

Factors Associated with Sleep Wake Disturbances in Adult Survivors
of Childhood Brain Tumors

A DISSERTATION SUBMITTED TO THE FACULTY OF THE GRADUATE
SCHOOL OF THE UNIVERSITY OF MINNESOTA
BY

Roxanna Gapstur

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE
DEGREE OF DOCTOR OF PHILOSOPHY

Advisor: Cynthia Gross, PhD

February, 2010

©2010 by Roxanna Gapstur

All rights reserved

Acknowledgements

I would like to acknowledge my dissertation committee for their guidance during this process.

Factors Associated with Sleep Disturbances

Dedication

This dissertation is dedicated to my family for all their love and support.

ABSTRACT

Sleep disturbances impact physical and mental health in brain tumor survivors, leading to sub-optimal participation in life activities. Technological advances in cancer treatments have improved five-year survival rates for childhood brain tumors to nearly 75%. With growing numbers of brain tumor survivors, mitigation of serious late sequelae from cancer treatments becomes increasingly important.

This study evaluated factors associated with sleep quality in adult survivors of childhood brain tumors and a population-based comparison group. The Cancer-Related Factors Affecting Sleep model developed by Vena et al. (2004) provided a conceptual framework for this study. Participants were recruited from the University of Minnesota and St. Jude Children's Research Hospital clinical treatment databases. The comparison group was recruited from a national mailing database service.

The first aim evaluated differences in global and component sleep quality between survivors and the comparison group. Using multiple variable linear regression and logistic regression, no differences in global sleep quality were detected between survivors and the comparison group. However, survivors were two and a half times more likely than the comparison group to have longer sleep latency, taking on average 33 minutes to fall asleep after going to bed. Females in both groups reported worse sleep quality, including more daytime dysfunction, and risk of poor sleep (PSQI global scores ≥ 10).

The second aim evaluated cancer treatment effects on sleep quality among brain tumor survivors. Tumor location and surgery were not significant predictors of sleep however, radiation to the hypothalamus approached significance among survivors for longer sleep latency. Exploratory analyses identified radiation to the hypothalamus and age at diagnosis < 5 as predictors of lower vigor subscale scores on the POMS. No treatment variables predicted abnormal BSI scores among the survivors.

The third aim evaluated a path model proposing post-treatment variables including obesity, depression, and fatigue as mediators of global sleep quality. In addition, gender, age, radiation to the hypothalamus and age at diagnosis < 5 were included in the model as exogenous variables. Obesity and depression were not strong predictors of global sleep quality however, gender and age at diagnosis < 5 predicted higher fatigue subscale scores. Fatigue itself significantly predicted higher (worse) global sleep quality scores within the model.

This study revealed new and surprising information about sleep latency in brain tumor survivors. It also confirmed known associations with sleep and gender and a strong relationship between fatigue and sleep quality. Given these findings, future studies can begin to focus on identifying additional factors impacting sleep in these survivors.

Table of Contents

Page No

ABSTRACT..... ii

LIST OF TABLES.....vii

LIST OF FIGURES.....ix

CHAPTER I. BACKGROUND..... 1

 A) Statement of the problem..... 1

 B) Rationale for the study..... 2

 C) Study overview.....3

CHAPTER II. LITERATURE REVIEW.....6

 A) Function of sleep..... 6

 B) Homeostatic and circadian sleep regulation mechanisms..... 7

 C) Neuroendocrine and metabolic functions affecting sleep..... 7

 D) Damage to the hypothalamus and sleep..... 9

 i. Age at diagnosis, tumor location, and radiation treatment

 ii. Craniopharyngiomas, melatonin deficiencies, obesity, and sleep

 iii. Excessive daytime sleepiness in non-craniopharyngioma survivors

 iv. Fatigue, depression, and sleep

CHAPTER III. CONCEPTUAL FRAMEWORK..... 20

 A) Factors associated with sleep wake disturbances..... 23

 i. Demographic factors

 ii. Psychological factors

 iii. Disease-related factors

 iv. Treatment and post –treatment factors

 B) Study Hypotheses..... 24

 i. Aim I hypotheses

 ii. Aim II hypotheses

Factors Associated with Sleep Disturbances

iii. Aim III hypotheses

CHAPTER IV. METHODS	27
A) Study design.....	27
B) Population.....	27
C) Recruitment.....	28
D) Data Collection Procedures and Instruments.....	29
E) Study variables.....	33
F) Statistical analysis.....	35
i. Descriptive analysis	
ii. Bivariate analysis	
iii. Multiple variable linear regression and logistic regression	
iv. Path analysis	
CHAPTER V. RESULTS	42
A) Aim I: Global Sleep Quality-All Subjects.....	42
i. Descriptive statistics	
ii. Analysis of research hypotheses H_{A-1}	
iii. Analysis of research hypotheses H_{A-1a}	
iv. Analysis of research hypotheses H_{A-1b}	
v. Analysis of research hypotheses H_{A-1c}	
B) Aim II: Treatment Factors and Sleep-Survivors.....	59
i. Descriptive statistics	
ii. Analysis of research hypotheses H_{A-2a}	
iii. Analysis of research hypotheses H_{A-2b}	
iv. Analysis of research hypotheses H_{A-2c}	
C) Aim II: Exploratory Analyses-POMS and BSI in Survivors.....	70
i. Tumor Location and POMS	
ii. Surgery and POMS	
iii. Radiation to Hypothalamus and POMS	

Factors Associated with Sleep Disturbances

- iv. Tumor Location, Surgery, Radiation and BSI
- D) Aim III: Obesity, Fatigue, Depression and Sleep Quality-Survivors.....80
 - i. Descriptive statistics
 - ii. Analysis of research hypotheses H_{A-3}
- CHAPTER VI. DISCUSSION AND CONCLUSIONS.....95**
 - A) Aim I: Global Sleep Quality-All Subjects.....95
 - B) Aim II: Treatment Impact on Sleep-Survivors.....98
 - C) Aim II: Exploratory Analyses-POMS and BSI-Survivors.....99
 - D) Aim III: Path Model Analysis: Post-Treatment Factors and Sleep.....101
 - E) Fit with the Vena Model.....102
 - F) Strengths and limitations.....105
 - G) Implications for nurses and recommendations for future research.....106
- REFERENCES.....108**
- APPENDIX 1: ST. JUDE IRB NOTIFICATION.....124**
- APPENDIX 2: UNIVERSITY OF MINNESOTA IRB NOTIFICATION.....125**
- APPENDIX 3: MEDICAL RECORD ABSTRACTION FORM.....126**

List of Tables	Page No.
Table 1. Sleep Terms and Definitions.....	4
Table 2. Home Visit Data Collection for Secondary Analysis.....	30
Table 3. Study variables.....	34
Table 4. Path Analysis Fit Indices.....	40
Table 5. Participant vs. Non-participant Characteristics-Survivors.....	43
Table 6. Education, Employment, Marital Status, and Living Situation.....	47
Table 7. Body Mass Index-All Subjects.....	48
Table 8. Sleep Medication Use-All Subjects.....	49
Table 9. Bivariate Associations-PSQI Global and Subscale Scores-All Subjects....	50
Table 10. Bivariate Logistic Regression-PSQI \geq 10-All Subjects.....	51
Table 11. Multiple Variable Linear Regression-PSQI Global Score and Subscales-All Subjects.....	53
Table 12. Multiple Variable Logistic Regression-PSQI \geq 10-All Subjects.....	54
Table 13. Bivariate Logistic Regression-Minutes Before Falling Asleep-All Subjects.....	56
Table 14. Multiple Variable Logistic Regression-Minutes Before Falling Asleep-All Subjects.....	57
Table 15. Disease and Treatment Characteristics-Survivors Only.....	60
Table 16. Bivariate Associations-PSQI Global and Subscale Scores-Survivors Only.....	63

