 3/16 submitted measurements at three collection time points (3.3%). The median score for anxiety and depression levels tended to be higher in the SOC group compared to the prehab intervention group (6 [3;8] vs 5 [2;7.5], p= .13 for the anxiety score and 5 [1;7] vs 3 [1;6], p= .37 for the depression score). The number of unfit patients (6MWT <400m) tended to be higher among the prehab intervention group (18.6% vs 8.7%, p= .17). The mean PSQI was around 12, with a standard deviation of 2.64 for the SOC group and 3.3 for the prehab group, which indicates clinically significant sleep difficulty (56). However, the median of the ISI was 7, which is under the sub-threshold clinical insomnia in both groups (76).

4.4.2.2 Actigraph Data

Actigraph data were collected for all participants; however, the actigraph data were missing for 10 participants (10/89 eligible after randomization, 11.2 %) because the participants forgot to wear the actigraph (9 with insufficient data) or the actigraph malfunctioned. After surgery, 73/89

(82%) participants remained; the actigraph data were missing for 8/73 participants, 7 had insufficient data, and one had malfunctioned actigraph. All sleep parameters assessed through actigraphy (SOL, TST and SE) fell within the normal range except the WASO, which was 57 min in the prehab vs 53 min in the SOC group, thus indicating that WASO time is around 26 minutes above the clinical threshold of sleep disturbances in both groups (97).

4.4.3 Effects of the Prehabilitation Intervention on Subjective Sleep Measurement

Table 3 shows mean scores obtained on subjective sleep outcome (PSQI) at each time point in both groups. The main group effects were insignificant, and the only simple between-groups significant difference was at preoperative (T1) on the total PSQI score, which was lower in the prehab group (p = .048). The prehab group showed a reduction of - 0.8 points on the PSQI total score from the baseline to the preoperative (from 12.7 to 11.9, d = .29) as compared to an increase of 0.3 for the SOC group (from 12.7 to 13, d = -.11). The between-group difference in the change in PSQI score between T1 and T0 significantly differed between groups, delta (T1-T0) = -1.1, 95% confidence interval from -2.1 to -.1 and p = .048. Therefore, the prehab group patients improved the perceived sleep quality symptoms assessed with the PSQI between the baseline and preoperative periods compared to the SOC group. Despite the statistical significance, a difference of 1.1 points from the total score of 12.7 may not be clinically significant as the score remains in the moderate sleep difficulty range. The analyses conducted at follow-ups after surgery indicated no significant difference in perceived sleep quality symptoms assessed with the PSQI between groups.

4.4.4 Effects of the Prehabilitation Intervention on Objective Sleep Measurement

Table 3 shows the estimated marginal mean scores obtained on objective sleep parameters at each time point in both groups from the linear mixed models. None of the group × time interactions (GxT) or the main group effects (G) were statistically significant (all ps > .05). Significant main-time effects (T) were obtained for the WASO (p = .02) and TST (p = .001) outcomes. However, simple effects revealed no significant between-group difference in these outcomes at any time assessment. More specifically, the prehab group showed a reduction in WASO of -1.8 min from the baseline to the preoperative (from 59.5 to 57.7, d = .07) compared to an increase of 1.1 min for the SOC group (from 53.4 to 54.5, d = .04). This increased value

was sustained even after 8 weeks after surgery for the SOC group (from 53.4 to 54.7, d = .06). In contrast to the prehab group, which showed sustainment of WASO min at 8 weeks after surgery relative to the baseline (from 59.5 to 59.5, d = .00). The difference between-group was -1.3 with a confidence interval of -10.9 to 8.3 and p = .80 was not significant. Moreover, the TST showed an increase of 34 minutes preoperatively in the prehab group (from 404 min to 438 min, d = .20) compared to 9 minutes increase (from 406 min to 415 min, d = .04) in the SOC group. At 4 weeks after surgery follow-up, the TST returned to the baseline value (~404 min) for the prehab group. However, it showed a reduction of 8 min relative to the baseline at the SOC group (from 406 min to 398 min, d = -.05). At the 8-week follow-up, the TST was 29 min more relative to the baseline in the prehab group and 23 min more than the baseline in the SOC group. The 6 min between-group difference was not statistically significant, having a small effect size (d = .03), a confidence interval of -60.2 to 72.2, and p = .82. Despite the significant main time effect, the lack of statistical significance for the group × time interactions indicate no evidence to show that the prehabilitation intervention improved sleep parameters compared to the SOC group.

4.4.5 Complementary Analyses

4.4.5.1 The Moderating Role of the Baseline Functional Walking Capacity

At the baseline, the number of fewer fit participants (6MWT<400m) was 11 (12.35%) vs 68 participants (76.4%) who had a walking capacity higher than 400m. To evaluate for possible differential intervention effects (moderator effect) by fitness level as measured by their baseline walking distance from the 6MWT, a mixed model with a three-way interaction term for study condition × walking capacity × time was performed on the primary sleep outcomes (PSQI, SOL, WASO, SE and TST). The three-way interaction term was not statistically significant (study condition × walking capacity × time) for the PSQI, SOL, SE, and TST variables, indicating that the effect of the prehabilitation intervention on PSQI, SOL, SE, and TST did not differ across baseline fitness levels (ps > .05; see supplementary file Table 2 and 5). A significant three-way interaction term only for the WASO variable suggests that the effect of the prehabilitation intervention on WASO differed by fitness level, Table 4. The prehab group experienced a 2.8-min decrease in WASO time from baseline to preoperative, whereas the SOC group exhibited a 16.2-min increase. The difference between groups for change in WASO between baseline and preoperative was 19 minutes (d=.56) with a CI between 1.2 and 37.2 minutes (p=.04). After

surgery, the improvement has shown in the opposite direction; the SOC group showed a reduction of 13.5 min, while the prehab group increased by 9.2 min of the WASO time and the difference between groups for change in WASO between visits after surgery was 22.7 minutes (d = .68), with a CI between 3.3 and 41.9 minutes (p= .02). Results showed significant changes over time that differed between study conditions. While the within-group changes are not statistically different, the rate of change between groups varies in opposite directions at specific time points.

4.4.5.2 The Moderating Role of Anxiety and Depression Level at Baseline

At the baseline, 14 participants (15.73%) reported high depression symptoms (HADS-D>6), while 75 participants (84.27%) reported normal depression scales. However, 62 participants (69.66%) had normal anxiety while 27 had higher anxiety symptoms (33.34%) (HADS-A>6). To evaluate for possible differential intervention effects (moderator effect) by depression and anxiety as measured by their baseline HADS score, a mixed model with a three-way interaction term for study condition × depression or anxiety × time was performed on the primary sleep outcomes (PSQI, SOL, WASO, SE and TST). A sensitivity analysis was performed to determine the robustness of our results by examining whether our conclusions might differ substantially if participants reported using hypnotic and anxiolytic medication (98). Thus, a variable for hypnotic and anxiolytic medication use (yes/no) was added as a covariable to the mixed models. The three-way interaction term was not statistically significant (study condition × depression or anxiety × time) for the outcomes of PSQI, SOL, SE, and WASO, indicating that the effect of the prehabilitation intervention on PSQI, SOL, SE, and TST did not differ by baseline anxiety/depression (*ps* > .05; see supplementary file Tables 3, 6 and 7). However, the three-way interaction term study condition × depression/anxiety × time was statistically significant for TST, suggesting that the effect of the prehabilitation intervention on TST differed between those with and without anxiety.

The “no Anxiety” subgroup of the prehab group showed an increase of 20 min in the TST at 8-week follow-up relative to the baseline (from 412 min to 432 min, d = .11) compared by 17 min increase in the SOC group (from 410 min to 427 min, d = 11). However, the “Anxiety” subgroup of the prehab group (10/23) showed an increase in TST over time for a total of 153 minutes only at the 8-week follow-up after the surgery relative to the baseline (from 368 min to

521, d = .57) compared to 43 minutes increased on the SOC group (from 396 to 439, d = .28). The difference between groups for change in TST between baseline and 8-weeks follow-up was 110 minutes (d = .51) with a CI between 92.3 and 127.7 minutes (p= .02). This finding indicates that the participants with "Anxiety", the prehab group were, on average, seeing an improvement in TST of 153 minutes compared to the SOC group only at the 8-week after-surgery follow-up.

The sensitivity analysis which added consumption of prescribed hypnotic and anxiolytic medications as a covariable showed consistent results. The covariable was not statistically significant in any of the mixed models and did not lead to a change in the statistical significance of the interaction terms in any of our mixed models. Therefore, none of the results discussed above changed.

4.5 Discussion

To assess the effectiveness of a multimodal prehabilitation program, our primary goal in this pilot RCT was to compare the impact of the intervention on sleep quality and duration during the preoperative period and at 4- and 8-weeks follow-ups after surgery. Our results did not support the initial study hypotheses. More specifically, the results of the mixed models comparing the two groups on subjective and objective sleep measures were consistent and showed no improvement after 4 weeks of a multimodal prehabilitation program.

Our results showed a small change in the PSQI only at the preoperative time point for the prehabilitation group compared to the SOC group (delta (T1-T0) = -1.1, 95% CI (-2.1 to -.1); *p* = .048). However, one point difference in the PSQI between groups may not be clinically significant. Furthermore, a significant difference in the rate of change of WASO between the prehab sub-group with limited walking capacity and the SOC group only at the preoperative time point (d = .56, 95% CI: 1.2 to 37.2, p = .04) was observed. Additionally, our results demonstrated a significant difference in the rate of change of TST between the prehab "Anxiety" sub-group compared to the SOC group (d = .51, 95% CI: 92.3 to 127.7, p = .02) over the study period (baseline to 8 weeks after surgery). These findings collectively indicate that the prehabilitation intervention might improve sleep quality and duration, particularly for specific patient subgroups identified by their limited walking capacity and anxiety levels. Our results contradict previous systematic reviews and meta-analyses that showed exercise interventions significantly reduced sleep disturbances in adults but with effect sizes of a small magnitude (99, 100). Nonetheless,

our results are partially consistent with the null effects previously observed in patients undergoing pancreatic surgery, where no significant changes were seen in subjective (PSQI) and actigraphy sleep measures (101). To our knowledge and date, there is no other study investigating this specific research question with a multimodal prehabilitation approach.

The results should be carefully interpreted and consider other factors that may have influenced the results, which will be addressed in the discussion. First, the lack of significant effects on actigraphic data and subjective sleep suggested that both interventions had a modest impact on participants' objective and subjective sleep. Second, no significant between-group differences in the improvement of objective and subjective sleep variables were observed either during the preoperative period or at follow-ups, as reflected by a lack of significant group-by-time interaction on all variables. One possible explanation for our unexpected results is the home-based format of the prehabilitation intervention. It is possible that the participant's adherence to the exercise program may not have been optimal during the limited 4-week period due to minimal supervision. A longer supervised exercise program may have a more significant impact on improving sleep between groups (100). Therefore, research comparing different delivery modes of exercise, specifically for prehabilitation interventions, is needed (102). Another explanation for the non-significant difference between groups is that we could not perform a blind study. The participants were informed regarding the intervention regimen; in addition, all participants received the enhanced recovery after surgery pathway for elective colorectal resection, which includes education on the benefits of a healthy lifestyle and physical activity but without specific tips on precise types and duration of exercises. Therefore, participants in the SOC group were encouraged and motivated to perform more physical activity and enhance healthy eating, thus leading to contamination bias. Second, although the walking capacity did not statistically differ between groups at baseline (493 m for the prehab group vs 508 m), four participants in the SOC group regularly performed exercise activities, which may have led to an underestimation of the effect of the prehabilitation intervention.

Findings of our physical and mental components provide a possible answer about the effectiveness of exercise intervention. The results of our moderator effect on walking capacity showed opposite directions on the WASO time improvement for the "6MWT<400m" sub-group and dependent on the specific period. Contrary to what was initially expected, while the prehabilitation group significantly improved the WASO before surgery (T0-T1), the SOC group

improved it after the surgery (T2-T3). Despite the statistically significant change between groups at specified time points (T0-T1 and T2-T3), this change might not be clinically significant, as a change of 15 minutes would have a clinical effect (97). It is difficult to explain the statistical significance of WASO in the opposite direction between groups; however, despite the change, all WASO values still fell over the 30 min clinical threshold.

Interestingly, the "Anxiety" subgroup participants in the prehabilitation intervention group exhibited a significant improvement in the rate of change of TST over time compared to the SOC group, with a difference of 110 minutes between baseline and 8-weeks after surgery. This difference between groups has statistical and clinical significance. This finding may confirm that improvement of the TST may not be due to the effect of the exercise intervention. Mainly, because it was only significant in the "Anxiety" subgroup participants, who were initially followed by a psychosocial clinician, in contrast to the "No anxiety" subgroup. The relationship between sleep difficulty and anxiety is perhaps not surprising, given that sleep difficulty is often considered a mood disorder symptom (103, 104). Furthermore, some evidence suggests a bidirectional association between sleep and mood disorder (105, 106). Sleep difficulty, anxiety symptoms, and physical functioning may represent a symptom cluster with multifaceted relationships. This indicates interventions targeting only one symptom, such as sleep habits, are likely to fail. Consequently, this explains our results on which participants with higher anxiety symptoms benefit more from the multimodal prehabilitation intervention than those with no anxiety symptoms. This finding was also similar for the participants in the SOC group. However, the potential reasons for the unexpected improvements for the participants in the SOC group are shortly discussed in the manuscript. Therefore, future research should focus on this population to determine whether individuals with high anxiety symptoms and a clinical threshold of insomnia or sleep difficulty at baseline may benefit more from a multimodal prehabilitation intervention. This will clarify, conceptualize, and address the intervention for the population that requires a more comprehensive approach.

These findings should be interpreted with caution because of methodological limitations. It is important to note that the number of participants who reported the subjective (PSQI) or objective (Actigraph) sleep variables is not the same over time. For instance, in the prehabilitation group, 43 participants report the PSQI score at the baseline. However, only 23/43 (53.48%) reported the PSQI score at the 8-week follow-up after surgery. This rate was similar

for the participants in the SOC group. The high differences in reporting the PSQI score were primarily due to the dropped out during the study (13 after randomization and 16 during the follow-ups, in both groups), in addition, to the missing data, which counted 47/73 (64.3%), as 73 participants had completed the measurements at all the four-time points. The adherence and agreement rate for the wrist-worn actigraphy over time was difficult to explain, despite the high daily adherence rate (22.43 h/day). For example, 79/89 (88.76%) participants had sufficient baseline data of actigraphy; however, it was surprising to find 37/79 (46.83%) participants committed to wearing the device for all 4 weeks of the intervention (from baseline to preoperative). After surgery, the adherence rate was similar; without counting participants who dropped out or decided not to continue the study, 65 participants had sufficient data at the 4-week follow-up; however, 32/65 (49.2%) participants committed to wearing the device for all 4 weeks of the intervention (from 4 to 8-week postoperative follow-ups).

To date, most of the experimental literature has tended to examine real-world sleep variability over short periods, which limits our understanding of the efficacy and potential adherence issues associated with more extended timescale sleep measurements (107). The present study measured naturalistic sleep variables derived from wrist actigraphy from 102 participants initially randomized (79/102 having sufficient data at baseline) for up to 4 consecutive weeks during two periods (pre and postoperative). Despite our attempts, the adherence rate with waist-worn actigraphy was low and is likely due to the undesirability of wearing the device on the wrist for an extended period and removing the device during sleep and replacement during waking hours. The present study does not aim to assess the adherence rate of wrist-worn actigraphy. However, in contrast to our expectations and given the low adherence rate, it is noteworthy to indicate that the long-term wearing of the device is considered an extra burden of our population in the context of surgery (pre-and postoperative period) and therefore limits the generalizability of our findings.

Although it would be desirable to conduct an additional analysis using cancer-specific clinical details, including stage and prior cancer treatment as a covariate, the smaller sample size in the present study, specifically during the follow-ups, made it unfeasible to carry out this. Likely, specific treatments (such as chemotherapy and radiation therapy) involved in cancer treatment and multiple comorbidities may influence individuals' sleep quality and duration (108, 109). Future studies with a more significant sample should investigate this issue. Finally, our

pilot trial was underpowered despite our attempt to calculate the sample size. To have 80% power to detect a difference of 0.26 standard deviations between groups at each time point, not correcting for multiple comparisons, would require 468 participants in the analysis (234 per group). Similarly, to detect a change over time of 0.26 standard deviations within participants, not correcting for multiple comparisons, would require 98 participants in the analysis (49 per group). In our study, we recruited and randomized 102 participants and analyzed 89 participants (43 vs 46). In that case, we could detect a 3-point difference in PSQI score between study groups at each time point. Future studies should use a specific statistical method to calculate the sample size and to ensure high overall statistical power. In addition, our moderation analysis shows unbalanced groups on the studied moderation variables, further underpowering those analyses. Future studies should use other randomization techniques like block randomization to ensure the balance between groups for potential effect moderators.

To our knowledge, this is the first pilot RCT comparing a multimodal prehabilitation intervention to a SOC for improving clinical sleep quality and duration in cancer patients. Strengths of this study include methodological aspects such as randomization, various subjective and objective sleep measures, and follow-up assessments to assess the sustainment of treatment gains over time. In addition, as Carli et al. (110) recommended, all prehabilitation group participants underwent a personalized program (exercise, nutrition, and psychosocial support) relative to their physical and mental condition before the intervention. In addition, in our attempt to reduce the risk of observation bias, a standardized procedure was conducted by the same person with the same equipment and interview guide for data collection. For instance, telephone counselling for the SOC group similar to that received by the prehabilitation group (weekly counselling) has been performed.

4.6 Conclusion

The present study was the first pilot RCT attempt to assess the impact of multimodal prehabilitation on sleep quality and duration for colorectal cancer patients. The study results do not totally support our initial hypothesis; however, it demonstrated that prehabilitation intervention might significantly improve sleep duration for participants with high anxiety symptoms. However, these findings need to be interpreted cautiously, given the methodological limitations that may prevent the generalizability of our results. A large-scale RCT using a clinical level of sleep

difficulty and anxiety symptoms as an inclusion criterion would be relevant in the future.

4.7 Sources of Finding

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4.9 Disclosures

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Figures and Table

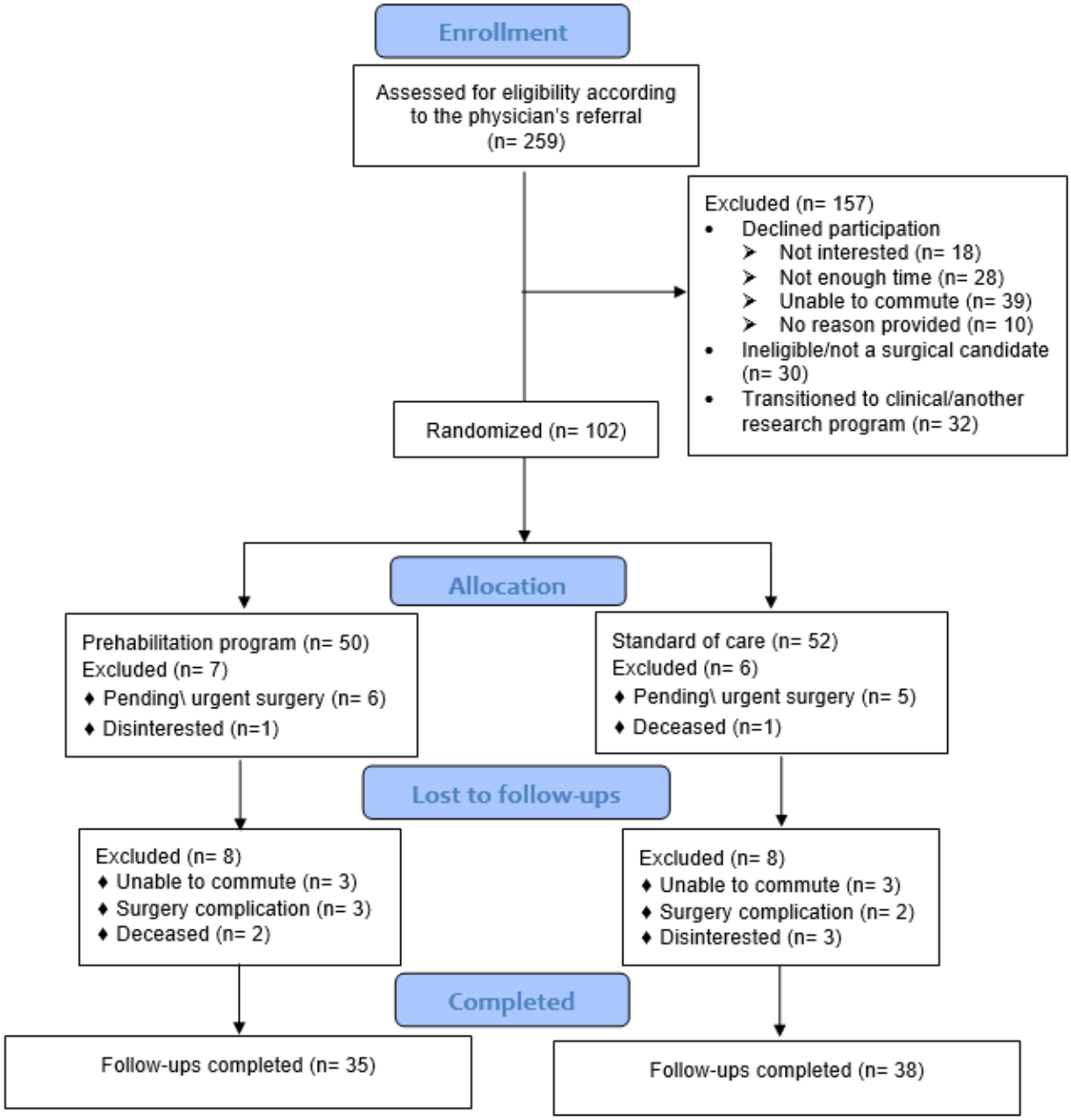

Figure 4-1: Consolidated standards of reporting trials (CONSORT) diagram showing the flow of participants through the trial.

Table 4-1: Participants' Characteristics at Baseline

	Study Group	
	Prehab (N=43)	**SOC (N=46)**
Age, Mean (SD)	65.56 (12.63)	64.48 (14.41)
Sex, n (%)		
Male	25 (58.14)	21 (45.65)
Female	18 (41.86)	25 (54.35)
BMI, Median [IQR]	25.78 [23.30;31.28]	27.57 [23.24;29.96]
ASA, n (%)		
1	14 (32.56)	19 (41.30)
2	23 (53.49)	22 (47.83)
3	6 (13.95)	5 (10.87)
CCI, n (%)		
1-2	3 (6.98)	7 (15.22)
3-4	17 (39.53)	14 (30.43)
≥5	23 (53.49)	25 (54.35)
Tumor stage, n (%)		
0	4 (9.30)	3 (6.52)
1-2	20 (46.51)	23 (50)
3+	19 (44.19)	20 (43.47)
Neoadjuvant therapy ‡, n (%)	7 (16.28)	8 (17.39)
Laparoscopic procedure, n (%)	38 (88.37)	43 (93.48)
Type of resection, n (%)		
Colon *	24 (55.81)	27 (58.70)
Rectal †	19 (44.19)	19 (41.30)
New stoma, n (%)	2 (4.65)	4 (8.70)
Alcohol consumption, n (%)	17 (39.53)	20 (43.48)
Smoking status, n (%)	6 (13.95)	1 (2.17)
Hypnotic/Anxiolytic medication, n (%)	7 (16.28)	5 (10.87)
6MWT (m), Median [IQR]	509.00 [446.50; 574.50]	502.50 [454.75; 591.75]
6MWT < 400 m, n (%)	8 (18.60)	4 (8.70)
Grip strength left hand, kg [IQR]	22 [16.00; 26.00]	20 [16.00; 30.00]
Grip strength right hand, kg [IQR]	22 [17.00; 30.00]	24 [16.50; 33.50]
Global PSQI score, Mean (SD)	12.43 (3.30)	12.21 (2.64)
ISI Total score, Median [IQR]	7.00 [3.00;10.00]	7.00 [4.00;13.00]
HADS- Anxiety, Median [IQR]	5.00 [2.00;7.50]	6.00 [3.00;8.00]
HADS- Depression, Median ([IQR]	3.00 [1.00;6.00]	5.00 [1.00;7.00]
CHAMPS total, median [IQR]	75.75 [32.50;158.50]	72.25 [35.25;152.12]
Physical component- (SF-36), Median [IQR]	60.70 [50.05;79.90]	71.70 [50.90;82.38]
Mental component- (SF-36), Median [IQR]	70.50 [46.15;80.05]	61.17 [46.07;77.67]
WHODAS, Median [IQR]	12.50 [2.08;30.21]	7.29 [2.08;27.08]
SOL (min), Mean (SD)	1.05 (1.48)	1.10 (1.51)
WASO (min), Mean (SD)	57.15 (25.66)	53.46 (26.68)
SE (%), Mean (SD)	87.11 (5.99)	87.84 (6.29)
TST (min), Mean (SD)	413.00 (145.68)	416.18 (139.55)

Data are presented as mean (SD), median [IQR], or n (%).

Prehab: Prehabilitation group, SOC: standard-of-care group. HADS: Hospital Anxiety and Depression Scale, ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index; SOL: sleep onset latency; WASO: wake after sleep onset; TST: total sleep time; SE: sleep efficiency; ASA = American Society of Anesthesiologists; CCI: Charlson Comorbidity Index; 6MWT = 6-min walk test; IQR = interquartile range; N/A = not applicable. ‡ Neoadjuvant therapy refers to chemotherapy or radiation therapy. * Includes right and left hemicolectomy and sigmoid resection. † Includes anterior resection, low anterior resection, and abdominoperineal resection.

Table 4-2: Postoperative outcomes

	Study Group	
	Prehab (N=43)	**SOC (N=46)**
Clavien classification		
0	33 (76.74)	39 (84.78)
Grade I	2 (4.65)	0 (0)
Grade II	5 (11.63)	4 (8.70)
Grade III+	3 (6.98)	3 (6.52)
Days in the hospital, median (IQR)	1.00 [0.50;3.00]	1.50 [0.25;2.75]
30-day emergency department visits	13 (30.23)	13 (28.26)
30-day readmission	10 (23.26)	8 (17.39)

Data are presented as median [IQR], or n (%).
IQR = interquartile range. Prehab: Prehabilitation group, SOC: standard-of-care group

Table 4-3: Treatment Effects Obtained on Subjective and Objective Sleep Variables by Groups

Outcome	**Baseline (T0)**		**Pre-operative (T1)**			**4-Week Post-op (T2)**		**8-Week Post-op (T3)**				
	N	Mean (CI)	**N**	Mean (CI)	d (T0-T1)	**N**	Mean (CI)	**N**	Mean (CI)	d (T1-T3)	Time effects	F
PSQI												
Prehab	**43**	12.7 (11.7, 13.6)	**32**	11.9 (11.0, 12.8)	0.29	**35**	12.2 (11.2, 13.2)	**23**	12.0 (10.9, 13.1)	0.04	*p =.99*	G: F =.12 *p* =.73 T: F =1.66 *p* =.18 GxT: F =1.96 *p* =.12
SOC	**46**	12.7 (11.6, 13.7)	**32**	13.0 (12.0, 13.9)	0.11	**31**	12.5 (11.4, 13.7)	**24**	11.7 (10.6, 12.9)	0.45	*p =.06*	
Group effects		*p =.99*		*p =.09*			*p =.63*		*p =.73*			
SOL												
Prehab	**40**	1.15 (0.90, 1.39)	**19**	1.02 (0.74, 1.29)	0.09	**32**	1.10 (0.86, 1.34)	**15**	0.93 (0.59, 1.27)	0.06	*p =.99*	G: F =.01 *p* =.93 T: F =1.09 *p* =.36 GxT: F =1.67 *p* =.11
SOC	**39**	1.08 (0.81, 1.34)	**18**	0.98 (0.69, 1.26)	0.07	**33**	0.82 (0.56, 1.07)	**17**	0.93 (0.59, 1.26)	0.04	*p =.99*	
Group effects		*p =.68*		*p =.84*			*p =.08*		*p =.97*			
WASO												
Prehab	**40**	59.5 (54.0, 65.0)	**19**	57.7 (51.8, 63.6)	0.07	**32**	60.2 (54.8, 65.6)	**15**	59.5 (52.4, 66.7)	0.07	*p =.99*	G: F =.2.79 *p* =.10 T: F =2.44 *p* =.02 GxT: F =.38 *p* =.92
SOC	**39**	53.4 (47.3, 59.4)	**18**	54.5 (48.3, 60.8)	0.04	**33**	54.3 (48.4, 60.2)	**17**	54.7 (47.4, 62.0)	0.01	*p =.99*	
Group effects		*p =.10*		*p =.42*			*p =.10*		*p =.31*			
TST												

Prehab	**40**	404 (371, 436)	**19**	438 (400, 476)	0.20	**32**	405 (369, 442)	**15**	433 (382, 485)	0.02	*p =.99*	G: F =.004 *p* =.95 T: F =3.44 *p* =.001 GxT: F =.62 *p* =.74
SOC	**39**	406 (371, 442)	**18**	415 (375, 455)	0.04	**33**	398 (358, 437)	**17**	429 (375, 482)	0.08	*p =.99*	
Group effects		*p =.90*		*p =.37*			*p =.75*		*p =.89*			
SE												
Prehab	**40**	86.3 (85.1, 87.6)	**19**	87.4 (86.0, 88.8)	0.18	**32**	86.1 (84.8, 87.4)	**15**	86.8 (85.0, 88.6)	0.10	*p =.99*	G: F =2.67 *p* =.11 T: F =2.65 *p* =.01 GxT: F =.50 *p* =.83
SOC	**39**	87.6 (86.2, 89.0)	**18**	87.6 (86.2, 89.1)	0.00	**33**	87.5 (86.1, 88.9)	**17**	87.7 (85.9, 89.5)	0.02	*p =.99*	
Group effects		*p =.12*		*p =.79*			*p =.10*		*p =.47*			

G: main group effect; T: main time effect; GXT: between group interaction; d: size effect. d = 0.20 = small effect; d = 0.50 = moderate effect; d = 0.80 = large effect.
Prehab: Prehabilitation group, SOC: standard-of-care group. PSQI: Pittsburgh Sleep Quality Index; SOL: sleep onset latency; WASO: wake after sleep onset; TST: total sleep time; SE: sleep efficiency.