Factors Associated with Sleep Disturbances

Table 17. Bivariate Logistic Regression-PSQI \geq 10 & Minutes Before Falling Asleep-Survivors only.....	65
Table 18. Multiple Variable Linear Regression-PSQI Global Score and Subscale Scores-Survivors only.....	68
Table 19. Multiple Variable Logistic Regression-PSQI \geq 10 & Minutes Before Falling Asleep-Survivors Only.....	69
Table 20. Bivariate Associations-POMS Global and Subscale Scores-Survivors Only.....	71
Table 21. Multiple Variable Linear Regression-POMS Global and Subscale Scores-Survivors only.....	73
Table 22. Bivariate Associations-BSI Global and Subscale Scores-All Subjects.....	74
Table 23. Bivariate Association-BSI Global and Subscale Scores-Survivors Only.....	76
Table 24. Multiple Variable Linear Regression-BSI Global and Subscale Scores-All Subjects.....	78
Table 25. Multiple Variable Linear Regression-BSI Global and Subscale Scores-Survivors Only.....	79
Table 26. Means and Standard Deviations-Path Model Variables-Survivors Only...	81
Table 27. Standardized Regression Weights-Path Model A (1)-Survivors Only.....	85
Table 28. Standardized Regression Weights-Path Model A (2)-Final Model.....	87
Table 29. Standardized Indirect Effects-Final Model.....	88
Table 30. Standardized Total Effects-Final Model.....	88
Table 31. Correlation Estimates prior to Path Model Analysis-Survivors Only.....	89
Table 32. Reproduced Path Model Correlation Estimates-Survivors Only.....	89
Table 33. Summary of Path Model Results-All Models.....	90

List of Figures	Page No
Figure 1. Brain Structures and Hypothalamus.....	10
Figure 2. Vena et al's (2004) Model of Cancer-Related Factors Affecting Sleep	21
Figure 3. Conceptual Model and First Path Model of Factors Affecting Sleep in Brain Tumor Survivors.....	22
Figure 4. Second Path Model Indicating Depression as the Outcome Variable.....	41
Figure 5. Study Recruitment and Participation.....	45
Figure 6. Fully Identified Path model A (1)-PSQI Global Score.....	91
Figure 7. Path Model A (1).....	92
Figure 8. Path Model B (1).....	93
Figure 9. Path Model A (2)-Final Revised Model.....	94

CHAPTER I. BACKGROUND

A) Statement of the problem

In 2009, the American Cancer Society estimates 1.479 million people will be diagnosed with cancer. Among those with a cancer diagnosis, 22,738 malignant brain tumors will be diagnosed in the United States, with 3,750 of these in children less than age 20. These tumors comprise 15 % to 20% of all malignancies in childhood and adolescence (American Brain Tumor Association, 2009; CBTRUS, 2005).

Although brain tumors are the second leading cause of death in children with cancer, technological advances in radiation therapy and aggressive chemotherapy regimens have improved the five-year relative survival rates in developed countries to 74% (Finlay, Erdreich-Epstein, & Packer, 2007; Jemal, Siegel, Ward, Hao, Xu & Thun, 2009).

Therefore, the population of adult survivors of childhood brain tumors continues to grow, approaching 40,000 individuals in the United States alone.

With increasing numbers of these survivors, there is a need to mitigate serious late sequelae from cancer treatments. These sequelae include neuropsychological deficits, endocrine deficiencies, growth delays, obesity, osteonecrosis, cardiovascular disease, pulmonary disease, second malignancies, late mortality, and infertility. As a late effect of treatment, sleep disturbances impact physical and mental health in brain tumor survivors (Armstrong, Liu, Yasui, Huang, Ness, Leisenring, et al., 2009; Diller, Chow, Gurney, Hudson, Kadin-Lottick, Kawashima et al., 2009; Gurney, Ness, Stovall, Wolden, Punyko,

Factors Associated with Sleep Disturbances

Neglia et al., 2003; Robison, Green, Hudson, Meadows, Mertens, Packer, et al., 2005).

Sleep research in this group of survivors is limited, and interventions identified for the specific causes of sleep disturbances are in their infancy.

B) Rationale for the study

In follow up studies of brain tumor survivors, sleep impairment negatively impacts several quality of life domains, including the ability of survivors to participate in life events such as school, athletics, and social activities (Anderson, Rennie, Zeigler, Neglia, Robison, & Gurney, 2001; Hudson, Mertens, Yasui, Hobbie, Chen, & Gurney, et al., 2003; Mostow, Byrne, Connelly, & Mulvihill, 1991; Pelletier, Verhoef, Khatri, & Hagen, 2002). There is evidence to suggest that survivors with particular risk factors may suffer more severe late effects from cancer treatments, including sleep disturbances. This study will investigate the differences in self-reported sleep quality in adult survivors of childhood brain tumors and a population-based comparison group, as well as look for other factors associated with sleep disturbances in childhood brain tumor survivors.

Survivors with craniopharyngioma tumors, a benign brain tumor, appear to have one of the highest rates of sleep disturbances among individuals with brain tumors. The causes of these sleep disturbances are multifaceted, but likely include damage to the hypothalamus, the sleep center of the brain. In addition, those individuals who have required higher doses of radiation therapy at younger ages, are at risk for developing more severe late effects from their cancer treatments (Chin & Maruyama, 1984). Other evidence indicates the sleep patterns of brain tumor survivors may be affected by neuro-

Factors Associated with Sleep Disturbances

endocrine disturbances, fatigue, and depression (Anderson, Getto, Mendoza, Palmer, Wang, Reyes-Gibby, et al., 2003; Fava, 2004; Piccinelli & Wilkinson, 2000). Evaluating factors associated with sleep wake disturbances in brain tumor survivors is important for targeting interventions to causes in order to improve sleep quality.

C) Study overview

Reported sleep disturbances in brain tumor survivors include insomnia, excessive daytime sleepiness, limb movement disorders, sleep apnea, and increased nightmare awakenings (di Gennaro, Autret, Mascia, Onorati, Sebastiano, & Quarato, 2004; Marcus, Trescher, Halbower, & Lutz, 2002; Szucs, Bodizs, Barsi, & Halasz, 2001; Zembelis, Paparrigopoulos, & Soldatos, 2002). This study will evaluate factors associated with self-reported sleep quality in adult survivors of childhood brain tumors and a population-based comparison group. This will be accomplished by determining the impact of several variables on the Pittsburgh Sleep Quality Index (PSQI) self-reported global and component sleep scores of brain tumor survivors. Variables that will be evaluated include tumor location and radiation/surgical treatment involving the hypothalamus, younger age at diagnosis, current age, gender, body mass index (BMI) indicating obesity, depression scores, and fatigue scores. Particular sleep patterns to be evaluated include excessive daytime sleepiness, sleep efficiency, and sleep latency, indicating insomnia. See Table 1 for sleep terms and definitions.

Factors Associated with Sleep Disturbances

Table 1.
Sleep Terms and Definitions

Sleep Terms	Sleep Definitions
Arousal	<ul style="list-style-type: none">• A sudden change from deeper sleep to a lighter stage of sleep or to wakefulness
Cataplexy	<ul style="list-style-type: none">• A brief, abrupt loss or weakness of skeletal muscle tone without any loss of consciousness; commonly precipitated by sudden emotional stimulus
Circadian Rhythm	<ul style="list-style-type: none">• A genetically programmed sleep-wake rhythm with a 24-hour cycle
Daytime Sleepiness or Dysfunction	<ul style="list-style-type: none">• The inability to stay awake and alert during the major waking episodes of the day, resulting in onset of drowsiness and sleep
Entrainment	<ul style="list-style-type: none">• Synchronization of the circadian rhythm using a biological time cue
Hypersomnia	<ul style="list-style-type: none">• Excessive daytime sleepiness (EDS) occurring all or nearly all of the time.
Insomnia	<ul style="list-style-type: none">• Difficulty in initiating sleep or maintaining sleep
Periodic Limb Movement Disorder	<ul style="list-style-type: none">• Disorder characterized by periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep
Sleep Architecture	<ul style="list-style-type: none">• The stages and cycles of sleep
Sleep Efficiency	<ul style="list-style-type: none">• The ratio of total sleep time to time in bed (>85% is considered normal)
Sleep Hygiene	<ul style="list-style-type: none">• Specific practices that promote sleep
Sleep Latency	<ul style="list-style-type: none">• The time from lights out until the onset of sleep (< 30 minutes is normal)
Total Sleep Time	<ul style="list-style-type: none">• The total amount of actual sleep in the sleep episode

Factors Associated with Sleep Disturbances

Primary aim

To identify differences in self-reported sleep quality in adult survivors of childhood brain tumors and a population-based comparison group.

Secondary aim

Identify variables associated with sleep wake disturbances in survivors of childhood brain tumors including the following:

- Tumor location involving the hypothalamus
 - Treatment effects (radiation and surgery)
 - Age less than 5 years at diagnosis
 - Current age
 - Female gender
 - Obesity (Body Mass Index ≥ 30)
 - Brief Symptom Inventory (BSI) Depression Score
 - Profile of Mood States-Brief (POMS) Fatigue Subscale Score
- Hypotheses:
 - Self-report of poor sleep quality will be greater in adult survivors of childhood brain tumors compared to a population-based comparison group.
 - Tumor location or treatment (radiation, surgery, or both) in or near the hypothalamus, younger age at diagnosis, and female gender will be associated with greater self-report of sleep wake disturbances.
 - Post-treatment factors (obesity, fatigue, and depression) are associated with greater sleep-wake disturbances in adult survivors of childhood brain tumors.