Table 4-4: Treatment effects Adjusted Means and Differences (Deltas) on WASO and TST for Each Level (6MWT < 400m vs > 400m and Anxiety vs No anxiety)

Outcome		*6MWT > 400m*			*6MWT < 400m*		
		Prehab (n = 33)	**SOC (n = 35)**		**Prehab (n = 7)**	**SOC (n = 4)**	
	Time	**Mean (CI)**	**Mean (CI)**	***t***	**Mean (CI)**	**Mean (CI)**	***t***
WASO	T0	58.7 (52.8, 64.6)	51.2 (44.8, 57.6)	t = -1.92, p = .06	62.7 (50.5, 74.8)	66.3 (50.6, 82.0)	t = -0.57, p = .57
	T1	51.1 (44.4, 57.7)	55.7 (49.0, 62.5)	t = -1.07, p = .29	59.9 (48.5, 71.3)	82.8 (65.4, 100.2)	t = 2.21, p = .03
	Delta (T1-T0)	-3, *ns*	-0.1, *ns*	t = -0.74, p = .46	-2.8, *ns*	16.2, *ns*	t = -2.09, p = .04
	T2	61.3 (55.5, 67.0)	58.4 (50.5, 66.3)	t = -2.36, p = .02	48.2 (34.8, 61.7)	67.7 (52.5, 82.8)	t = 1.93, p = .06
	T3	52.1 (45.8, 58.5)	55.4 (47.4, 63.4)	t = -0.57, p = .71	57.4 (40.8, 73.9)	54.2 (36.6, 71.8)	t = -0.26, p = .79
	Delta (T3-T2)	-2.9, *ns*	3.3, *ns*	t = -1.34, p = .18	9.2, *ns*	-13.5, *ns*	t = 2.29, p = .02
TST		*No Anxiety*			*Anxiety*		
		Prehab (n = 30)	**SOC (n = 26)**		**Prehab (n = 10)**	**SOC (n = 13)**	
	T0	412 (376, 448)	410 (369, 450)	t = -0.11, p = .92	368 (308, 429)	396 (341, 451)	t = 0.70, p = .49
	T1	447 (404, 490)	419 (373, 466)	t = -0.93, p = .35	439 (370, 508)	418 (356, 480)	t = -0.47, p = .64
	Delta (T1-T0)	35, *ns*	9, *ns*	t = 1.06, p = .29	71, *ns*	22, *ns*	t = 1.42, p = .16
	T2	402 (362, 442)	384 (340, 429)	t = -0.64, p = .52	461 (389, 534)	447 (383, 510)	t = -0.31, p = .76
	T3	432 (380, 484)	427 (370, 484)	t = -0.14, p = .89	521 (397, 644)	439 (346, 532)	t = -1.06, p = .29
	Delta (T3-T2)	30, *ns*	43, *ns*	t = -0.49, p = .63	60, *ns*	-8, *ns*	t = 1.07, p = 29

ns: not significant.

T0: Baseline; T1: Pre-operative; T2: 4-Week Post-op; T3: 8-Week Post-op

Prehab: Prehabilitation group, SOC: standard-of-care group. WASO: wake after sleep onset; TST: total sleep time. 6MWT = 6-min walk test.

Online Supplement

4.11 Additional Tables

Table 4-1: Estimated marginal means over time according to linear mixed effects. Analysis for the subjective outcomes.

Outcome by group	Baseline		Pre-operative		4 Weeks Post-op		8 Weeks Post-op		p of group*time
	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	
PSQI									
Prehab	43	12.7 (11.7, 13.6)	32	11.9 (11.0, 12.8)	35	12.2 (11.2, 13.2)	23	12.0 (10.9, 13.1)	0.12
SOC	46	12.7 (11.6, 13.7)	32	13.0 (12.0, 13.9)	31	12.5 (11.4, 13.7)	24	11.7 (10.6, 12.9)	

Table 4-2: Estimated marginal mean PSQI scores over time by study group within patients with 6MWT<400 and patients with 6MWT≥ 400

PSQI by group	Baseline		Pre-operative		4 Weeks Post-op		8 Weeks Post-op		p of group*time *6MWT
	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	
6MWT<400									0.85
Prehab	8	12.7 (10.9, 14.6)	4	12.1 (10.1, 14.1)	3	11.7 (9.0, 14.4)	1	10.1 (6.1, 14.1)	
SOC	4	13.3 (10.7, 15.8)	3	12.6 (10.4, 14.8)	4	12.2 (9.8, 14.6)	1	11.4 (7.3, 15.5)	
6MWT≥400									
Prehab	35	12.7 (11.6, 13.7)	28	11.9 (11.0, 12.8)	32	12.3 (11.2, 13.3)	22	12.1 (11.0, 13.2)	
SOC	42	12.6 (11.5, 13.7)	29	13.0 (11.9, 14.0)	27	12.6 (11.4, 13.8)	23	11.8 (10.6, 12.9)	

Table 4-3: Estimated marginal mean PSQI scores over time by study group within patients' subgroups

PSQI by group	Baseline		Pre-operative		4 Weeks Post-op		8 Weeks Post-op		p of group*time *moderator
	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	
No depression									0.64
Prehab	38	12.4 (11.4, 13.4)	26	11.5 (10.7, 12.4)	29	11.7 (10.7, 12.7)	19	12.0 (10.8, 13.2)	
SOC	37	12.3 (11.3, 13.4)	24	12.3 (11.3, 13.3)	26	12.2 (11.2, 13.3)	19	12.0 (10.7, 13.2)	
Depression									
Prehab	5	14.0 (11.9, 16.2)	6	13.3 (11.8, 14.8)	6	14.3 (12.6, 15.9)	4	11.1 (9.0, 13.3)	
SOC	9	13.8 (12.1, 15.5)	8	14.7 (13.4, 16.0)	5	13.7 (11.9, 15.6)	5	10.8 (8.8, 12.8)	
No Anxiety									0.67
Prehab	32	12.5 (11.4, 13.5)	27	11.6 (10.7, 12.5)	31	12.1 (11.1, 13.1)	21	12.3 (11.1, 13.4)	
SOC	30	12.5 (11.4, 13.7)	22	12.3 (11.3, 13.4)	25	12.2 (11.1, 13.4)	19	11.9 (10.7, 13.2)	
Anxiety									
Prehab	11	13.0 (11.4, 14.5)	5	13.3 (11.7, 14.9)	4	12.7 (10.6, 14.8)	2	9.1 (6.2, 12.0)	
SOC	16	12.8 (11.4, 14.2)	10	14.1 (12.9, 15.3)	6	13.5 (11.6, 15.4)	5	10.9 (8.9, 12.8)	

Table 4-4: Estimated marginal means over time according to linear mixed effects. Analysis for the objective outcomes

Time	WASO				TST				Sleep Efficiency				Latency			
	SOC		Prehab		SOC		Prehab		SOC		Prehab		SOC		Prehab	
	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)
Pre-op																
Week 1	39	53.4 (47.3, 59.4)	40	59.5 (54.0, 65.0)	39	406 (371, 442)	40	404 (371, 436)	39	87.6 (86.2, 89.0)	40	86.3 (85.1, 87.6)	39	1.08 (0.81, 1.34)	40	1.15 (0.90, 1.39)
Week 2	38	53.8 (47.9, 59.7)	36	56.4 (51.0, 61.8)	38	411 (375, 446)	36	404 (371, 436)	38	87.7 (86.3, 89.1)	36	87.0 (85.8, 88.3)	38	1.10 (0.84, 1.36)	36	1.12 (0.88, 1.36)
Week 3	31	50.4 (44.4, 56.4)	33	54.2 (48.8, 59.6)	31	405 (368, 442)	33	394 (360, 428)	31	88.4 (87.0, 89.8)	33	87.3 (86.1, 88.6)	31	1.14 (0.87, 1.41)	33	0.84 (0.60, 1.08)
Week 4	18	54.5 (48.3, 60.8)	19	57.7 (51.8, 63.6)	18	415 (375, 455)	19	438 (400, 476)	18	87.6 (86.2, 89.1)	19	87.4 (86.0, 88.8)	18	0.98 (0.69, 1.26)	19	1.02 (0.74, 1.29)
Post-op																
Week 1	33	54.3 (48.4, 60.2)	32	60.2 (54.8, 65.6)	33	398 (358, 437)	32	405 (369, 442)	33	87.5 (86.1, 88.9)	32	86.1 (84.8, 87.4)	33	0.82 (0.56, 1.07)	32	1.10 (0.86, 1.34)
Week 2	31	54.2 (48.2, 60.2)	29	58.7 (53.1, 64.3)	31	394 (352, 437)	29	391 (351, 430)	31	87.2 (85.7, 88.7)	29	86.2 (84.8, 87.6)	31	1.12 (0.86, 1.38)	29	1.07 (0.82, 1.31)
Week 3	29	56.5 (50.1, 62.8)	23	60.4 (54.2, 66.5)	29	396 (350, 443)	23	397 (352, 485)	29	87.0 (85.4, 88.6)	23	85.8 (84.3, 87.4)	29	0.94 (0.66, 1.22)	23	1.00 (0.72, 1.28)

Week 4	17	54.7 (47.4, 62.0)	15	59.5 (52.4, 66.7)	17	429 (375, 482)	15	433 (382, 485)	17	87.7 (85.9, 89.5)	15	86.8 (85.0, 88.6)	17	0.93 (0.59, 1.26)	15	0.93 (0.59, 1.27)
P of group*time	0.9182				0.7433				0.8337				0.1104			

Table 4-5: Estimated marginal mean WASO, TST, SE over time by study group within patients with 6MWT<400 and patients with 6MWT≥400

	WASO								p of group *time* 6MWT	TST								p of group *time* 6MWT
Time	6MWT≥400				6MWT<400					6MWT≥400				6MWT<400				
	SOC		Prehab		SOC		Prehab			SOC		Prehab		SOC		Prehab		
	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)		N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	
Preop									0.02									0.07
Week 1	35	51.2 (44.8, 57.6)	33	58.7 (52.8, 64.6)	4	66.3 (50.6, 82.0)	7	62.7 (50.5, 74.8)		35	402 (363, 441)	33	403 (368, 438)	4	422 (330, 514)	7	400 (328, 471)	
Week 2	35	52.0 (45.8, 58.3)	29	55.8 (50.0, 61.6)	3	63.2 (47.0, 79.4)	7	58.4 (46.8, 70.0)		35	407 (368, 447)	29	410 (374, 445)	3	413 (316, 510)	7	364 (292, 436)	
Week 3	28	48.7 (42.3, 55.1)	26	53.2 (47.4, 59.1)	3	59.4 (43.6, 75.3)	7	57.1 (45.8, 68.3)		28	399 (358, 440)	26	397 (360, 435)	3	431 (332, 531)	7	365 (290, 440)	
Week 4	16	51.1 (44.4, 57.7)	13	55.7 (49.0, 62.5)	2	82.8 (65.4, 100.2)	6	59.9 (48.5, 71.3)		16	405 (361, 449)	13	447 (403, 490)	2	500 (387, 612)	6	391 (307, 474)	
Post																		
Week 1	29	52.1 (45.8, 58.5)	28	61.3 (55.5, 67.0)	4	67.7 (52.5, 82.8)	4	48.2 (34.8, 61.7)		29	395 (351, 439)	28	410 (370, 449)	4	404 (300, 509)	4	361 (260, 462)	
Week 2	27	53.0 (46.5, 59.6)	25	58.4 (52.4, 64.3)	4	60.1 (45.0, 75.1)	4	57.2 (43.1, 71.3)		27	398 (350, 445)	25	398 (354, 442)	4	361 (250, 472)	4	323 (212, 435)	
Week 3	26	54.8 (48.0, 61.6)	19	60.9 (54.2, 67.5)	3	66.2 (49.5, 83.0)	4	54.1 (39.5, 68.8)		26	401 (349, 453)	19	407 (358, 457)	3	349 (219, 478)	4	319 (197, 441)	

Week 4	14	55.4 (47.4, 63.4)	12	58.4 (50.5, 66.3)	3	54.2 (36.6, 71.8)	3	57.4 (40.8, 73.9)		14	446 (385, 506)	12	432 (374, 490)	3	337 (195, 479)	3	390 (249, 530)	
	SE								p of group *time* 6MWT	Latency								p of group *time* 6MWT
	6MWT≥400				6MWT<400					6MWT≥400				6MWT<400				
	SOC		Prehab		SOC		SOC			SOC		Prehab		SOC		Prehab		
	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)		N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	
Preop									0.25									0.43
Week 1	35	88.0 (86.5, 89.5)	33	86.4 (85.1, 87.8)	4	85.1 (81.5, 88.8)	7	86.0 (83.2, 88.8)		35	1.13 (0.85, 1.42)	33	1.11 (0.84, 1.38)	4	0.64 (0.00, 1.37)	7	1.36 (0.79, 1.92)	
Week 2	35	88.0 (86.5, 89.4)	29	87.4 (86.0, 88.7)	3	86.3 (82.6, 90.1)	7	85.8 (83.0, 88.5)		35	1.12 (0.84, 1.40)	29	1.12 (0.85, 1.38)	3	0.92 (0.14, 1.69)	7	1.17 (0.64, 1.70)	
Week 3	28	88.7 (87.2, 90.2)	26	87.7 (86.3, 89.0)	3	86.4 (82.7, 90.1)	7	86.3 (83.6, 88.9)		28	1.11 (0.82, 1.40)	26	0.74 (0.47, 1.01)	3	1.48 (0.73, 2.23)	7	1.22 (0.71, 1.73)	
Week 4	16	87.9 (86.4, 89.5)	13	88.2 (86.5, 89.8)	2	86.0 (81.9, 90.2)	6	86.3 (83.5, 89.1)		16	0.98 (0.67, 1.29)	13	1.00 (0.66, 1.33)	2	0.99 (0.12, 1.85)	6	1.07 (0.56, 1.57)	
Postop																		
Week 1	29	87.9 (86.3, 89.4)	28	85.8 (84.4, 87.2)	4	85.6 (81.9, 89.2)	4	89.2 (85.8, 92.5)		29	0.86 (0.58, 1.14)	28	1.13 (0.88, 1.39)	4	0.47 (0.00, 1.16)	4	0.78 (0.14, 1.41)	
Week 2	27	87.5 (85.9, 89.1)	25	86.4 (84.9, 87.8)	4	85.8 (82.1, 89.5)	4	86.6 (83.0, 90.2)		27	1.10 (0.82, 1.39)	25	1.09 (0.82, 1.36)	4	1.26 (0.59, 1.92)	4	0.82 (0.16, 1.47)	
Week 3	26	87.4 (85.6, 89.1)	19	86.0 (84.3, 87.6)	3	84.6 (80.4, 88.9)	4	86.7 (82.9, 90.5)		26	0.94 (0.64, 1.24)	19	1.09 (0.78, 1.40)	3	1.00 (0.24, 1.76)	4	0.55 (0.00, 1.21)	

Week 4	14	88.0 (86.0, 90.0)	12	86.9 (84.9, 88.9)	3	86.0 (81.5, 90.5)	3	88.0 (83.7, 92.4)		14	0.87 (0.50, 1.24)	12	0.75 (0.37, 1.13)	3	1.21 (0.43, 1.99)	3	1.37 (0.62, 2.12)	

Models control for smoking status (imbalanced between groups at baseline), weekend/weekday, and season

Table 4-6: Estimated marginal mean WASO, TST, SE over time by study group within patient with and without anxiety

	WASO								p of group *time* 6MWT	TST								p of group *time* 6MWT
Time	No anxiety				Anxiety					No anxiety				Anxiety				
	SOC		Prehab		SOC		Prehab			SOC		Prehab		SOC		Prehab		
	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)		N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	
Preop									0.87									0.02
Week 1	26	50.6 (44.0, 57.2)	30	61.1 (55.2, 66.9)	13	58.3 (49.3, 67.2)	10	55.7 (45.9, 65.5)		26	410 (369, 450)	30	412 (376, 448)	13	396 (341, 451)	10	368 (308, 429)	
Week 2	25	51.4 (44.7, 58.1)	26	57.9 (51.9, 63.9)	13	58.5 (49.6, 67.5)	10	53.1 (43.4, 62.8)		25	407 (365, 448)	26	426 (388, 463)	13	420 (364, 475)	10	349 (288, 409)	
Week 3	22	48.3 (41.5, 55.2)	23	55.0 (48.8, 61.1)	9	55.2 (45.5, 64.8)	10	52.1 (42.4, 61.9)		22	401 (358, 444)	23	421 (383, 460)	9	417 (357, 476)	10	343 (279, 406)	
Week 4	12	53.8 (46.4, 61.1)	12	58.3 (51.4, 65.2)	6	57.9 (48.2, 67.6)	7	55.2 (44.8, 65.5)		12	419 (373, 466)	12	447 (404, 490)	6	418 (356, 480)	7	439 (370, 508)	
Postop																		
Week 1	24	51.7 (45.0, 58.3)	25	58.7 (52.7, 64.7)	9	61.7 (52.1, 71.3)	7	64.9 (54.3, 75.4)		24	384 (340, 429)	25	402 (362, 442)	9	447 (383, 510)	7	461 (389, 534)	
Week 2	23	52.4 (45.7, 59.1)	22	57.9 (51.8, 64.1)	8	60.2 (50.5, 69.8)	7	60.1 (49.7, 70.6)		23	388 (341, 435)	22	384 (343, 428)	8	426 (359, 494)	7	456 (379, 533)	
Week 3	21	55.8 (48.9, 62.6)	18	59.2 (52.8, 65.6)	8	60.4 (50.4, 70.3)	5	56.7 (45.1, 68.4)		21	396 (346, 447)	18	394 (347, 441)	8	413 (340, 486)	5	461 (373, 550)	
Week 4	14	50.9 (43.7, 58.2)	14	55.9 (49.0, 62.7)	3	68.0 (55.0, 80.9)	1	61.2 (45.2, 77.2)		14	427 (370, 484)	14	432 (380, 484)	3	439 (346, 532)	1	521 (397, 644)	

	SE								p of group *time* 6MWT	Latency								p of group *time* 6MWT
	No anxiety				Anxiety					No anxiety				Anxiety				
	SOC		Prehab		SOC		SOC			SOC		Prehab		SOC		Prehab		
	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)		N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	
Preop									0.36									0.37
Week 1	26	88.3 (86.7, 89.9)	30	86.4 (85.0, 87.8)	13	86.2 (84.1, 88.4)	10	86.2 (83.9, 88.6)		26	1.11 (0.79, 14.2)	30	1.13 (0.85, 1.41)	13	1.00 (0.57, 1.43)	10	1.20 (0.72, 1.67)	
Week 2	25	88.4 (86.8, 90.0)	26	87.3 (85.9, 88.7)	13	86.2 (84.1, 88.3)	10	86.6 (84.3, 88.8)		25	0.98 (0.67, 1.29)	26	1.13 (0.86, 1.41)	13	1.32 (0.90, 1.74)	10	1.11 (0.67, 1.55)	
Week 3	22	88.7 (87.1, 90.3)	23	87.7 (86.3, 89.1)	9	87.7 (85.4, 89.9)	10	86.6 (84.3, 88.8)		22	1.12 (0.81, 1.43)	23	0.76 (0.48, 1.04)	9	1.16 (0.71, 1.62)	10	1.05 (0.62, 1.48)	
Week 4	12	88.4 (86.7, 90.1)	12	87.1 (85.4, 88.7)	6	86.2 (83.9, 88.5)	7	88.3 (85.8, 90.7)		12	0.94 (0.59, 1.28)	12	0.97 (0.64, 1.31)	6	1.02 (0.56, 1.47)	7	1.15 (0.69, 1.62)	
Postop																		
Week 1	24	87.9 (86.4, 89.5)	25	86.0 (84.6, 87.4)	9	86.8 (84.5, 89.1)	7	86.6 (84.0, 89.2)		24	0.81 (0.51, 1.10)	25	1.03 (0.77, 1.30)	9	0.78 (0.33, 1.23)	7	1.36 (0.88, 1.84)	
Week 2	23	87.7 (86.0, 89.3)	22	85.7 (84.2, 87.3)	8	86.5 (84.0, 88.9)	7	88.1 (85.4, 90.8)		23	1.18 (0.89, 1.47)	22	0.98 (0.70, 1.26)	8	0.91 (0.45, 1.36)	7	1.40 (0.91, 1.88)	
Week 3	21	87.5 (85.7, 89.3)	18	85.3 (83.6, 87.0)	8	86.0 (83.3, 88.6)	5	88.3 (85.1, 91.6)		21	1.00 (0.69, 1.31)	18	1.00 (0.69, 1.31)	8	0.70 (0.21, 1.19)	5	1.02 (0.42, 1.61)	
Week 4	14	88.4 (86.4, 90.5)	14	86.5 (84.6, 88.5)	3	85.5 (81.9, 89.1)	1	87.7 (82.8, 92.5)		14	0.92 (0.56, 1.28)	14	0.84 (0.49, 1.20)	3	0.95 (0.22, 1.67)	1	1.75 (0.71, 2.79)	

Models control for smoking status (imbalanced between groups at baseline), weekend/weekday, and season

Table 4-7: Estimated marginal mean WASO, TST, SE over time by study group within patients with and without depression

	WASO								p of group *time* 6MWT	TST								p of group *time* 6MWT
Time	No depression				Depression					No depression				Depression				
	SOC		Prehab		SOC		Prehab			SOC		Prehab		SOC		Prehab		
	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)		N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	
Preop									0.75									0.26
Week 1	31	52.0 (45.9, 58.2)	36	61.3 (55.8, 66.7)	8	58.6 (47.4, 69.8)	4	46.7 (31.9, 61.4)		31	417 (378, 456)	36	416 (381, 450)	8	385 (314, 455)	4	301 (209, 394)	
Week 2	30	52.9 (46.7, 59.1)	32	58.1 (52.5, 63.6)	8	58.3 (47.1, 69.4)	4	45.1 (30.6, 59.6)		30	426 (387, 465)	32	423 (388, 458)	8	383 (313, 454)	4	288 (196, 379)	
Week 3	24	49.5 (43.0, 55.9)	29	55.2 (49.5, 60.9)	7	56.3 (44.8, 67.7)	4	46.0 (31.3, 60.7)		24	420 (380, 460)	29	418 (382, 453)	7	388 (317, 460)	4	286 (193, 378)	
Week 4	13	55.5 (48.6, 62.5)	16	59.6 (53.4, 65.9)	5	57.2 (45.9, 68.5)	3	41.5 (25.9, 57.0)		13	439 (396, 482)	16	465 (426, 503)	5	387 (316, 458)	3	339 (242, 436)	
Postop																		
Week 1	28	52.5 (46.3, 58.7)	30	60.1 (54.5, 65.7)	5	66.9 (54.7, 79.2)	2	63.1 (46.4, 79.9)		28	409 (370, 448)	30	426 (391, 461)	5	416 (341, 492)	2	369 (267, 472)	
Week 2	26	53.6 (47.3, 59.8)	27	59.0 (53.3, 64.7)	5	61.5 (49.6, 73.5)	2	55.6 (38.9, 72.4)		26	412 (373, 451)	27	411 (375, 447)	5	380 (306, 455)	2	400 (297, 503)	
Week 3	24	57.2 (50.7, 63.6)	21	59.3 (53.3, 65.4)	5	59.1 (46.8, 71.5)	2	55.2 (37.2, 73.2)		24	422 (382, 462)	21	418 (381, 456)	5	355 (279, 432)	2	335 (226, 444)	
Week 4	15	54.1 (47.2, 60.9)	15	57.3 (50.8, 63.7)	2	56.6 (40.5, 72.7)	0	NA		15	447 (405, 490)	15	471 (432, 511)	2	412 (316, 508)	0	NA	

	SE								p of group *time* 6MWT	Latency								p of group *time* 6MWT
	No depression				Depression					No depression				Depression				
	SOC		Prehab		SOC		SOC			SOC		Prehab		SOC		Prehab		
	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)		N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	N	Mean (CI)	
Preop									0.43									0.03
Week 1	31	88.1 (86.6, 89.5)	36	86.2 (84.9, 87.5)	8	85.8 (83.2, 88.5)	4	86.4 (82.9, 89.8)		31	1.12 (0.85, 1.38)	36	1.13 (0.89, 1.36)	8	0.80 (0.31, 1.29)	4	0.80 (0.16, 1.45)	
Week 2	30	88.3 (86.9, 89.8)	32	87.0 (85.7, 88.4)	8	85.0 (02.4, 87.7)	4	86.4 (83.0, 89.9)		30	1.02 (0.75, 1.29)	32	1.17 (0.92, 1.41)	8	1.29 (0.80, 1.79)	4	0.48 (0.00, 1.11)	
Week 3	24	88.7 (87.2, 90.3)	29	87.5 (86.2, 88.9)	7	86.6 (83.9, 89.3)	4	86.0 (82.5, 89.5)		24	1.09 (0.80, 1.38)	29	0.88 (0.62, 1.13)	7	1.20 (0.69, 1.71)	4	0.49 (0.00, 1.14)	
Week 4	13	88.2 (86.5, 89.8)	16	87.3 (85.8, 88.8)	5	85.4 (82.7, 88.1)	3	89.0 (85.3, 92.7)		13	0.93 (0.60, 1.26)	16	1.08 (0.79, 1.38)	5	1.03 (0.53, 1.53)	3	0.54 (0.00, 1.26)	
Postop																		
Week 1	28	87.9 (86.5, 89.4)	30	86.4 (85.0, 87.7)	5	85.4 (82.5, 88.3)	2	83.9 (80.0, 87.9)		28	0.82 (0.55, 1.09)	30	1.14 (0.89, 1.39)	5	0.73 (0.15, 1.30)	2	1.09 (0.28, 1.89)	
Week 2	26	87.7 (86.2, 89.1)	27	86.3 (85.0, 87.7)	5	84.6 (81.8, 87.4)	2	86.4 (82.4, 90.3)		26	1.11 (0.84, 1.39)	27	1.06 (0.81, 1.32)	5	1.16 (0.61, 1.72)	2	1.81 (1.00, 2.61)	
Week 3	24	87.4 (85.9, 88.9)	21	86.3 (84.8, 87.7)	5	84.3 (81.4, 87.2)	2	85.4 (81.2, 89.7)		24	1.02 (0.74, 1.31)	21	1.06 (0.78, 1.34)	5	0.52 (0.00, 1.11)	2	1.08 (0.18, 1.98)	
Week 4	15	88.1 (86.5, 89.7)	15	87.7 (86.2, 89.3)	2	86.7 (82.9, 90.5)	0	NA		15	0.95 (0.63, 1.27)	15	1.02 (0.71, 1.34)	2	0.48 (0.00, 1.34)	0	NA	

Models control for smoking status (imbalanced between groups at baseline), weekend/weekday, and season.

Chapter 5 Bidirectional temporal associations between sleep parameters and physical activity levels in colorectal cancer patients during prehabilitation

Sleep and physical activity are complex, dynamic health behavior components. The limitations of cross-sectional study designs hinder the comprehensive understanding of dynamic health behaviors and inherent complexity across varying timeframes.

The pilot RCT in Chapter 4 revealed limited improvements in perceived sleep quality for the prehabilitation group at the preoperative time point. Furthermore, the associations were moderated by baseline walking capacity and anxiety symptoms. While this study provided valuable insights, it is important to investigate the complex interplay between sleep and physical activity in everyday life.

Acknowledging the limitations of cross-sectional study designs, this chapter delves deeper into this complex relationship by examining day-to-day changes in behavior and exploring the bidirectional associations between sleep and physical activity. This chapter is an ancillary analysis of the previous pilot RCT, which aims to provide a more comprehensive understanding of dynamic health behaviors and their inherent complexity across varying timeframes. The study proposes that increased physical activity levels on a given day would be temporally associated with better sleep the following night. Inversely, it was posited that disrupted sleep on a particular night would lead to diminished physical activity levels the following day.

The research article, entitled ‘Bidirectional Temporal Associations between Sleep Parameters and Physical Activity Levels in Colorectal Cancer Patients during Prehabilitation’ has been submitted to the Behavioral Sleep Medicine journal and is currently under review. The main manuscript is accompanied by an online supplement containing an extended materials and methods section, offering additional details and context.

Bidirectional temporal associations between sleep parameters and physical activity levels in colorectal cancer patients during prehabilitation

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5.1 Abstract

Objective: The current study investigated the temporal bidirectional associations between physical activity and sleep parameters in colorectal cancer patients during the preoperative period. **Methods:** A subgroup of participants with colorectal cancer (N= 59) enrolled in a randomized controlled trial, 30 in prehabilitation intervention and 29 in the standard of care, completed actigraph measurements of physical activity and sleep for 30 consecutive days during the preoperative period. **Results:** Adjusted models revealed greater levels of daily activity counts and moderate to vigorous physical activity (MVPA) on a given day were significantly associated with lower total sleep time (TST) on the following night (β *(SE)*= - .23 (.08)*;* p = .005 and - .17 (.08); p = *.04*, respectively) at between-subject (BS) levels. Insignificant effect was found at within-subject (WS) levels. Conversely, greater TST was associated with lower daily activity counts (p_{BS} = .006 and p_{WS} < .001) and lower MVPA (p_{BS} = .04 and p_{WS} = .002) the following day. The effects did not differ between groups. **Conclusions:** There is a complex interplay between physical activity levels and sleep duration. Although physical activity may not directly impact sleep patterns daily, a longer sleep duration consistently leads to reduced physical activity levels the next day. This suggests the need for personalized considerations of sleep and activity patterns when designing preoperative interventions for colorectal cancer patients.

5.2 Introduction

Sleep and physical activity (PA) are considered significant contributors to the cancer patient's quality of life (1, 2), and both are significantly impaired because of the short- and long-term effects of cancer and its treatment (3, 4). The preoperative period might be the most appropriate time to intervene as patients often have better physical conditions than after surgery (5). Older cancer patients undergoing surgery often show poor physical performance (6) and a high incidence of sleep disorders (7) preoperatively. Before surgery, 59% of cancer patients reported sleep disorder (28 with an insomnia syndrome), and at 18 months after surgery, the prevalence declined but remained significant (36%) (3). Furthermore, 25% to 84% of cancer are not sufficiently active (8-10), and physical activity levels significantly decrease after a cancer diagnosis (4, 11). The relationship between sleep and physical activity is complex and involves multiple physiological and psychological factors (12). Understanding these associations may have clinical implications, specifically for preoperative care interventions.

Different associations between PA and sleep have been found when sleep was self-reported or objectively measured. A systematic review conducted by Atoui et al. including seven interventional studies (13), examined the effect of physical activity on sleep outcomes in cancer patients during the preoperative period. Results showed an absence of evidence of improving the perceived sleep outcomes. However, a significant improvement in the sleep parameters objectively determined, particularly with sleep efficiency (SE) and total sleep time (TST), was observed. Consistent with our results, two meta-analyses showed a negligible effect of exercise on the perceived sleep quality (14) and sleep onset latency (SOL) objectively determined (15). In addition, another showed no significant impact on cancer patients' subjective or objective sleep parameters (16). The limited effect of the physical activity might be due to the interindividual heterogeneity effects underestimated with the traditional trial that only provides an estimate of impact at the group level, neglecting intra-individual (within-subject) differences (17).