CHAPTER II: LITERATURE REVIEW

A) Function of sleep

The importance of adequate sleep for humans and animals cannot be over-stated.

Theories postulated about the function of sleep in human beings include mental and physical restoration (including immune processes, natural killer cell activity, synaptic efficacy), thermoregulatory set points, brain restorative effects, and memory consolidation (Buzsaki, 1998; Sejnowski & Destexhe, 2000; Pilcher & Huffcutt, 1996; Vena, Parker, Cunningham, Clark, & McMillan, 2004). Sleep deprivation affects survival in both human and animal studies (Rechtschaffen, Bergmann, Everson, Kushida, & Gilliland, 2002; Spiegel, Leproult, & van Cauter, 1999), as energy producing systems in the brain dissipate, with severely decreased brain glycogen reserves and depletion of ATP levels (Saper, Scammell, & Lu, 2005). Chronic sleep deprivation produces body temperature irregularities, increased metabolism, decreased functioning of hypothalamic neurons, immune dysfunction, and eventually, death (Rechtschaffen & Bergmann, 2002).

In cancer patients, Mormont, Waterhouse, Bleuzen, Giacchetti, Jami, & Bogdan, et al., (2000) researched the rest/activity rhythms of colon cancer patients using wrist actigraphy during chrono-modulated chemotherapy cycles. Colon cancer patients with poor circadian rhythmicity, indicating altered rest/activity rhythms, had a five-fold risk of dying within two years compared with patients who had better circadian rhythmicity.

B) Homeostatic and circadian sleep regulation mechanisms

Three neurological processes coincide to promote regulation of sleep. These include a homeostatic process mediating the rise of sleepiness and its dissipation during sleep, a circadian clock-like mechanism determining alternate periods of sleep and wake, and an ultradian process during sleep episodes alternating between non-REM (rapid eye movement) and REM sleep (Borbely & Achermann, 1999). The suprachiasmatic nuclei (SCN) in the pre-optic hypothalamus generates wake-promoting signals counteracting the increase in sleep propensity associated with sustained wakefulness, and encourages sleep at night by generating hypnotic signals (Dijk & Czeisler, 1995; Turek, 2004; Turek, Dugovic, & Laposky, 2004). The SCN is composed of a multi-oscillatory structure in which individual neurons are synchronized to generate the overt circadian rhythm (Kunz & Achermann, 2003). A detailed model of SCN cells genetically controlled to provide circadian rhythmicity in humans has been established (Wager-Smith & Kay, 2000). Neurons in the SCN fire in a 24-hour cycle within a transcriptional-translational loop, persisting even when neurons are in cell culture (Czeisler, Duffy, Shanahan, Brown, Mitchell, Rimmer, et al., 1999; Reppert & Weaver, 2002). The SCN is re-set by light during the day and melatonin secretion at night.

C) Neuroendocrine and metabolic functions affecting sleep

Sleep is a complex process associated with rhythmic physiological changes in hormone release, thermoregulatory mechanisms, regulation of breathing, cardiovascular control, convulsive thresholds, and gastrointestinal alterations (Taheri, Zeitzer, & Mignot, 2002).

Factors Associated with Sleep Disturbances

In addition, adrenergic signaling from central nervous system neurotransmitters, such as dopamine and growth hormone, play a role in the maintenance of waking and the regulation of REM sleep (Ouyang, Hellman, Abel, & Thomas, 2004). A key component of the neuro-endocrine regulation of sleep is melatonin secretion. Melatonin is driven by the light-sensitive pacemaker located in the SCN (Shanahan & Czeisler, 1991) and functions to stabilize circadian rhythms, core temperature, and sleep-wake rhythms. It is released from the pineal gland at night and peaks concurrently with temperature nadir and sleepiness (Akerstedt, Froberg, Friberg, & Wetterberg, 1979). Changes in the sleep EEG parallel the melatonin rhythm (Dijk, Shanahan, Duffy, Ronda, & Czeisler, 1997). The melatonin profile, when examined along with recordings of temperature and sleep activity, provides diagnostic assistance for detection of some circadian rhythm sleep disorders (Claustrat, Brun & Chazot, 2005).

Silber & Rye (2001) discovered two peptides, hypocretin 1 and 2, thought to be related to sleep regulation in lateral and posterior hypothalamic cells. During waking, hypocretins promote arousal through excitation of neurotransmitters in the brain which send homeostatic and circadian signals to peripheral organs. Destruction of hypocretin neurons contributes to the development of narcolepsy, a disorder manifested by extreme hyper-somnia (Selbach & Haas, 2006; Taheri, et al., 2001).

D) Damage to the hypothalamus and sleep

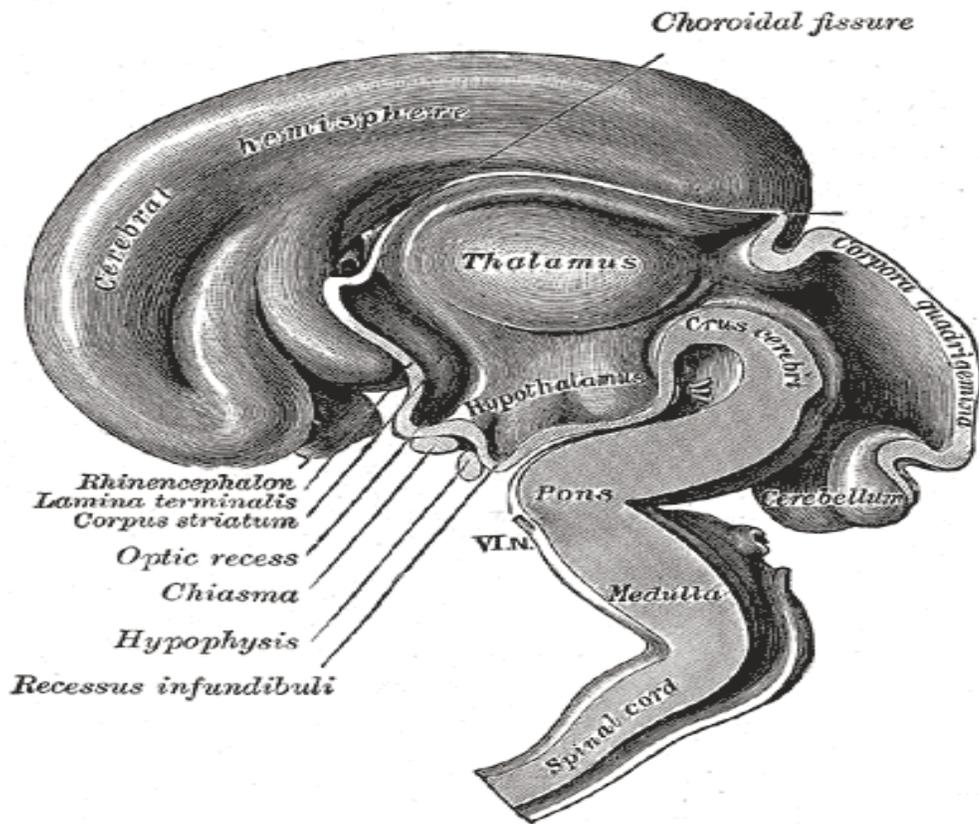
A key contributor impacting sleep-wake disturbances in brain tumor survivors is destruction of the hypothalamus, a radio-sensitive sleep-wake structure susceptible to long-term damage (Constine, Woolf, Cann, Mick, McCormick, Raubertas, 1993; Heikens, Michiels, Behrendt, Endert, Bakker, & Fliers, 1998). The hypothalamus may sustain damage due to the type of tumor and tumor location, as well as, cancer treatments impacting this area of the brain. Cranial radiation therapy alters the hypothalamo-pituitary axis, with slow, progressive deterioration creating associated hormonal abnormalities (Constine, et al., 1993), neuro-cognitive, sensory, and motor defects, as well as, impaired sleep patterns (Fouladi, Gilger, Kocak, Wallace, Buchanan, Reeves, et al., 2005).

i. Age at diagnosis, tumor location, and radiation treatment

Tumor location affects the type and severity of sequelae expected after a brain tumor diagnosis. Typically, brain tumors are categorized anatomically as supra-tentorial, infra-tentorial, or hypothalamic/parasellar.. In children, about half of tumors arise in the supra-tentorial and hypothalamic regions, which tend to result in greater morbidity than infra-tentorial tumors (Anderson, Rennie, et al., 2001). Hypothalamic tumors are more likely to contribute to impaired sleep wake rhythms (www.Wikipedia.com) (Figure 1).