Examining the sleep impact on physical activity is more complex due to the limited investigations on this topic, particularly in patients with cancer undergoing surgery. However, it has been interestingly demonstrated that sleep loss impairs the functional recovery of muscles following injury (18-20). Potential physiological mechanisms may involve that elevated levels of cortisol and inflammation and decreased levels of testosterone and growth hormone observed

during acute and chronic sleep loss (21-23). This has particular importance in the context of surgery and preoperative care, as physical exercise intervention during this period has shown improvements in functional capacity and muscle strength preoperatively and in recovery (24-27). We hypothesized that sufficient sleep during the preoperative period might contribute to exercise performance, tissue repair, and growth, consequently improving surgical outcomes and recovery. Future studies are needed to confirm our affirmations.

The lack of a consistent conclusion might be due to the failure to address the dynamic nature of health behaviors (28). The traditional group-level approaches may not be well suited to health diagnostics and treatments toward ones that are individualized, contextualized, timely and consequently have unique responses to behavioral treatment. (28, 29). Therefore, it would be challenging to answer the more clinically relevant question of how a specific individual will respond to that specific treatment or intervention. Furthermore, health behaviors are best seen as a multifactorial, dynamic process, and their characteristics may even change on a daily basis (29). For instance, a high degree of intraindividual variability (also called night-to-night inconsistency) in sleep parameters is joint among older adults (30-32). Furthermore, physical activity intervention manifested and measured under laboratory conditions is not representative of behavior performed in daily life outside of the laboratory, as contextual and environmental variables may influence physical activity levels (33, 34). Additionally, some studies suggest that older adults show more significant intraindividual variability than the young and that such variability is negatively related to performance (35, 36). The qualitative and quantitative analyses of systematic review and meta-analysis conducted by Atoui et al. (37) examining the temporal bidirectional associations between physical activity and sleep parameters results did not support bidirectional daily associations. However, it showed a higher wake after sleep onset latency (WASO) was significantly associated with decreased physical activity levels only at within-subject levels. Also, higher SE and sleep quality were significantly associated with increased physical activity levels the following day only at between-subject levels. However, high physical activity levels were associated with low total sleep time (TST) the next night at between-subject levels. The results of this analysis showed the high variability that can be found at the different levels and highlighted the importance of further investigations on this topic. However, the results of this systematic review cannot be generalized as limited by the baseline participants' physical status and comorbidities and include only one trial of patients with cancer.

To date, there has been no investigation of the temporal bidirectional associations between physical activity and sleep in cancer patients during the preoperative period. A better understanding of how sleep and physical activity are interrelated daily in cancer and surgery context will likely provide relevant information to refine future prehabilitation interventions. The present study investigated the temporal bidirectional associations between sleep and physical activity objectively determined in participants with a multimodal program (prehab) or a standard-of-care (SOC) group (no formal intervention) in colorectal cancer adults during the preoperative period. Second, we wanted to determine whether the relationship differs between the prehab and SOC groups. It was questioned whether increased levels of physical activity (daily activity counts and moderate to vigorous physical activity (MVPA)) on a given day would be temporally associated with better sleep (lower SOL, WASO, higher SE and TST) the following night. Conversely, disturbed sleep (greater SOL, WASO, and lower SE and TST) on a given night would be temporally associated with lower levels of physical activity (daily activity counts and MVPA) the next day.

5.3 Methods

This investigation is an ancillary analysis of a pilot randomized controlled trial evaluating the effect of multimodal prehabilitation on sleep quality and parameters in patients undergoing elective resection of colorectal cancer. For the current study, only the preoperative period data were used. The study was approved by the McGill University Health Centre Research Ethics Board, Montreal, Quebec, Canada.

5.3.1 Participants

Patient enrollment was initiated in November 2020 and completed in November 2022 at a single university-affiliated tertiary hospital center in Montreal, Canada. Adult patients (> 18 years) undergoing elective colorectal resection for cancer were eligible for inclusion. Participants were not eligible if they did not speak English or French or had comorbid conditions that contraindicated exercise. Patients with sleep disorders other than insomnia (e.g., sleep-disordered breathing) or who received psychotherapy specifically for insomnia and night-shift workers were deemed ineligible (38).

5.3.2 Study Design

Detailed protocol and study design were registered at http://clinicaltrials.gov (NCT04270500). Four weeks before each patient's scheduled operation, a medical examination was conducted, and participants completed baseline questionnaires and biochemical, functional, and anthropometric measurements. Upon completing the initial steps, participants were randomly assigned by a research assistant on a 1:1 ratio by computer-generated random numbers to receive either multimodal prehabilitation intervention (Prehab) or standard of care (SOC). No group stratifications were performed. Group allocation was concealed by using sequentially numbered sealed envelopes. Right after randomization, participants in the prehab group started a multimodal intervention 4 weeks before surgery. During this time, participants in both groups were asked to wear an actigraph monitor (Actigraph wGT3X-BT) on their non-dominant arms for 4 consecutive weeks. This allowed for the real-time assessment of participants' daily life during the intervention period. All collected data were entered and managed in Redcap, a secure clinical trials management system.

5.3.2.1 Intervention Group

The multidisciplinary multimodal prehabilitation program comprises exercise training, nutritional intervention, and psychological support. Participants followed the program home-based with a weekly phone call follow-up by a research assistant to maintain adherence to the intervention. The exact interventions are detailed in the supplementary file (Table 1).

5.3.2.2 Standard of Care Group

Routine standard preoperative clinical care does not include particular interventions. Participants in the SOC group were encouraged to maintain a healthy lifestyle without specific tips on precise types and duration of exercises.

5.3.3 Outcomes Measures

5.3.3.1 Sociodemographic and Clinical Characteristics

Participants were asked to complete questionnaires during the baseline assessment, and biochemical, functional, and anthropometric measurements were performed. To assess the severity of insomnia and depression, and anxiety symptoms, participants complete the Insomnia Severity Index (ISI) (39) and the Hospital Anxiety and Depression Scale (HADS) (40). The ISI

has been empirically validated among cancer patients and a score of 8 or greater is used to detect clinically significant insomnia symptoms (95% sensitivity), while a score of 15 or greater suggests the presence of an insomnia syndrome (41). The HADS provides summary measures on a scale of 0–21, with scores exceeding 6 points in anxiety or more than 8 in depression, suggesting the presence of a disorder (42).

5.3.3.2 Objective Measurement of Physical Activity and Sleep

Physical activity and sleep were objectively measured using ActiGraph. The Actigraphy (wGT3X-BT) is a small, waterproof, non-intrusive device worn on the wrist. Participants in both groups were instructed to wear the actigraphic recorder for 4 consecutive weeks, 24-hr periods on their nondominant wrist. Actigraphic data had to be completed in at least seven consecutive 24-hour periods to be included in the analyses. By calculating orientation and movement, the Actigraph estimates sleep-wake activity and objectively measures the sleep parameters. Actigraphic data was also used in the current study to measure the participant's physical activity levels objectively. The validity of Actigraphy has been demonstrated for evaluating sleep quality and duration (43) and the level of physical activity (44) in cancer patients. The Standards of Practice Committee of the American Academy of Sleep Medicine recommends that at least three consecutive 24-hour periods of accelerometry recording time are needed for sleep assessment to obtain reliable sleep estimates. Seven consecutive days of measurement provide a good representation of PA and sleep-wake estimation, as recommended by Quante et al. (45).

*Physical activity***.** Two physical activity variables were obtained from wake-time actigraphic data: daily activity counts (i.e., the sum of daily counts per minute during each wake-time period) and daily MVPA minutes. Daily MVPA minutes were the number of minutes per wake-time period with activity counts of 1952 counts/min or more determined by Freedson et al. (46). The cutoff point was chosen based on a previous validation study of the Actigraph GT3X (47). Data was processed in 60-second epochs. Non-wear time was defined as intervals of at least 60 consecutive minutes of zero counts (48). At least 600 minutes (10 hours) of daily wear time and no excessive counts (>20,000 counts per minute) were required to be considered valid wear days.

*Sleep parameters***.** The sleep parameters design the sleep period spent during the night and are recommended to characterize sleep disorders in the general population and oncology (43, 49). Data were evaluated with ActiLife software Version 6.13.4. We used a sampling rate of

32 Hz, 1-minute epoch setting, and the sleep period scoring option of Cole Kripke (50, 51). This algorithm was specially designed for adults wearing the device on the wrist. For the sleep period detection, the algorithm of ActiGraph was used, which does not depend on wearing location (52). The ActiGraph algorithm implemented the Tudor-Locke algorithm with an automatic sleep period detection. ActiGraph and ActiLife provided information on the following parameters: SOL; time from lights out to sleep onset, WASO; time spent awake after initial sleep onset, TST; the sum of all sleep periods from initial sleep onset until the last awakening, SE; TST divided by total time in bed [TIB] (53, 54).

5.3.4 Statistical Analyses

Data analysis began by calculating descriptive statistics for the study variables (dependent variables, independent variables, and covariates). Frequency and percentage were reported for categorical variables. Means and standard deviations were reported for normally distributed continuous variables while medians and interquartile ranges were reported for non-normally distributed continuous variables. These descriptive statistics were reported overall for the entire sample and by study condition. Chi-square tests (categorical variables), independent samples t-tests (normally distributed continuous variables), and Wilcoxon rank sum tests (non-normally distributed continuous variables) were used to compare the distribution of study variables across study conditions (control vs. prehabilitiation).

Statistical modeling began by examining intraclass correlation coefficients (ICCs) of models for physical activity (daily counts and MVPA) and sleep (SOL, WASO, TST and SE) to determine whether multilevel modeling is required to address the study research questions. ICCs were calculated by estimating intercept-only models with subject specific random intercepts (i.e., a model with no fixed effects variables and a random intercept for subject) and investigating the ratio of the between-subject variance to the total variance of the dependent variable. The ICCs tell us the proportion of total variance in the dependent variable that is accounted for by variations in subjects. ICC values range from 0 to 1, with higher values indicating strong variability between patients and suggesting the need to include these subject effects as random intercepts in multilevel linear models (MLM). The ICC values for the study dependent variables were as follows: 0.59 for MVPA, and 0.54 for daily counts, 0.26 for SOL, 0.38 for SE, 0.36 for TST, 0.37 for WASO, supporting the use of multilevel modeling to address the research questions.

To examine the reciprocal relationships between sleep and physical activity MLMs were used. MLMs were chosen because (a) they take into account the hierarchical structure of the data, (b) they maximize the information from subjects with a variable number of within-subject observations, and (c) they allow examination of whether a within- and/or between- subject variation of the independent variables is associated with the dependent variable. To examine whether increased physical activity (higher daily counts and MVPA) on a given day was temporally associated with better sleep the following night (lower SOL and WASO and higher SE and TST), MLMs with sleep variables on a given day (SOL_t, SE_t, TST_t, $WASO_t$, where *t* is the time of measurement) as the dependent variable and physical activity variables the previous day (daily $counts_{t-1}$ and $MVPA_{t-1}$, where *t*-1 is the lagged value) as independent variables were estimated. The physical activity independent variables were entered into the MLMs in two ways. First, physical activity was entered as a study period average level of physical activity for each person (the between-subject fixed effect). Secondly, the physical activity was entered as a subject-centered daily variation calculated as the variation of daily physical activity around the study period average (the within-subject random effect). The set of MLMs to examine whether disturbed sleep on a given night (greater SOL and WASO and lower SE and TST) would be temporally associated with lower levels of physical activity the next day (low daily activity counts and MVPA) were identical to the ones described above except that physical activity parameters during the day were the dependent variables and sleep parameters on the previous night were the independent variables. As described in detail above, the sleep parameters were entered in the MLMs as both between- and within-subject variables.

Before estimating the MLMs, all dependent and independent variables were standardized into z-score metrics between- and within subjects. This conversion was completed to facilitate the interpretation of the regression coefficients. All MLMs adjusted for the following subject level covariates: age, sex, smoking status, body mass index, cancer stage, cancer treatment, ISI score, antidepressant and hypnotic usage, HADs anxiety score, HADs depression score, device wear time, season, and weekday/weekend. These study covariates were chosen as they had been observed in the primary trial and shown in previous literature to be associated with poor sleep and low physical activity levels in cancer patients (55-57). All analyses were conducted in R version 4.1.2 using the dplyr and nlme packages (58, 59). A p-value < 0.05 was used to determine statistical significance.

5.4 Results

Data from 59 participants were available for these ancillary analyses. Thirteen participants were excluded after randomization due to undergoing urgent surgery (within two weeks) or not being a surgical candidate. Thirty participants were excluded because the actigraph data was incomplete (<7 consecutive days of 24-hour actigraph data or missing sleep or physical activity data) (supplementary file, Figure 1). The sample characteristics are presented in Table 1. The mean age of the final sample was 67 years (*SD* = 12.1) and 51% were female. The participants' characteristics were similar in both groups. Furthermore, the intervention group (prehab) does not show a significant impact on the relationship between physical activity and sleep. This means that the relationship between physical activity and sleep was consistent across both the prehab and SOC groups. Therefore, observations collected from both groups were combined for analysis purposes. Participants were observed for an average of 26 (*SD* = 6.15) consecutive 24-hour periods.

5.4.1 Physical Activity Predicting Sleep Parameters

The first set of MLM analyses examined the between- and within-subject relationships of physical activity on a given day (daily activity counts and MVPA) with sleep parameters on the following night (SOL, WASO, SE, and TST). Adjusted models showed significant relationships only at the between-subject levels indicating that the relationships were stronger when using the study period average than the daily variation. As shown in Table 2, greater levels of daily activity counts and MVPA on a given day were significantly associated with lower TST on the following night (p = .005 and p = .04 respectively). There were no statistically significant relationships between MVPA or daily counts on a given day and SOL, WASO, nor SE the following night.

5.4.2 Sleep Parameters Predicting Physical Activity

The second set of MLM analyses examined the between- and within-subject relationships of sleep parameters on a given night (SOL, WASO, SE, and TST) with physical activity on the following day (daily activity counts and MVPA). Adjusted models showed significant relationships between TST and physical activity (both daily counts and MVPA). Both the between-subject and within-subject levels were significant. As shown in Table 3, greater TST

was associated with lower daily activity counts (p_{BS} = .006 and p_{WS} < .001) and lower MVPA (p_B = .04 and $_{WS}$ < .002) the following day. There were no statistically significant relationships between the sleep measures of SOL, WASO, and SE and the physical activity measures of daily counts and MVPA the following day.

5.5 Discussion

The current study used daily objective measures to examine the temporal bidirectional associations between sleep parameters and physical activity in participants with a multimodal program or SOC group in colorectal cancer adults during the preoperative period for an average of 26 consecutive 24-hour periods. Our results confirmed the hypothesis testing and supported a bidirectional relationship between sleep and physical activity, but results showed negative associations. The design with multiple repeated measurements enabled us to study this relationship at the group level while considering the heterogeneity of individuals.

Our results show higher daily activity counts and MVPA on a given day would be associated with lower TST the following night only at between-subject levels. Contrary to our finding, the results of Bernard et al. (38), showed that higher daily activity count variations were significantly associated with a greater WASO, TWT, and TST the following night only at within-subject levels. This contradiction in results is probably due to fundamental differences in samples and the intervention. In our study, participants showed normal sleep behavior (Median of the ISI total score is 7). However, Bernard et al. study exclusively included breast cancer patients with insomnia, and the Actigraph data was collected before the exercise intervention.

While our finding suggests that there may be a relationship between physical activity and TST only at the group level (between-subject), it is essential to note that this relationship may not apply to all individuals' daily life (within-subject). Possible mechanisms may explain this result. The timing of exercise interventions could be a crucial factor affecting sleep outcomes. Individuals who engage in higher levels of daily activity and MVPA might be more susceptible to sleep disturbances, mainly if they engage in these activities close to bedtime. Consequently, it may cause physiological arousal, thereby affecting subsequent sleep (60). In lung cancer patients, it has been shown that exercising >4 hr before bedtime was associated with better TST and SOL (60). According to sleep hygiene experts' recommendations, exercising 4–5 hr. before bedtime should be avoided to prevent sleep disturbance (61). Another potential mechanism to consider

in our interpretation is daylight exposure, as lacking daylight stimuli increases melatonin secretion (62). Despite the lack of evidence, experimental evidence shows exercising with exposure to daylight is significantly related to improving perceived sleep quality (63-65). Depression and anxiety symptoms may also contribute to the relationship between physical activity and sleep. Theoretical propositions research findings suggest that psychological functioning, such as depression and anxiety, may mediate the relationship between physical exercise and sleep (66-68).

Conversely, higher TST on a given night is associated with lower daily activity counts and lower MVPA between and within-subject levels the next day. Our results were also consistent with the findings of Bernard et al. (38) and other studies on the general population (69-71). It might have a threshold where the proposed restorative features of sleep (e.g., energy conservation, tissue repair and regeneration) do not increase the probability of engaging in physical activity the next day (72). As previously shown, longer sleep duration was associated with a reduced likelihood of ≥20 minutes of accumulated MVPA the following day (73). The long-term impact of sleep duration on exercise is still unexplored, and investigation would be a valuable area of future research (12). However, improving daily physical activity levels may also be related to other mechanisms underestimated in this investigation. For instance, long sleep duration may be associated with an increased risk of obesity and type 2 diabetes mellitus (T2DM) through multiple possible compounding mechanisms, including poor sleep quality, sedentary lifestyle, unhealthy dietary choices, and desynchrony between circadian and behavioral states (74). Furthermore, long sleepers with evening chronotype have more significant difficulties synchronizing their endogenous circadian rhythms with the day–night rhythm imposed by the 24-h day and interlinked societal norms (74). Thus, it might prevent individuals from engaging in health promotion physical activities.

Surprisingly, the relationships examined between physical activity did not differ between the prehab intervention and the SOC groups. Therefore, the data for both groups were pooled for analysis. An explanation for the lack of differences between the groups, and a possible limitation of this study, is the lack of blinded intervention, as it might have contamination or bias between groups (75). Notably, the SOC group was encouraged and motivated to keep a healthy lifestyle. Furthermore, the weekly follow-ups (phone calls to remind them to keep wearing the Actigraph) of the SOC participants could create psychological expectations. It would be more relevant for

future studies to examine this research question in patients with and without sleep disturbances (e.g., insomnia) or compare the prehabilitation intervention with other interventions (e.g., cognitive behavioral therapy).

Two methodological limitations should be considered while interpreting and may also limit the generalization of the findings. Data were exclusively limited to colorectal cancer patients who might not be similar to other types of cancer or other medical conditions. Second, participants in the prehab group received multimodal interventions (exercise, nutrition, and psychological support). However, our daily basis analyses only include a subset of domains (physical activity and sleep) involved in these complex homeostatic networks. In the current study, we did not include daily measures of eating, stress, light, noise, temperature, or other factors. Future research into these networks could be enhanced by including biological correlates of the daily measures and the use of newer technology that assesses light, temperature, eating habits, and mood.

To the best of our knowledge, no previous study has investigated the temporal dynamics bidirectional associations between sleep and physical activity objectively assessed in colorectal cancer patients observed for an average of 26 days during the prehabilitation intervention period. The hypothesis of a bidirectional relationship between sleep and physical activity was confirmed, but results showed negative associations. The presence of substantial heterogeneity within individuals confirmed the critical role of studying some behavioral and psychological aspects (e.g., eating and mood disorders) in daily life. A greater understanding of the directions and mechanisms for these associations could explain how physical activity; sleep; eating; mood; cognition; and their underlying neural, physiologic, and molecular processes affect energy, interact in more complex networks, and help identify targets for the prehabilitation interventions.

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Tables and Figures

Table 5-1: Participants' Characteristics at Baseline by Study Group

	Study Group	
	Prehab (N=30)	**SOC (N=29)**
Age, Mean (SD)	66.10 (13.08)	68.90 (10.95)
Sex, n (%)		
Male	14 (46.67)	15 (51.72)
Female	16 (53.33)	14 (48.28)
BMI, Mean (SD)	27.55 (4.45)	26.86 (6.15)
Tumor stage, n (%)		
0	2 (6.67)	4 (13.79)
1-2	17 (56.67)	16 (54.17)
3+	11 (36.67)	9 (31.03)
Neoadjuvant therapy ‡, n (%)	5 (16.67)	3 (10.34)
Laparoscopic procedure, n (%)	30 (100)	26 (89.66)
Type of resection, n (%)		
Colon *	17 (56.67)	19 (65.52)
Rectal †	13 (43.33)	10 (34.48)
Alcohol consumption, n (%)	12 (40)	9 (31.03)
Smoking status, n (%)	13 (43.33)	9 (31.03)
Hypnotic/Anxiolytic medication, n (%)	5 (16.67)	5 (17.24)
ISI Total score, Median [IQR]	6.5 (3.25; 12.75)	7 (3; 10)
ISI Total score > 7, n (%)	13 (43.33)	12 (41.38)
HADS- Anxiety, Median [IQR]	5.5 (3; 8)	5 (3; 8)
HADS- Depression, Median [IQR]	4 (1; 7)	4 (1; 6)
SOL (min), Median [IQR]	0 (0; 1.88)	1 (0; 1.5)
WASO (min), Mean (SD)	48.45 (19.29)	64.34 (22.89)
SE (%), Mean (SD)	89.46 (4.52)	85.49 (5.94)
TST (min), Median [IQR]	452.5 (337.75; 511.25)	384 (351; 457)
Daily counts, Median [IQR]	143.73 (306.50)	144.63 (421.92)
MVPA (min), Median [IQR]	18.33 (39.21)	17.69 (56.43)

Data are presented as mean (SD), median [IQR], or n (%). Prehab: Prehabilitation group, SOC: standard-of-care group. IQR = interquartile range; HADS: Hospital Anxiety and Depression Scale, ISI: Insomnia Severity Index; SOL: sleep onset latency; WASO: wake after sleep onset; TST: total sleep time; SE: sleep efficiency. ‡ Neoadjuvant therapy refers to chemotherapy or radiation therapy. * Includes right and left hemicolectomy and sigmoid resection. † Includes anterior resection, low anterior resection, and abdominoperineal resection.

Table 5-2: Sleep Parameters Predicted from Daily Counts and MVPA Minutes

Predictors	SOL		WASO		SE		TST	
	β(SE)	*t*	*β(SE)*	*t*	*β(SE)*	*t*	*β(SE)*	*t*
Daily activity counts								
BS	.05 (.07)	.74	- .06 (.09)	- .61	- .10 (.09)	-1.17	- .23 (.08)	-2.94**
WS	.001 (.02)	.04	- .02 (.02)	- .88	.03 (.02)	1.49	.03 (.02)	1.72
MVPA								
BS	.003 (.07)	.05	- .08 (.09)	- .85	- .05 (.09)	- .63	- .17 (.08)	-2.10*
WS	.02 (.02)	1.08	- .02 (.02)	- 1.26	.02 (.02)	1.72	.02 (.02)	.88

Note. SOL = sleep onset latency; WASO = wake after sleep onset; SE = sleep efficiency; TST = total sleep time; BP = between-subject; WP = within-subject; MVPA = moderate to vigorous physical activity. * $p < .05$, adjusted. ** $p < .01$, adjusted. *** $p < .001$, adjusted.

Table 5-3: Total Daily Counts and MVPA Minutes Predicted from Sleep Parameters

Predictors	Total Daily Counts		MVPA	
	β(SE)	*t*	*β(SE)*	*t*
SOL				
BS	.09 (.11)	.80	.01 (.12)	.10
WS	.01 (.02)	.85	.01 (.02)	.45
WASO				
BS	- .07 (.11)	- .61	- .10 (.12)	- .85
WS	.002 (.01)	.10	.00 (.01)	.21
TST				
BS	- .30 (.10)	- 2.92**	- .24 (.12)	- 2.08*
WS	- .09 (.02)	- 5.54***	- .03 (.01)	-3.04***
SE				
BS	- .14 (.12)	- 1.15	- .08 (.13)	- .61
WS	- .01 (.02)	- .77	- .001 (.01)	- .06

Note. SOL = sleep onset latency; WASO = wake after sleep onset; SE = sleep efficiency; TST = total sleep time; BP = between-subject; WP = within-subject; MVPA = moderate to vigorous physical activity. * $p < .05$, adjusted. ** $p < .01$, adjusted. *** $p < .001$, adjusted.

Online Supplement

5.10 Detailed Methods

Table 5-1: Description of the Multimodal Prehabilitation Program

Intervention	Events	Content	Study outcome measures
Exercise - Goal progression every week if program well tolerated	Home-based *At least 3 times/week*	1. Intensity: based on the rate of perceived exertion (Borg scale) from the 6-min walk test (6MWT). The Karvonen formula [(220 − age) − (resting heart rate × % intensity) + resting heart rate] is used to determine the heart rate to be maintained to achieve the desired, prescribed intensity. 2. 5-min warm-up, 3. Aerobic: 20 minutes at a moderate intensity of any aerobic exercise (brisk walking, jogging, or a machine) 4. Resistance: 20 min of whole-body resistance training with elastic bands provided. Eight exercises targeting major muscle groups x 8-12 repetitions maximum. 5. 5-minute cooldown. 6. Provide participants: - Three resistance bands (light, moderate, and/or vigorous). - Exercise booklet and exercise record for each day, the type of exercise performed and the duration and intensity (perceived effort according to the modified Borg scale). - Actigraph is worn for 4 consecutive weeks, 24 h period continuously, and then returned at the preoperative follow-up (4 weeks after the baseline assessment).	- Objective sleep quality (SOL, WASO, TST and SE) - Objective physical activity (daily counts and MVPA)
1–4	Weekly	1. A researcher counseled walking	

	exercise telephone counseling	exercise group participants through the telephone every week. 2. The researcher reminded participants to complete the exercise record table every week and wear the Actigraph.	
Nutrition	*- 1 first visit* *- Phone calls follow-ups between weeks 1-4, as needed* *- 1 follow-up visit at the preoperative*	**Nutritional education:** - Balanced meals - Correct portion size - Timing and spacing of meals - Mindful eating - Protein importance and sources **Nutritional intervention** - Nutritional assessment - Ensure balanced macronutrient intake - Weight management - Optimize glycemic control - Adequate protein intake 1.2-1.5g/kg/day - Whey protein supplement to guarantee adequate daily protein intake (Immunocal®; Immunotec Inc., Vaudreuil, Quebec, Canada) at a quantity that matched the estimated dietary deficit - Protein supplement consumed within one h of their exercise regimen to capitalize on postexercise muscle protein synthesis	
Psychosocial *- If score in HADS-A>6 or HADS-D >8*	Weeks 1- 4	- Cognitive reframing - Relaxation and deep breathing exercises - Anxiety coping strategies	**Hospital Anxiety and Depression Scale (HADS)**
Standard of care group	Weeks 1-4	- Participants were encouraged to maintain a healthy lifestyle without specific tips on precise types and duration of exercises. - Actigraph is worn for 4 consecutive weeks, 24 h period continuously, and then returned at the preoperative follow-up (4 weeks after the baseline assessment).	- Objective sleep quality (SOL, WASO, TST and SE) - Objective physical activity (daily counts and MVPA)

		- The researcher reminded participants to complete the exercise record table every week and wear the Actigraph.	

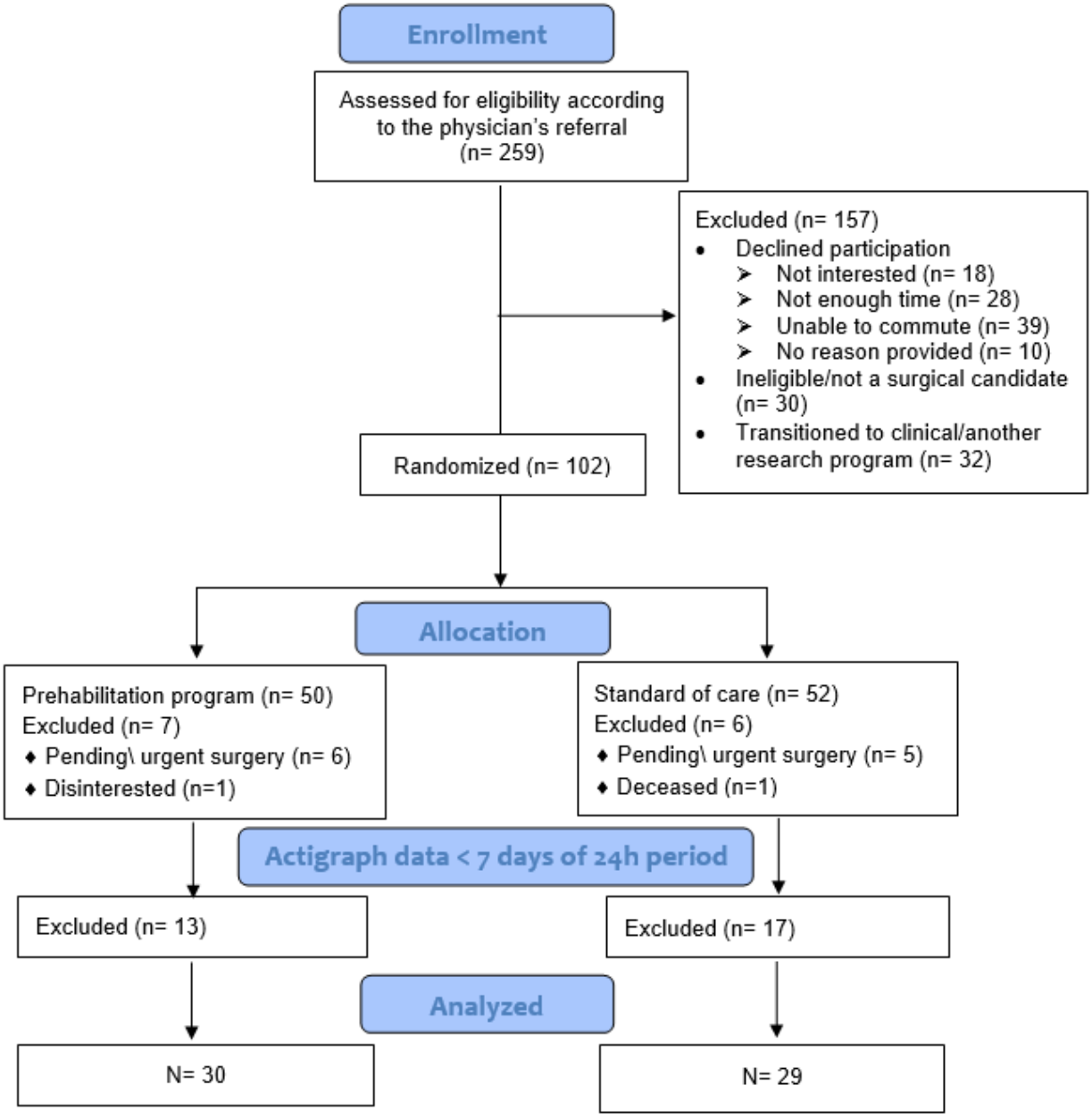

Figure 5-1: Consolidated standards of reporting trials (CONSORT) diagram showing the flow of participants through the trial.