Factors Associated with Sleep Disturbances

Figure 1. Brain Structures including Hypothalamus (www.Wikipedia.com)



Factors Associated with Sleep Disturbances

During initial cancer treatment, sleep-wake disturbances in adults and children with brain tumors are associated with radiation therapy. There is evidence of a “somnolence syndrome” emerging in approximately 60-75% of children with acute lymphoblastic leukemia or non-Hodgkin lymphoma, treated with prophylactic radiation to the central nervous system. In addition, adults with primary brain tumors have been found to experience the same syndrome. Approximately four to six weeks after initial treatment with cranial radiation, the symptoms of sleepiness, abnormal sleep/wake schedules, anorexia, lethargy, fever, and cataplexy appear. The syndrome is dose-dependent with an indicated symptom threshold of 3500 cGy and radiation fractions given over shorter time periods. Use of steroids during therapy has demonstrated improvement in the syndrome (Faithfull, 1991; Faithfull & Brada, 1998; Parker, Malpas, Sandland, Sheaff, Freeman, & Paxton, 1978; Uzal, Ozyar, Hayran, Zorlu, Atahan, & Yetkin, 1998). The long-term impact of this acute syndrome is unknown, however damage to the specialized cells which stimulate melatonin production or hypocretin proteins, or to suprachiasmatic nuclei may be responsible for long term loss of function.

Young children with CNS tumors often require aggressive cancer treatments in order to achieve a cure. Almost 20% of CNS tumors in children occur in those younger than 3 years old (American Brain Tumor Association, 2009). Use of chemotherapy regimens is common in these young children in order to delay radiation treatment and preserve neuro-cognitive functioning (Packer, MacDonald, & Vezina, 2008). However, despite the best efforts, treatment is often needed when the brain is still undergoing maturation.

Factors Associated with Sleep Disturbances

Significant differences in neuro-cognitive effects have been detected between children who received no radiation therapy, localized radiation therapy, or full cranio-spinal irradiation. Although sample sizes are small, all studies examining age at treatment have demonstrated significantly greater deficits in children who receive treatment with cranio-spinal irradiation at less than 5 years old, or in those who have supra-tentorial or hemispheric tumors (Fouladi, et al., 2005). The late effects from treatment include the need for special education, and low IQ scores due to neuro-cognitive, motor, and sensory defects, such as blindness (Chin & Maruyama, 1984; Heikens, Michiels, Behrendt, Endert, Bakker, & Fliers, 1998; Packer, Gurney, Punyko, Donaldson, Inskip, Stovall, et al., 2003).

ii. Craniopharyngiomas, melatonin deficiencies, obesity, and sleep

While not malignant, craniopharyngiomas arise in the hypothalamic-pituitary axis and are treated with surgical excision, making these patients an excellent model in which to study the effects of damage to the hypothalamus. Up to 95% of craniopharyngioma patients have significant hypothalamic pituitary damage related to the tumor itself. This damage results in irregular melatonin secretion, increased body mass index (BMI), secondary narcolepsy, and excessive daytime sleepiness. Without adequate supplies, or sufficient rhythmic secretion of this important neuro-endocrine hormone, these survivors suffer various sleep abnormalities.

Factors Associated with Sleep Disturbances

Hypothalamic obesity is an intractable weight gain syndrome noted to occur in survivors with brain tumors whose tumor or treatment result in damage to the hypothalamus. This damage is subsequent to surgical resection or radiation treatment to the hypothalamus, and results in further risks for sleep disorders, such as sleep apnea. Researchers from St. Jude Children's Research Hospital identified age at diagnosis, radiation dose to the hypothalamus, and tumor location as associated with risk for obesity after diagnosis of a brain tumor (Lustig, Post, Srivannaboon, Rose, Danish, Burghen et al., 2003). A tendency toward higher body mass index (BMI) in these survivors, compounds impaired daytime alertness and insomnia, and negatively influences brain tumor survivors' ability to engage in usual activities like school or work. In 921 survivors with a variety of brain tumors, Gurney, et al., (2003) discovered the BMI distribution of survivors did not differ significantly from population norms. However, females with younger age at diagnosis and radiation to the hypothalamus were more likely to experience obesity as long-term sequelae. In a follow up report, a review of 7195 childhood cancer survivors from the Childhood Cancer Survivor Study (CCSS) demonstrated that the BMI distribution of brain tumor survivors did not differ from population norms, but females diagnosed at younger age and treated with cranial irradiation were at risk for obesity (Meacham, Gurney, Mertens, Ness, Sklar, Robison & Oeffinger, 2005). Patients with craniopharyngioma were excluded from the cohort.

German researchers evaluated a group of patients with hypothalamic pilocytic astrocytomas and craniopharyngiomas, comparing them to healthy controls. They

Factors Associated with Sleep Disturbances

reported craniopharyngioma survivors with severe obesity (BMI Standard Deviation Scale > 4) had higher scores on the Epworth Sleepiness Scale (>10) than normal weight or less obese survivors. Decreased nocturnal melatonin levels correlated with excessive daytime sleepiness and obesity (Muller, Handwerker, Wollny, Faldum, & Sorenson, 2002).

More recent studies with craniopharyngioma survivors have indicated that damage to the hypothalamus results in significant sleep problems. Higher scores on the Epworth Sleepiness Scale, with corresponding obesity, and lower quality of life were reported by Poretti, Grotzer, Ribi, Schonle, & Boltshauser (2004). Similarly, shortened sleep periods and multiple awakenings with a decreased nighttime melatonin production were observed in a 14-year-old boy with a pineal tumor (Etzioni, Luboshitzky, Tiosano, Ben-Harush, Golsher, & Lavie, 1996). In one study of craniopharyngioma survivors, the frequent awakenings were severe enough to be classified as a Disorder of Maintaining Sleep according to the Association of Sleep Disorders Centers 1979 Classifications (Palm, Nordin, Elmqvist, Blennow, Persson, & Westgren, 1991).

A recent report from the Children's Cancer Survivors Study (CCSS) with a large sample of 2,645 childhood cancer survivors, including 398 with a variety of childhood brain tumors, identified 16.7% of the total sample self-reporting disrupted sleep on the Pittsburgh Sleep Quality Index (PSQI) and 14% with increased daytime sleepiness. Obese survivors with any cancer diagnosis were more likely to experience daytime

Factors Associated with Sleep Disturbances

sleepiness and sleep disruptions. Those survivors with soft tissue sarcoma reported more significant sleep disturbances than survivors with other cancer diagnoses. Survivors reporting sleep disturbance and daytime sleepiness had lower physical functioning, role performance, and general health scores. No relationship between radiation therapy dose and sleep disturbance was detected in the brain tumor survivors in their sample, although patients reported more fatigue if radiation therapy was part of their cancer treatment (Mulrooney, Ness, Neglia, Whitton, Green, Zeltzer et al., 2008).

Intervention studies with small sample sizes have supported the hypotheses implicating hypothalamic injury with decreased nocturnal melatonin levels as a predictor of excessive daytime sleepiness. Muller, Handwerker, Gebhardt, Faldum, Emser, Kolb, et al (2006), administered a 6 mg evening melatonin substitution to seven adult and three childhood survivors of childhood craniopharyngioma and pilocytic astrocytoma experiencing the most severe excessive daytime sleepiness from their 2006 study. All ten patients had Epworth Sleepiness Scale scores > 10 . In addition, the severely obese patients had lower melatonin concentrations at nighttime than other subjects. In all ten survivors receiving melatonin supplementation, the degree of excessive daytime sleepiness improved significantly based on activity diaries, administration of the Epworth Sleepiness Scale (median score on ESS 7 while under treatment), self-assessment questionnaires, and actigraphy. Others have also demonstrated improvement with melatonin supplementation or the use of stimulants (Etzioni, et al, 1996; Marcus, et al., 2002).

iii. Excessive daytime sleepiness in non-craniopharyngioma survivors

Retrospective research designs with brain tumor survivors have identified excessive daytime sleepiness from damage to hypocretin cells within the hypothalamus. These cells are crucial for arousal mechanisms, and loss of these specialized neurons may result in secondary narcolepsy. In 14 children with brain tumors evaluated at a sleep clinic, Rosen, Bendel, Neglia, Moertel, & Mahowald (2003) identified excessive daytime sleepiness exhibited by one or more of the following: 1) increase in total sleep time per 24 hours; 2) increased daytime naps previously discontinued at a younger age; 3) inability to awaken in the morning to begin usual activities; and 4) inability to remain awake during daytime activities, such as school. Children with the most severe sleepiness had evidence of hypothalamic-pituitary injury with deficiencies in both anterior and posterior pituitary hormones. A case report supporting the effects of hypocretin cell loss post-surgically describes excessive daytime sleepiness and increased REM sleep with a low cerebrospinal fluid hypocretin level in a 16-year-old girl after removal of a pilocytic astrocytoma (Arii, Kanbayashi, Tanabe, Ono, Nishino, & Kohno, 2001).

iv. Fatigue, depression, and sleep

A significant and often-reported symptom of cancer and its treatment is fatigue. More than 70% of cancer patients undergoing radiation and chemotherapy report feeling tired and weak (Winningham, M.L., Nail, L. M., Barton-Burke, M. B., Brophy, Cimprich, Jones et al., 1994). Fatigue has been identified by cancer survivors as one of the most

Factors Associated with Sleep Disturbances

distressing areas impacting quality of life (Langeveld, Ubbink, & Smets, 2000). It is described subjectively as excessive tiredness resulting in a lack of physical energy (Barton-Burke, 2006).

Since the etiology of fatigue is due to multiple factors, it is a difficult symptom to treat in patients and survivors. Typically cancer-related fatigue is not influenced by rest, and has been associated with disrupted sleep in breast cancer survivors (Broeckel, J., Jacobsen, P.B., Horton, J., Balducci, & Lyman, 1998) and childhood brain tumor survivors (Mulrooney, et al., 2008), as well as, depression in studies of adult cancer survivors (Bower, Ganz, Desmond, Rowland, Meyerowitz, & Belin, 2000).

How fatigue is related to sleep has not been determined in any group of cancer survivors. Recently, in a review by the Children's Cancer Survivors Study, which included childhood survivors with brain tumors as well as multiple other types of cancers, higher fatigue scores were associated with female gender, radiation therapy treatment, congestive heart failure, or pulmonary fibrosis in a large population of survivors. Those reporting more fatigue, and those with congestive heart failure, were more likely to be in the sleep-disturbed and daytime-sleepy groups. For those in the most fatigued, most sleep disturbed, and daytime sleepiness groups, the associated quality of life scores on the SF-36 were lower (Mulrooney, et al., 2008).

Factors Associated with Sleep Disturbances

Sleep dysfunction is experienced by 40% to 60% of outpatients with major depressive disorder (Armitage, 2000) and is part of the diagnostic criteria for depression (Diagnostic and Statistical Manual IV). Gender differences in depression are genuine and females in the general population report more appetite, fatigue and sleep disturbances than males (Piccinelli & Wilkinson, 2000). The relationships between sleep and depression are complex and include dysfunctional sleep patterns, like insomnia and daytime sleepiness. Between 10 and 20% of patients with Major Depressive Disorder, especially the atypical form, have excessive daytime sleepiness (Baldwin & Papakostas, 2006). However, more commonly insomnia is a risk factor for development of mood disorders (Ford & Kamerow, 1989) and also a symptom of depression, with 35% to 45% of patients with chronic insomnia experiencing a psychiatric disorder (Buysse, Reynolds, Hauri, et al., 1994). Typically, there is an inability to fall asleep at bedtime or night time awakenings. Poor sleep efficiency is often a component of poor sleep quality. In addition, insomnia can be exacerbated, or be the result of side effects of antidepressant treatment (Fava, 2004).

The link between depression, fatigue, and sleep disturbance may be complex in adult survivors of childhood brain tumors related to the many late treatment effects in this group. A cancer diagnosis can often lead to situational depression and require treatment with anti-depressants, at least for a period of time. In addition, late effects of cancer treatments can prohibit survivors' ability to achieve developmentally appropriate milestones, which may impact mood. Pelletier, Verhoef, Khatri, & Hagen (2002)

Factors Associated with Sleep Disturbances

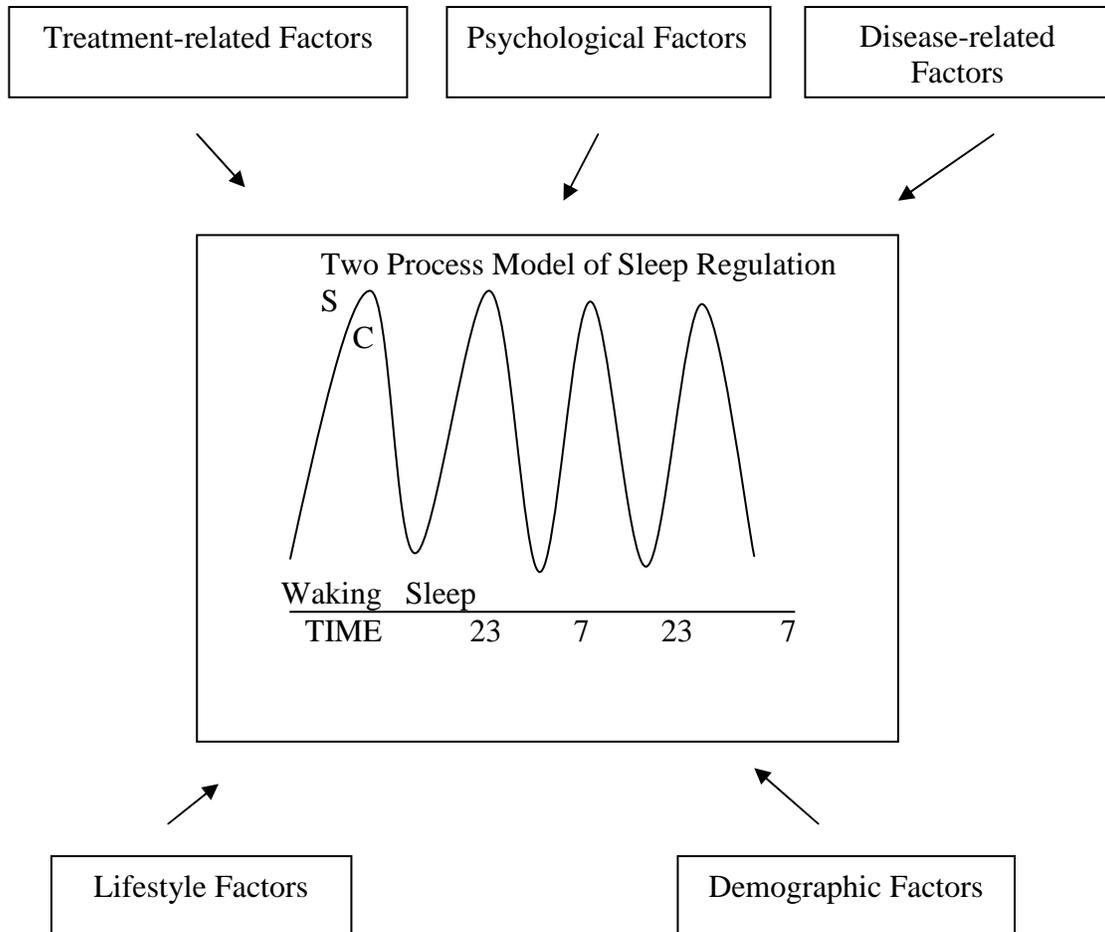
identified depression as the single most important predictor of quality of life in one cohort of brain tumor patients. They did not evaluate sleep in their study. In one recent study comparing adult patients with cancer, patients with depression, and community-dwelling adults, sleep disturbance was a significant predictor of severe fatigue in the cancer patient group. Both the cancer patients and the depressed patients reported frequent sleep disturbances (Anderson, Getto et al., 2003). In a study reporting psychological outcomes of 1,101 childhood survivors of brain tumors, survivors reported more symptoms of distress, especially on the depression subscale, than the sibling controls, after accounting for other risk factors, such as gender, socioeconomic status, and physical health. Female gender and low socioeconomic status were risk factors for distress among the survivors. Treatment intensity was not directly related to psychological outcomes in this sample (Zebrack, Gurney, Oeffinger, Whitton, Packer, Mertens, et al., 2004).