Chapter 6 : Discussion

The work of this thesis sought to examine sleep behaviors and associations during the preoperative period with a particular focus on physical activity. In the first study, the associations between sleep and physical activity were investigated through a cross-sectional study design using a nationally representative sample of U.S. adult cancer survivors. In the second part, we performed a systematic review and comprehensively analyzed the literature examining the preoperative exercise intervention or a multimodal prehabilitation impact on sleep outcomes. Following this, we conducted a pilot randomized controlled trial to investigate the effect of multimodal prehabilitation on sleep quality and parameters by comparing a multimodal program with standard-of-care (no formal intervention) in colorectal cancer adults during the preoperative period and after surgery. Finally, the associations between physical activity and sleep parameters were also analyzed on a micro-scale in the context of prehabilitation in the daily life of colorectal cancer patients.

This thesis work demonstrated that cancer survivors who engage in greater MVPA might experience more restorative sleep, as they are less likely to feel overly sleepy during the day even though they report fewer hours of sleep. However, greater time spent in sedentary behavior is associated with a few hours of sleep, independent of the daily time spent in MVPA. Also, the systematic review shows a limited improvement of the exercise intervention alone on sleep quality and disturbances in cancer patients during the preoperative period. On the other hand, in colorectal cancer patients, a multimodal prehabilitation which combines exercise, nutrition and psychological interventions might improve sleep quality (self-reported and objectively determined) preoperatively. However, it might improve sleep duration only at 8 weeks after the surgery. Multimodal prehabilitation seems to have a more beneficial impact on sleep patterns for specific sub-groups, as it significantly improved sleep quality and duration for patients with limited walking capacity and high anxiety sub-groups. Finally, we demonstrate that physical activity levels may not necessarily impact patients' sleep quality and duration at the within-subject levels during the preoperative period. As only at the between-subject levels, colorectal cancer patients with greater daily physical activity tend to have shorter total sleep time. Interestingly, the relationship appears to be reciprocal as longer sleep duration is associated with

reduced physical activity levels the following day.

The following sections of the thesis will closely examine the prehabilitation and sleep outcomes, followed by a discussion on the associations between sleep outcomes and physical activity, ending with a summary of clinical implications.

6.1 Sleep Outcomes and Physical Activity

Multiple physiological and psychological pathways are involved in the complex interactions between sleep and physical activity (1). Despite evidence suggesting that exercise intervention can induce modifications in sleep patterns, it remains uncertain whether the observed improvements following a training period are attributable to the direct impact of exercise on sleep or the amelioration of factors that may adversely influence sleep, such as comorbidities and depression (2). Two primary hypotheses may explain the effects of physical exercise on sleep patterns and quality: the thermoregulatory hypothesis and the metabolic hypothesis (2). Despite these hypotheses, alternative propositions emphasize the role of additional factors, such as cytokines, especially pro-inflammatory cytokines, which are substantially influenced by physical exercise, as potential mediators of sleep improvement (3). Cytokines are polypeptides released by almost every cell type and are among the key substances that effectively contribute to sleep regulation (3). They potentially impact a complex neuronal network acting on thermoregulation, food intake, sleep and behavioral patterns (4). It was recently suggested that moderate exercise might mitigate the chronic inflammation accompanying some pathologies (5). This hypothesis of a partial reduction of inflammation in chronic illnesses is justified by two aspects: pro-inflammatory cytokine plasma concentrations decreased simultaneously with an increase in anti-inflammatory cytokine plasma concentrations and receptor antagonists. Through this mechanism, it is possible that physical training may decrease sleep disturbances, by decreasing IL-6 and TNF-α plasma concentration (3). However, the effects of exercise on sleep are not evident before 8 weeks of training (2). Consequently, the exercise training effect may depend on the global overload training and is more apparent in individuals with elevated pro-inflammatory plasma concentrations caused by insomnia and other pathologies associated with increased IL-6 plasma concentration (6).

Using a large US sample of cancer survivors, we examined the cross-sectional associations between self-reported and device-measured MVPA, self-reported SB, and sleep-

related outcomes in Chapter 2. Our findings suggest that higher levels of physical activity (self-reported) might lead to a reduction in total sleep duration. On the other hand, extended periods of sedentary behavior could negatively impact sleep duration and contribute to excessive daytime sleepiness, regardless of the time spent engaging in physical activity. Interestingly, our results also suggest that participating in more MVPA may have a positive impact on reducing daytime sleepiness; however, it may be associated with waking up too early in the morning.

These results suggest that more physical activity is associated with improved sleep outcomes in specific aspects, while the relationship remains inconclusive or complex in others. For instance, participants with a higher daily duration of MVPA reported fewer hours of sleep per night. Despite sleeping less, they were less likely to feel overly sleepy during the day. The results showed that for every 60 minutes increase of device-measured MVPA, participants were 14% less likely to feel rarely/sometimes overly sleepy during the day. This finding suggests that participants might be experiencing a more restorative sleep, as they are less likely to feel overly sleepy during the day even though they report fewer hours of sleep. On the other hand, spending more time on sedentary behavior negatively impacts sleep quality and increases daytime sleepiness.

This complex relationship between physical activity, sedentary behavior, and sleep outcomes highlights the need for a nuanced understanding of these factors when designing interventions or strategies to promote better sleep quality and overall health in cancer survivors. While it is essential to develop approaches encouraging patients to engage in MVPA, it is equally important to establish strategies to decrease sedentary behavior, given their potential effects on sleep quality and sleep-related outcomes. While this thesis did not specifically investigate the preoperative sedentary behavior of cancer patients, this data may have significant implications. Mainly, sedentary behavior, and poor preoperative physical fitness are modifiable risk factors for surgery and a large percentage of cancer patients (25% to 84%) are not sufficiently active (7-9). Cancer treatment and recovery phases may exacerbate prolonged periods of sitting, and these habits may ultimately contribute to enjoying sedentary hobbies and result in further functional decline over time (10). Practitioners and researchers should adopt strategies to reduce prolonged sitting throughout the day and break up time-spent sitting. Notably, most strategies were implemented in healthy populations rather than cancer patients. Therefore, additional research is required to the appropriate strategy for cancer patients to implement during and after treatment.

The findings from this study highlight the importance of developing interventions to improve sleep outcomes in cancer patients, particularly during the cancer treatment period. Importantly, exercise intervention helps manage symptoms by targeting specific treatment side effects, such as inflammation, and can positively influence immune system parameters (11). This further emphasizes the need to consider the long-term impacts of these interventions and develop tailored programs for cancer patients that promote an active lifestyle even after completing treatment. Regular physical activity and minimizing sedentary behavior benefit sleep quality and overall well-being. For instance, by initiating interventions during the preoperative phase, healthcare professionals can capitalize on the window of opportunity to facilitate positive lifestyle changes that may lead to better sleep outcomes. Preoperative interventions can help patients manage stress, maintain a better quality of life throughout their cancer journey, and may also address sleep disturbances effectively.

6.2 Prehabilitation and Sleep Outcomes

In Chapter 3, the systematic review examining the preoperative exercise intervention impact on sleep outcomes demonstrated insufficient knowledge and inconsistent results between included studies. Furthermore, most studies showed non-significant improvements in sleep disturbances, suggesting that preoperative exercise alone may not have a strong overall effect on sleep. However, the limited number of high-quality studies and the substantial heterogeneity in interventions make it difficult to draw definitive conclusions.

The sleep–immunity relationship raises relevant clinical implications for promoting sleep health and improving or controlling inflammatory responses by targeting sleep. This may translate into addressing sleep as a lifestyle approach, along with diet, psychological support, and physical activity to benefit overall public health. This thesis did not clinically investigate the sleep and inflammatory biological mechanisms; however, theoretically, a multimodal prehabilitation program that includes nutrition, psychosocial and exercise interventions is supposed to have a powerful impact on preoperative sleep disorders. To our knowledge, no previous studies have adopted multimodal strategies preoperatively to enhance sleep quality and duration among cancer patients. A study issued from a thesis dissertation published in 2022 investigated the impact of prehabilitation on psychological health and sleep for patients awaiting pancreatic resection (12). This study showed no intra- or between-group difference in global

PSQI scores. However, the results from the Actigraph showed an improvement in the TST by 1.22h (73 minutes) in the prehab group compared to the control group. Notably, the baseline mean (±SD) of sleep duration was 7.0 ± 0.8 and 6.6 ± 1.3 for the prehab and control groups, respectively.

The results of this study contradict our findings presented in Chapter 4. Our pilot RCT identified small positive changes in perceived sleep quality preoperatively; however, significant improvements were only observed in WASO time and TST for specific subgroups. Preoperatively, the prehab group with a limited walking capacity at the baseline (6MWT< 400m) showed a reduction of 2.8 min, while the SOC showed a 16.2 min increase in WASO time. After surgery, the improvements changed between groups in opposite directions. On the other hand, the prehab group showed an increase in TST over time for a total of 153 minutes relative to the baseline (368 min) compared to a 43-minute increase in the SOC group (396 min) only at the 8-week follow-up after the surgery. The statistical differences were exclusively significant for the patients with high anxiety symptoms subgroup at the baseline (HADS >6). Several methodological limitations may explain the differences between the results—first, the differences in samples and characteristics. For instance, the mean (±SD) global PSQI scores at baseline were 5.6 ± 3.0 and 7.4 ± 5.3 for the prehab and control groups, respectively. However, our study's global PSQI scores were 12.43 (3.30) and 12.21 (2.64) at baseline for the prehab and SOC groups. Generally, a global PSQI score > 5 differentiates a poor sleeper from a good sleeper, indicating severe difficulty in at least two or moderate difficulty in at least three components. Furthermore, the sample size differences between studies may create further issues. At baseline, only 7 patients have Actigraphy data of one week in the control group, against 12 patients in the prehab group, similarly, for the self-reported PSQI global score. Also, the actual interval between actigraphy recordings seems to be only two rather than 4 weeks, as reported by the authors. Contrary, our study represents a larger sample size and strictly included 7-day recall data for 4-consecutive weeks. Finally, the study was not a randomized controlled trial; thus, a lack of randomization could have introduced potential selection bias.

The small positive changes in perceived sleep quality, although not observed in Actigraph sleep measures, suggest that multimodal prehabilitation may positively affect sleep quality. However, this finding could be due to the multifaceted approach of the prehabilitation program which may better address patients' individual needs and preferences compared to single-

component interventions. For instance, Mercier et al. (13) conducted a non-inferiority RCT to evaluate the efficacy of a 6-week home-based aerobic exercise program (EX) compared to a 6-week self-administered cognitive-behavioral therapy (CBT) in the reduction of insomnia severity (measured with the Insomnia Severity Index; ISI) after adjuvant treatment in cancer patients. The results indicated that the EX-intervention was statistically inferior to CBT in reducing ISI scores after treatment but was non-inferior at 3-and 6-month follow-ups. Notably, both therapies significantly improve subjective sleep outcomes (ISI, PSQI, SOL, WASO, and SE). The results of this study may be replicated in the prehabilitation setting as it might more effectively address patients' active engagement in managing their well-being.

As an example of managing sleep disorders preoperatively using a multimodal approach, patients with severe insomnia symptoms at baseline may derive more significant benefits from psychosocial interventions than exercise. However, various challenges could limit the intervention's efficacy in addressing sleep disorders. First, most patients, particularly older adults, tend to be less active and have a higher risk of malnutrition before surgery (14). Consequently, the prehabilitation healthcare team primarily focuses on optimizing physical and nutritional patients' status. This approach often results in patients being instructed to follow a multimodal program that combines at least exercise and nutrition components. This scenario may also lead to ignoring the management of other factors like sleep disorders. Second, the time frame of cancer patients awaiting surgery is around 4 weeks which might also limit the interventions' benefits, specifically in sleep management. The optimal duration of exercise interventions required to achieve meaningful improvements in sleep remains unclear, as most studies have only examined sleep at baseline and post-intervention (15). However, clinical evidence indicates that an exercise intervention should be implemented regularly, such as three to five times per week with a specific duration of each time and for around 8 consecutive weeks (16). Therefore, 4 weeks of exercise interventions might not be sufficient to induce the necessary improvement of sleep outcomes. This aspect may potentially account for the findings in our subgroup analysis. The moderator analysis revealed a more favorable impact on the "Anxiety" and "6MWT<400" subgroups. It is worth noting that only patients with HADS-Anxiety scores greater than 6 received psychosocial intervention. This result may further support our hypothesis that psychosocial interventions, rather than exercise interventions, could be responsible for the improvements in TST observed in the "Anxiety" prehab subgroups. However, the study design

of the current pilot RCT cannot definitively confirm our assertion.

On the other hand, our results also may suggest that the impact of the prehabilitation interventions might be more substantial for specific patient populations such as those with baseline physical performance limitations or anxiety. In line with prior research indicating that older patients tend to be less active and have poor diets, they are more likely to have advantages from prehabilitation than other patients (17, 18). A previous investigation revealed that colorectal cancer patients with diminished baseline functional walking capacity (6MWT <400m) are more likely to experience a meaningful improvement in physical function from prehabilitation before and after colorectal surgery, compared with those with higher baseline walking capacity (6MWT >400m) (19). Nevertheless, exploring sleep disorders in frail, geriatric patients remain an unexplored topic in prehabilitation research.

To effectively customize and optimize multimodal intervention, it is crucial to deeply understand the complex interactions between various behaviors, such as sleep and physical activity. This knowledge is invaluable in designing targeted and efficient interventions addressing each patient's needs. Although cross-sectional and laboratory designs, particularly experimental (randomized) approaches, have several strengths, they are inadequate for addressing complex, dynamic, and multi-causal behaviors (20). Cross-sectional studies provide a static representation of processes, while prospective studies offer a limited static picture of operations and may thus prevent a closer examination of the dynamic processes that, indeed, are present in most behavioral phenomena (20). On the other hand, assessments that require participants to reflect on the intensity or frequency of a symptom or behavior over an extended period, such as a week or a month, are associated with retrospective recall biases, leading to memory errors (21). These traditional assessments also typically ask participants about their past emotions, experiences, and behaviors, which may not accurately reflect the actual history of those emotions, experiences, and behaviors (22).

Maintaining a consistent daily healthy lifestyle may be particularly challenging due to day-to-day fluctuations in individuals' emotions, interactions, obstacles encountered, and environmental contexts (23). The ability to move out of the laboratory into real life is crucial for research areas where the psychological and environmental context may impact the individual (20). Real-time data capture strategies such as Ecological Momentary Assessment (EMA) allow a more refined comprehension of natural dynamic behavioral changes (24). The EMA may

improve our understanding of behaviors through three key areas: 1) *Synchronicity*—2) *Sequentially*—and 3) *Instability.*

1-Synchronicity: The traditional measurement approaches can examine inter-individual (i.e., between-person) effects or differences. Still, they cannot determine whether there are also intra-individual (i.e., within-person) effects that operate across time and space. Preliminary research suggests that certain behaviors, such as physical activity levels, affective states, beliefs, attitudes, and contextual exposures, may experience substantial fluctuations over time (e.g., on a daily basis) and across different environments (e.g., from one setting to another) (25). Through repeated measures, EMA can capture between-person effects at the individual level and within-person impacts occurring at lower units of analyses (e.g., shorter time periods) that are conceptually nested within individuals.

2- Sequentially: EMA methods can help better understand the potential causal sequences surrounding behaviors. Evidence from intervention studies has shown that changing one health behavior can result in positive changes in other health behaviors (26-28). For instance, Fleig et al. (28) showed that an exercise self-regulation intervention increased exercise behavior and fruit and vegetable consumption. Furthermore, individuals may also feel more motivated because of previous achievements in other domains (27). On the other hand, negative consistency, also referred to as disinhibition (29), occurs when one unhealthy behavior leads to another unhealthy behavior. Previous studies indicated that physical activity triggers various other healthy behaviors (28, 30), suggesting that physical activity may be a keystone habit that provokes changes in eating habits and other health-related behaviors (26).