CHAPTER III. CONCEPTUAL FRAMEWORK

Treatment regimens for childhood brain tumors lead to late effects which impact multiple physical, cognitive, psychological, and social achievements. Given the paucity of sleep research in brain tumor survivors, the question of which factors predict sleep disturbance arises. In order to better elucidate the factors associated with sleep disturbances in brain tumor survivors, Vena, et al.'s (2004) Cancer-Related Factors Affecting Sleep Model was used as a framework for this study (Figure 2) (Berger, Parker, Young-McCaughan, Mallory, Barsevick, Beck, et al., 2005). The Vena et al., (2004) Model describes potential influences on sleep patterns in cancer patients including demographic, lifestyle, psychological, disease, and treatment-related factors. These factors and their relationship to homeostatic and circadian sleep processes are easily transferred to the survivor experience.

Factors Associated with Sleep Disturbances

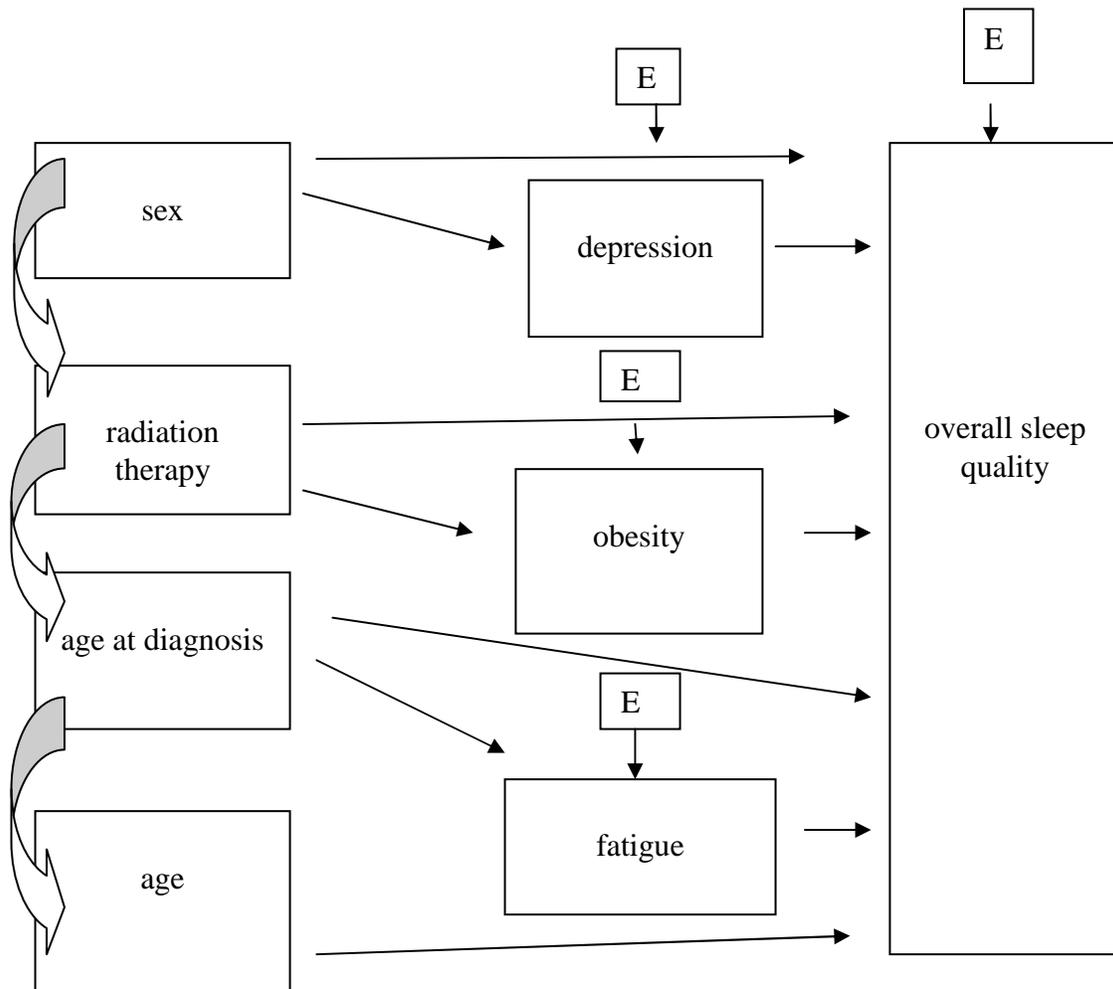
Figure 2. Vena et al., (2004) Model of Cancer-related Factors Affecting Sleep



Note. S = Process S (homeostatic sleep process). C = Process C (circadian rhythm process).

Factors Associated with Sleep Disturbances

Figure 3. Conceptual Model and First Path Model of Factors Affecting Sleep



This study proposes potential relationships among the variables identified by Vena and presents them in a conceptual model (Figure 3). This new model indicates a sleep experience impacted by the various associated factors. The categories and the proposed relationships identified for this study have clinical and empirical utility for childhood brain tumor survivors, as multiple disease and treatment-related factors continue long after acute treatment ends, affecting sleep-wake cycles.

Factors Associated with Sleep Disturbances

A. Factors associated with sleep wake disturbances

i. Demographic factors

Age less than 5 at diagnosis, current age, and female gender: As noted previously, there is evidence that younger age at diagnosis, while the brain is undergoing development, may affect the severity of sleep wake disturbances in brain tumor survivors. In addition, those survivors who have experienced radiation therapy tend to have more neuro-endocrine and neuro-cognitive deficiencies as time goes on suggesting the long-term impacts of radiation therapy are significant, with tissue damage and loss of function over time. Age and sex are known variables affecting sleep quality over the lifespan.

ii. Psychological factors

Depression: One of the cardinal symptoms of depression is disordered sleep patterns, especially insomnia or hyper-somnolence. Depression may be a result of biochemical changes in the brain or related to despair over effects of treatment, including poor functional status.

iii. Disease-related factors

Tumor location in or near hypothalamus: A brain tumor by itself can create damage to any area of the brain through invasion of cellular structures or increased pressure. In addition, the hypothalamus is the sleep center of the brain. It contains several kinds of specialized cells which are essential for homeostasis. Neuro-endocrine deficiencies,

Factors Associated with Sleep Disturbances

especially melatonin dys-regulation and lack of orexin-producing cells, from damage to the hypothalamus impacts sleep disturbances in patients and survivors with brain tumors.

iv. Treatment and post-treatment factors

Radiation, surgery, obesity, and fatigue: Radiation and surgery can damage the hypothalamus and pituitary gland leading to deficiencies of growth hormone and melatonin. These long-term neuro-endocrine deficiencies may contribute to obesity. Fatigue can be a lingering late effect of treatment with radiation therapy which continues into the survivorship period.

B) Study Hypotheses

All of the following sub-hypotheses will be tested individually in Bivariate analyses and then in multivariate and path analyses as follows:

i. Aim 1 and hypotheses

HA-1: The disease variable of brain tumor survivor is associated with significantly higher global scores on the Pittsburgh Sleep Quality Index, indicating greater sleep wake disturbances, than a population-based comparison group.

HA-1a: When compared to a population-based comparison group, adult survivors of childhood brain tumors will have higher scores on the sleep latency subscale of the Pittsburgh Sleep Quality Index.

HA-1b: When compared to a population-based comparison group, adult survivors of childhood brain tumors will have higher scores on the sleep efficiency subscale of the Pittsburgh Sleep Quality Index.

Factors Associated with Sleep Disturbances

HA-1c: When compared to a population-based comparison group, adult survivors of childhood brain tumors will have higher scores on the daytime dysfunction subscale of the Pittsburgh Sleep Quality Index.

ii. Aim 2 and hypotheses

HA-2: Among adult survivors of childhood brain tumors, the disease/treatment variable damage to the hypothalamus is associated with significantly higher global and subscale scores for sleep latency, sleep efficiency, and daytime dysfunction on the Pittsburgh Sleep Quality Index.

HA-2a: The disease variable, tumor location in or near the hypothalamus (hypothalamic) is associated with significantly higher global and subscale scores for sleep latency, sleep efficiency, and daytime dysfunction on the Pittsburgh Sleep Quality Index.

HA-2b: The treatment variable surgery is associated with significantly higher global and subscale scores for sleep latency, sleep efficiency, and daytime dysfunction on the Pittsburgh Sleep Quality Index, indicating greater sleep wake disturbances.

HA-2c: The treatment variable radiation to the hypothalamus (none, hypothalamus) is associated with significantly higher global and subscale scores for sleep latency, sleep efficiency and daytime dysfunction on the Pittsburgh Sleep Quality Index.

iii. Aim 3 and hypotheses

HA-3: Among adult survivors of childhood brain tumors, psychological, treatment, and post-treatment variables are associated with significantly higher global scores on the Pittsburgh Sleep Quality Index.

Factors Associated with Sleep Disturbances

HA-3a: Adult survivors of childhood brain tumors who were diagnosed at age less than 5 years, had radiation to the hypothalamus, and are female will have more obesity, depression, and fatigue thereby increasing the global scores on the Pittsburgh Sleep Quality Index.

HA-3b: Adult survivors of childhood brain tumors with elevated scores on the Brief Symptom Inventory depression subscale will have significantly higher global scores on the Pittsburgh Sleep Quality Index.

HA-3c: Adult survivors of childhood brain tumors with elevated scores on the POMS fatigue subscale, indicating current fatigue and lack of energy, will have significantly higher global scores on the Pittsburgh Sleep Quality Index.

HA-3d: Adult survivors of childhood brain tumors with a BMI ≥ 30 will have significantly higher global scores on the Pittsburgh Sleep Quality Index.

CHAPTER IV. METHODS

A) Study Design

This is a secondary analysis of a cross-sectional study comparing adult survivors of childhood brain tumors with a population-based comparison group. A cross-sectional design is excellent for generating hypotheses about association and in this instance, created the opportunity to study a group of individuals with a less common cancer diagnosis. This design allows the researcher to gather information on multiple associations between brain tumor survivorship and subsequent clinical outcomes of interest. The study employed a randomly sampled population-based comparison group with frequency matching of sex, age, and geographic location.

B) Population

The sample for this secondary analysis consists of 78 adult survivors of childhood brain tumors aged 18 years or older, randomly recruited from clinical databases (1970-2000) at the University of Minnesota Children's Hospital and St. Jude Children's Research Hospital. Cases were identified from a population of 423 potentially eligible participants treated at the above institutions.

The comparison group included 78 of 1247 individuals who were selected randomly by mailed invitation and frequency matched to tumor survivor's ages (18-29, 30-39, 40-49, 50-59 years), gender, and zip code.

C) Recruitment

Recruitment for the brain tumor subjects was conducted by mailing a letter to randomly selected individuals from the clinical treatment databases at the two study sites. The letter introduced the study and an outline of the assessment process. The letter also indicated that a study coordinator would contact the participant within one week to discuss the study and invite them to participate. If a telephone call did not result in initial contact within ten attempts or two weeks, a second letter and phone call was attempted. If a brain tumor subject declined participation, was determined ineligible, or was lost to follow-up after rigorous searching, the next subject on the list was recruited.

The comparison group was selected from lists of randomly selected names and residential addresses generated for same gender and age group individuals within the zip codes of eligible brain tumor survivors using Melissa Data Services (www.melissadata.com), a full mail support company, with a state-of-the art United States zip code database. They were recruited through a single mailed invitation with a return postcard to indicate interest/disinterest. There were no additional attempts to contact comparison group members. Both brain tumor subjects and comparison group members were reimbursed for participation. The University of Minnesota and St. Jude Institutional Review Boards for the protection of human subjects approved this study (Appendix 1 and 2).

Inclusion criteria required survivor participants to be 5+ year brain tumor survivors diagnosed at younger than 21 years of age, currently 18 years or older, understand

Factors Associated with Sleep Disturbances

English, treated at the University of Minnesota (Fairview) or St. Jude Children's Research Hospital, and diagnosed between 1970 and 2000. Exclusion criteria were: pregnant women or patients being treated for an active tumor.

D) Data Collection Procedures and Instruments

The brain tumor subjects and comparison group members were visited at home by a physical therapist or psychology examiner who obtained informed consent, determined final study eligibility, and completed the entire assessment. The physical therapist or a psychology examiner (degree in psych counseling) was trained to administer the tests by the primary investigator for the parent study. Intra- and inter-rater reliability was evaluated until 95% agreement was obtained between the psychology examiner, physical therapist, and the primary investigator. Standardized protocols were used for all measures. The assessment lasted two to four hours and included history/assessment, strength, balance, activity, performance, intelligence, symptom, environment, quality of life, pain, sleep and mood evaluations. The home visit helped allay participation bias related to poor physical function and inability to travel to the hospital for assessment. Table 2 summarizes the data collection instruments for this secondary analysis. Following the table is a description of the data collection instruments.

Factors Associated with Sleep Disturbances

Table 2.
Home Visit Data Collection for Secondary Analysis

History and assessment
Brief symptom inventory-18 (BSI-18)
Profile of mood states (POMS)
Pittsburgh sleep quality index (PSQI)

Consent, history and assessment. The examiner reviewed the study procedures and plans for the evaluation with the study participant and/or caregiver. They reviewed the participant's prescription medications, and conducted a comprehensive examination, including demographic information, current and past medical history, review of systems (with particular attention to vision, hearing, cranial nerve function, reflexes, sensory perception, pain, and muscular fatigue), and family history. Body weight and standing height to the nearest centimeter were measured with a portable electronic scale and tape measure. Body Mass Index (BMI) was calculated using weight in kilograms divided by height in meters squared. BMI calculated from weight and height is a reliable indicator of body fat. For the purposes of this analysis, obesity was defined as a BMI ≥ 30 .

Treatment variables. Participants were asked for consent to release their medical records. Trained abstractors followed the medical record abstraction protocol from the Children's Cancer Survivor Study (Robison, Mertens, Boice, Breslow, Donaldson, Green et al., 2002) to abstract treatment variables from the medical record (Appendix 3). Tumor type and location, surgery or biopsies, and chemotherapy drugs and doses were recorded. Radiation therapy dosage was abstracted from the medical record, treatment diagrams,

Factors Associated with Sleep Disturbances

and photographs taken in treatment positions. Four different anatomic segments were identified and included (1) posterior fossa, (2) temporal lobe (Segment 2 Radiation includes the hypothalamus), (3) frontal cortex, and (4) parietal/occipital cortex from methods developed by Packer, et al., (2003).

Emotional performance. Emotional functioning was evaluated by having the participant complete the 18-item Brief Symptom Inventory (BSI-18), an instrument designed to evaluate mental health both globally and across three subscales (depression, somatization, and anxiety). A global score is calculated as the sum of the scores from the three subscales. The four raw scores are converted to t scores ($M = 50$, $SD = 10$). A t score greater than or equal to 63 indicates poor emotional health or emotional distress. The questionnaire asks how distressed or bothered the individual is in the previous seven days. The BSI-18 has been validated in both childhood cancer survivors, including those with brain tumors, and population controls and is highly correlated with a longer instrument, the Symptom Checklist-90-Revised ($r = 0.93$), and the Minnesota Multiphasic Personality Inventory (MMPI) ($r = 0.60$) (Derogatis, 2000; Recklitis, Parsons, Shih, Mertens, Robison, & Zeltzer, 2006; Recklitis & Rodriguez, 2007).

Physical performance. The Profile of Mood State (POMS) Brief consists of 30 words or adjectives with response on a 5-point Likert scale ranging from 1 (Not at all) to 5 (Extremely), based on how the respondent is feeling during the past week, including today and how they feel right now. For a healthy individual, it takes five minutes to complete the survey. The 5-item Brief Profile of Mood States fatigue subscale was used in this analysis to measure fatigue, defined conceptually as a subjective mood state

Factors Associated with Sleep Disturbances

marked by feelings of being worn out or exhausted. Normative data for the POMS has been done on college students, outpatient psychiatric patients, adults in the general population aged 18-94 and adults in the general population aged 55-94. Internal consistency for the POMS demonstrates a Cronbach's alpha of 0.63 to 0.96 (McNair, Loo, & Droppleman, 1981; Nyenhuis, Yamamoto, Luchetta, Terrien, & Parmentier, 1999). The POMS-Brief has been used extensively in studies of cancer patients, and has been shown to be reliable and sensitive to change in studies of drug therapies and other interventions.

Sleep. The Pittsburgh Sleep Quality Index (PSQI) is a widely used sleep questionnaire for both cancer and non-cancer populations. The instrument was developed to provide a clinically useful, reliable, and valid tool for discrimination between "good" and "poor" sleepers. The PSQI includes 19-items measuring subjective sleep quality. It takes 5-10 minutes to complete. Seven component scores are generated: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The items are scored on a 0-3 scale and then summed to yield a global PSQI score ranging from 0-21. Higher scores indicate worse sleep quality. A global score of > 5 distinguishes good and poor sleepers with excellent sensitivity and specificity for most populations (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989).