3- Instability: The extent of fluctuation (i.e., degree of within-subject variation from the individual's average level) in certain factors that may represent underlying characteristic variability patterns (23). Still, one person might display a more stable exercise routine, whereas the other experiences significant fluctuation or instability around that level. By collecting time-intensive repeated measures, EMA methods have the potential to capture change and instability of factors.

Recent technological advancements such as smartphones and wearable devices have facilitated the real-time collecting information on daily life behaviors (31, 32). In Chapter 5, we attempted to investigate the bidirectional sequences between sleep and physical activity objectively determined in participants with a multimodal program (prehab) or a standard-of-care

(SOC) group (no formal intervention) in colorectal cancer adults during the preoperative period for an average of 26 consecutive 24-hour periods. The results showed bidirectional negative associations between sleep and physical activity levels with no significant differences between the prehab and SOC groups. Our findings reveal that higher daily activity counts and MVPA on a given day are associated with lower TST the following night, but only at between-subject levels. This indicates that patients with higher average physical activity levels over the study period experienced changes in sleep parameters, such as shorter total sleep time. However, the daily variations in physical activity did not show significant associations with sleep parameters on the following night within individual subjects. This suggests that while group-level results show that physical activity may lead to reduced sleep hours at night, the individual's physical activity levels may not have the same impact on sleep duration. Furthermore, no statistically significant associations were observed between MVPA or daily counts on a particular day and SOL, WASO, or SE the next night. When interpreting these results, it is essential to consider both the between-subject and within-subject findings and their implications for making recommendations on sleep and exercise. The group-level findings can help inform general guidelines and exercise interventions, but it is necessary to acknowledge the potential variability in individual responses to these interventions. Overall, the results suggest that factors other than physical activity may influence sleep patterns. Several factors can influence sleep patterns, including physical environmental exposure (e.g., light exposure), sleep patterns (e.g., insomnia) and chronotype, medications, cognitive and emotional factors and nutrition (33) and sedentary time. As demonstrated in Chapter 2, moderate to vigorous physical activity may impact sleep duration depending on the daily time spent in sedentary behaviors. However, sedentary time affects sleep duration independently of the time spent in moderate to vigorous physical activity.

On the other hand, higher TST on a given night is associated with lower daily activity counts and MVPA at both individual and group levels. This implies that extended sleep duration negatively affects the subsequent day's physical activity levels for individuals and groups alike. The significant relationships observed at both the between-subject and within-subject levels suggest that the association between sleep duration and physical activity is consistent across individuals and from day to day within the same individual. This implies that the relationship between sleep and physical activity is robust and generalizable. The observed consistency across individuals and days highlights the potential significance of sleep duration in influencing

physical activity levels. This finding emphasizes the need to consider sleep duration when developing interventions to promote physical activity as it may be a critical factor in the program's success. In light of these findings, it is crucial to consider sleep patterns when making recommendations or developing exercise interventions for both individuals and groups. For instance, when planning interventions to promote physical activity, it is crucial to address sleep patterns, as optimizing sleep duration could enhance a patient's ability to participate actively and gain maximum benefits from exercise programs. The timing of exercise interventions (e.g., close to or long before bedtime, with or without daylight and schedule regularity) could be a crucial factor affecting sleep outcomes, which was not investigated in our study. Although the optimal exercise timing in the population with cancer is unclear, expert-proposed sleep hygiene principles recommend avoiding exercising 4–5 hr before bedtime to prevent sleep disturbance (34). In lung cancer patients, not exercising close to bedtime (> 4-hour group before bedtime) was associated with improved perceived sleep quality (total PSQI score) and objective sleep parameters (TST and SOL) (35). Furthermore, the current study did not investigate the optimal exercise dosage required to improve sleep. In breast cancer patients receiving chemotherapy, thrice weekly supervised exercise training demonstrates that a higher dose of aerobic exercise (50–60 min) was statistically superior to a standard dose of aerobic exercise (25–30 min) in improving the perceived sleep quality (total PSQI score, sleep quality and SOL components) (36). Similarly, a randomized dose-response trial among colon cancer survivors aiming to compare usual-care control, low-dose (150 min\week), and high-dose (300 min\week) aerobic exercise at home-based treadmills for six months (37). Results demonstrated that the high-dose aerobic exercise group significantly improved the perceived sleep quality (sleep quality and SOL components of the PSQI) over six months compared to the low-dose group. Overall, these findings demonstrated that a high dose of exercise intervention might have a more beneficial impact in improving sleep quality, which may also explain the limited effect of multimodal prehabilitation in improving sleep quality and duration. For instance, the actigraph data showed that none of the prehab group patients achieved the daily vigorous intensity levels of physical activity, defined by 5725 - 9498 counts per minute. Similar findings were observed in the CHAMPS questionnaire, which showed no significant variation between moderate to vigorous physical activity levels reported at the initial assessment and at the preoperative time points. The deliverance mode of the home-based intervention might be a factor in the lack of compliance

with the prescribed exercise intensity despite high reported adherence. When the exercise intervention is supervised, there is typically a better assurance that the participants adhere to the exercise sessions' intensity and duration guidelines. Another factor that could account for the marginal improvement observed is the timing of the sleep outcome assessment. Most studies have indicated a notable improvement in sleep parameters over six months, as opposed to daily or within 4 weeks, which was the case in our study. Exercise interventions might substantially impact sleep outcomes in the long term rather than producing immediate effects. Nevertheless, further investigation is warranted in this area to confirm this assertion.

No previous study has investigated the movement behavior sequence change between sleep and physical or other behaviors in the prehabilitation and surgical contexts. Nevertheless, the findings of our analyses should be interpreted with caution, given the methodological limitations. In summary, addressing sleep disorders during the preoperative period may be effectively achieved through a comprehensive multimodal prehabilitation strategy. However, tailoring the intervention to optimally manage the physical, nutritional, psychological, and sleep-related aspects is crucial and requires more investigation. Sleep disorders are frequently underdiagnosed and inadequately managed, especially in perioperative patients. As a preliminary measure, it is crucial to enhance healthcare professionals' and patients' awareness of the importance of addressing sleep disorders and their consequences and conducting a rigorous preoperative diagnosis and assessment of sleep issues. Furthermore, further research should explore these mechanisms to understand the causal pathways better and identify potential intervention targets.

6.3 Clinical Implications

As introduced at the start of this thesis, clinical trials specifically designed to investigate sleep behaviors preoperatively have yet to be conducted. Through raising awareness of this topic, we hope to stimulate interest and research on the importance of managing sleep preoperatively. Treatment of sleep disorders may represent another key element, along with diet and physical activity, to promote lifestyle changes with benefits on health. The research area in this topic requires more investigation to understand sleep's biological and physiological mechanisms and develop an individualized multimodal approach that promotes overall health and well-being.

Despite the hard work of developing strategies to engage patients in physical activity,

developing strategies to reduce sedentary behavior might be equally important, which requires more investigation in the prehabilitation context. Our findings also highlight the importance of considering the long-term effects of exercise interventions on sleep and physical activity behaviors even after cancer treatment. It may be necessary to reevaluate and adjust intervention strategies to ensure continued effectiveness periodically.

This thesis work indicates that prehabilitation interventions targeting sub-group populations may effectively improve wakefulness during the night and sleep duration objectively determined. Furthermore, prehabilitation might also improve the global sleep quality perceived preoperatively. First, the disparity observed between subjective and objective sleep outcomes underscores the importance of considering subjective and objective measures of sleep disturbances to understand patients' experiences comprehensively. These findings also underscore the need for further research to refine and target prehabilitation interventions that effectively address sleep disturbances and quality in cancer patients.

While insights from cross-sectional and laboratory designs are essential, longitudinal research designs and innovative data collection methods, such as momentary ecological assessment (EMA), may help further to provide a more nuanced understanding of behaviors' dynamic processes. Using a comprehensive approach that includes other behaviors may also refine the prehabilitation intervention. For example, an intervention that promotes a balance between physical activity and sleep along with diet and psychological support may help optimize patients' overall health and well-being, ultimately supporting their recovery following surgery. Different analysis and data approaches for real-time monitoring in the prehabilitation context may be adopted to understand the dynamic, multi-causal between other behaviors, such as diet and emotional states, which can help make the behavior's complexities more manageable.

When developing interventions, it might be equally essential to include components that balance sleep and activity. This could involve educating patients about the relationship between sleep duration and physical activity and suggesting balance strategies, such as consistent sleep schedules or daytime activity planning. Tailored strategies may be developed for those with longer sleep durations to gradually increase physical activity without altering sleep patterns. For example, introducing light physical activity in the morning could be an approach for someone with a longer sleep duration. Patients may also be advised to focus on sleep hygiene practices to improve overall sleep, as SOL, WASO, and SE were not significantly related to physical activity.

Additionally, monitoring both sleep and activity during the intervention could allow for adjustments based on individual patterns, potentially leading to more effective interventions. Since sleep duration may affect motivation and energy levels for physical activity, psychological support and motivational strategies can be part of the intervention to help patients overcome barriers related to sleep duration.

As sleep patterns and requirements vary among individuals, researchers should emphasize the importance of individualized and designed sleep recommendations, as personal factors may influence the relationship between sleep and physical activity. By considering the impact of sleep duration on physical activity, interventions can be tailored more, potentially leading to greater success in promoting physical activity among patients.

Limitations and Future Directive

Studies within this thesis have important limitations. First, in Chapter 2, the population that examined the cross-sectional associations between physical activity, sedentary behavior, and sleep-related outcomes includes cancer survivors. While the research questions and findings are undoubtedly significant, the current thesis did not precisely aim to investigate sleep disorders in cancer survivors or following cancer remission. Given the critical and significant impact of sedentary time on overall health outcomes and precisely sleep patterns, it would be pertinent for future studies to replicate the study design within the context of prehabilitation, as current findings may not be generalized to the preoperative period.

Second, our systematic review focuses on exercise interventions to improve sleep disturbances. Given the scarcity of knowledge on preoperative sleep, it might be more relevant to perform a scoping review that includes other interventions rather than exclusively concentrating on the preoperative exercise interventions. For instance, the beneficial impact of psychological treatments, such as cognitive behavioral therapy (CBT), which has been recommended as the first-line intervention for cancer-related insomnia (38, 39), has been widely investigated. Including such studies in a scoping review would help identify the types of available evidence and examine how research is conducted on this topic in addition to helping identify and analyze knowledge gaps prior to conducting a systematic review (40). Furthermore, such a review may also clarify the potential impact and benefits of the multimodal intervention approaches shown in our pilot RCT study.

Another limitation in our pilot randomized controlled trial (Chapter 4) was the choice of study arms. While incorporating control groups into these interventions has advantages, it may also present limitations. Due to the distinctive nature of the preoperative care period and the prehabilitation clinic, the close attention and care provided to patients and the emphasis on maintaining a healthy lifestyle may increase the risk of contamination bias between patient arm groups. In contrast, comparing two interventions, such as exercise and CBT treatment, could yield more pertinent information regarding the potential advantageous effects of each intervention on sleep. Moreover, patients experiencing insomnia or high anxiety and depression symptoms may respond differently to the interventions compared to other patients. Although we carefully adjusted our analyses for certain variables and confounders (smoking status, season,

and day of the week, hypnotic and anxiolytic medication), it might be more appropriate to have stricter inclusion criteria, such as including patients with insomnia symptoms (as indicated by a score ≥ 8 on the insomnia severity index [ISI]). This approach could also help identify and target the population that may benefit the most from our interventions.

A robust statistical plan and sample size determination based on pre-specified principles, methodologies, and procedures ensures adequate power to detect statistical significance (41). This aspect may not be entirely met in our current study protocol and might be a reason for the insignificant differences between groups detected in most analyses. Despite our efforts, the present research design may require further optimization to align with the rigorous randomized controlled trial study design fully. For instance, our moderators' analysis had a small sample size, low statistical power to address this question, and was not controlled for potentially unbalanced covariates (i.e., confounding). Moreover, the sample size determination did not consider the study design aspects of our ancillary analysis, which sought to explore the bidirectional sequences between sleep and physical activity (Chapter 5). For the real-time data approach, performing a sample size calculation specific to this study design might be more appropriate. Additionally, this study was constrained by collecting data on a daily life basis only for physical activity and sleep despite the presence of other interventions such as psychosocial and nutrition components. Another factor potentially limiting the generalizability of our findings is the exclusive inclusion of colorectal cancer patients; thus, our results may not be replicated or generalized to other cancer types or surgical procedures. Finally, although the significant impact of sedentary behavior on sleep outcomes were reported in Chapter 2, it is essential to note that we did not specifically examine or control for this factor in our pilot randomized controlled trial (RCT) study. Future research should consider incorporating assessments of sedentary behavior to provide a more comprehensive understanding of its role in sleep outcomes among cancer patients.

Despite the limitations outlined earlier, the strengths of this thesis are considerable and noteworthy. A key strength is a different approach to exploring sleep behaviors, employing various measurement methodologies and study designs, offering a comprehensive perspective. Additionally, focusing on a specific phase of the colorectal cancer trajectory provides valuable insights uniquely tailored to this critical period. Another significant strength lies in the relatively large sample size of 102 patients for a pilot study, which enhances the reliability and

generalizability of the findings within the colorectal cancer population. These strengths collectively contribute to the quality and significance of the research presented in this thesis.

Given the complex relationship between sleep and physical activity, investigating the role of psychological factors, such as anxiety and depression, or physiological factors, such as pain and fatigue, would be relevant. Furthermore, the results highlight the need for individualized approaches to prehabilitation interventions, given the observed heterogeneity within patients, as some patients may respond differently to an intervention or have advantages from some interventions over others. The study's conclusions highlight the importance of monitoring behavioral aspects in patients' day-to-day lives. By considering the complex interplay between behaviors in patients' daily lives, healthcare providers can develop and refine targeted prehabilitation interventions that address patients' individual needs and preferences, ultimately supporting their postoperative recovery and overall well-being. In the prehabilitation context, progressively moving beyond approaches focused on average group responses toward individualized and contextualized may promote precision initiatives in the health behavior change domain (42, 43). Future studies that aim to develop prehabilitation interventions should adopt different approaches that better take individual variability into account, such as Ecological momentary assessment (EMA) and idiographic approach (i.e., “N-of-1” study) (42).

Conclusion and Perspectives

In conclusion, we have established the relationships between sleep behaviors, physical activity, and prehabilitation interventions in cancer patients. This thesis advances the current state of knowledge by examining these issues from various methodological approaches and perspectives. Notably, we have demonstrated that more intense physical activity, such as MVPA, can result in more restorative sleep despite shorter sleep periods. In contrast, a sedentary lifestyle is associated with shorter sleep durations, independent of the time spent in MVPA. The systematic review shows a limited improvement of the exercise intervention alone on sleep quality and disturbances in cancer patients during the preoperative period. The research also illustrates the significance of multimodal prehabilitation, which incorporates exercise, nutrition, and psychological aspects, in improving sleep quality among colorectal cancer patients preoperatively, and sleep duration after surgery, particularly for sub-groups with limited mobility and elevated anxiety levels. Significantly, the research also underscores a complex reciprocal connection between physical activity and sleep; sleep duration can substantially influence the following day's physical activity levels. This emphasizes the importance of considering sleep patterns in planning interventions to increase physical activity, as optimized sleep duration could promote active participation and maximize the benefits of exercise programs. Integrating personalized sleep assessments and tailored interventions within the multimodal prehabilitation approach can enhance sleep patterns and physical activity levels. This contributes to the overarching goal of improving health outcomes for cancer patients set for surgery. The findings from this research underscore the significance of tailored and comprehensive interventions in optimizing sleep and physical activity patterns among cancer patients.

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