Carpenter & Andrykowski (1998) evaluated the PSQI with adult cancer patients and survivors. Individuals with sleep problems, poor sleep quality, and sleep restlessness had

Factors Associated with Sleep Disturbances

significantly higher PSQI scores. Their study indicated a cut off score of 8 on the PSQI global scale as indicative of poor sleep quality in cancer patients. In a more recent study, Mulrooney et al., (2008) used the PSQI to evaluate sleep disturbances in over 2000 adult survivors of childhood cancer. They determined a PSQI global scale score cut off of ≥ 10 identified poor sleepers, and included 398 childhood brain tumor survivors in their sample. Brain tumor subjects for this analysis are most similar to Mulrooney's sample, and thus, a PSQI global score cut off of ≥ 10 was used to identify poor sleepers for this analysis.

E) Study variables

All study variables are summarized in Table 3 and operational definitions are provided.

Factors Associated with Sleep Disturbances

Table 3.
Study Variables

Variables	Measurement Method/Operational Definition	Variable	Type of Variable
Demographic		Gender (male, female)	Categorical
		Age at diagnosis (< 5 or ≥ 5)	Categorical
		Current age (18-24, 25-29, 30+)	Continuous/Categorical
	Body Mass Index Weight (kg)/ Height (m ²)	Obesity status	Categorical <30 or ≥ 30
Disease		Tumor location (hypothalamic, posterior fossa, supratentorial)	Categorical
Treatment		Surgery (no, yes)	Categorical
		Segment 2 Radiation (none, hypothalamus)	Categorical
Emotional Performance	Brief Symptom Inventory (BSI-18) Depression subscale 18 items measuring mental health	Measures emotional distress	Continuous/Categorical T score ≥ 63 = distress
Sleep	Pittsburgh Sleep Quality Index (PSQI) 7 subscales with 19 items measuring sleep quality	Sleep quality Component scales include: - subjective sleep quality - sleep latency - sleep duration - habitual sleep efficiency - sleep disturbances - use of sleep medication - daytime dysfunction	Categorical/Continuous PSQI dichotomous outcome with cut off of ≥10 Minutes before falling asleep cut off >30
Fatigue	Profile of Mood States (POMS)- Brief Fatigue subscale 5 items measuring fatigue	Measures fatigue	Continuous

F) Statistical Analysis

All analyses were based on data collected by the study from the clinical databases at the University of Minnesota Children's Hospital and St. Jude Children's Research Hospital. Statistical analyses were performed in SAS 9.2 (Cary, NC) and AMOS 7.2 (Chicago, IL). Comparisons of sleep quality were made between childhood brain tumor survivors and the population-based comparison group and within the brain tumor survivors by treatment, post-treatment, psychological, and demographic variables.

i. Descriptive analysis

All study variables were analyzed descriptively. Numbers and percents were provided for dichotomous and polychotomous variables. Continuous variables were compared between groups with two-sample t-tests and categorical variables were compared with Fisher's exact tests (Fisher, 1922).

ii. Bivariate analysis

The bivariate analyses were used first to examine the relationship between each of the predictor variables and outcome variables. For all subjects, the bivariate analysis used two-sample t-tests and reported mean scores, standard deviations, and p values for each variable. For survivors only, a bivariate analysis using a one-sample t-test compared mean differences for obesity, chemotherapy, radiation, surgery, tumor location, sex, and age at diagnosis for the PSQI global score and PSQI component scales-sleep efficiency, sleep latency, daytime dysfunction and minutes before falling asleep, the BSI global and component scales, and the POMS global and component scales. For age categories, linear regression was used to compare mean PSQI global and component scores. Bivariate

Factors Associated with Sleep Disturbances

analyses using logistic regression (Hosmer & Lemeshow, 2000) for all subjects examined two dichotomous outcomes-PSQI global score ≥ 10 and Minutes before falling asleep > 30 . The 95% confidence intervals of the odds ratios for each variable and associated p-values were reported. For survivors only, the bivariate logistic regression model tested the following predictors: surgery (none/resection), chemotherapy (none, any), segment 2 radiation (none,hypothalamus), tumor location (hypothalamic, posterior fossa, supratentorial), and age at diagnosis (< 5 and ≥ 5). The 95% confidence intervals of the odds ratios for each variable and associated p-values were reported.

iii. Multiple variable linear regression and logistic regression

To evaluate differences in sleep quality between childhood brain tumor survivors and the population-based comparison group, multiple variable linear regression (Howell, 2002) was used for continuous outcomes. The dependent outcome variables included the global PSQI score, and subscale scores including: sleep efficiency, sleep latency, daytime dysfunction, and minutes before falling asleep. The independent variables included survivor status or comparison group member, adjusted for age and sex.

To identify disease or treatment and post-treatment-related factors associated with poor sleep quality in brain tumor survivors, a multiple variable linear regression model used the significant predictor variables ($p < 0.05$) from the bivariate analysis and important theoretical variables from the literature search or path model as independent variables. These included sex, age, radiation to the hypothalamus and age at diagnosis. The

Factors Associated with Sleep Disturbances

dependent outcome variables included the global PSQI score, and subscale scores including: sleep efficiency, sleep latency, daytime dysfunction, and minutes before falling asleep, the BSI global scores and subscale scores, and the POMS global scores and subscale scores. Parameter estimates, standard errors, and p-values were reported for the global score and each subscale.

To identify factors associated with poor sleep quality for all subjects and for survivors for the categorical outcomes (PSQI global score ≥ 10 or < 10 and Minutes before falling asleep ≤ 30 and > 30), a multiple variable logistic regression model (Hosmer & Lemeshow, 2000) used the significant ($p \leq 0.05$) predictor variables from the bivariate analysis. The all subjects analysis adjusted for current age and gender, while the survivors only analysis adjusted for age, gender, age at diagnosis, and radiation to the hypothalamus.

Participants in this study were matched on age and gender which creates confounding by the matched factors, and therefore, this was adjusted in the analysis (Rothman, Greenland, & Lash, 2008). Whether or not a survivor achieved higher education, an independent living situation, were married, or employed were not considered confounders in this analysis, but rather long-term consequences of the brain tumor and its treatment. All patients developed their brain tumors as a child, prior to finishing their education, becoming married, and seeking employment. Therefore, it is likely the brain tumor

Factors Associated with Sleep Disturbances

impacted their current living situation, as well as, their ability to obtain employment or seek higher education (Armstrong, et al., 2009; Bhopal, 2002).

iv. Path Analysis

Path analysis is a form of multiple variable regression originally developed by Wright (1934) and may be used to test theoretical models that indicate relationships between observed variables. To examine Aim 3 and hypotheses HA-3a-d, a path analysis using manifest variables evaluated which independent variables from the path model predicted the continuous dependent variable, global sleep quality (PSQI global score). Two path models were initially analyzed for this study. The first identified depression, obesity, and fatigue as mediators of the associations between demographic and treatment factors and sleep quality (Figure 3). The second identified sleep quality, obesity, and fatigue as mediators of the associations between demographic and treatment factors with the outcome, or dependent variable as depression (Figure 4). Female gender, Segment 2 dose (radiation to the hypothalamus), age at diagnosis, and current age were proposed as antecedent variables to depression, fatigue and obesity in the first model, and sleep quality, obesity, and fatigue in the second model, affecting the consequent or outcome variable, either sleep quality or depression.

The single-headed straight arrows represent a unidirectional “path”, where the variable at the point of origin is exerting an influence on the variable the arrow is pointing toward. The curved, double-headed arrows represent a covariance or correlation between two variables. No assumptions regarding causal inference are made between variables

Factors Associated with Sleep Disturbances

thought to covary. The path analysis process includes the identification of covariances for all exogenous variables (those to the far left of the model). AMOS 7.2 software (Chicago, IL) estimates a path coefficient for each straight, single-headed arrow in the figure. Path coefficients represent the size of the effect that a given independent variable has on the dependent variable. After the path coefficients have been estimated, a review of their relative size determines which independent variables have the strongest effects on the dependent variable. The final step is verifying that the model is over-identified. A model is said to be over-identified when it includes more equations than unknowns. The estimation of an over-identified model will result in only one set of parameter estimates for a given sample of data. Over-identified models can be tested for overall goodness of fit. The chi-square statistic is a general goodness of fit statistic and should be used in applied settings with care (Joreskog & Sorbom, 1989). Some researchers divide the Chi-square by the numbers of degrees of freedom. This approach compensates for sample size (Hatcher, 1994). Additional fit indices were used for this analysis, including the Normed Fit Index (NFI) (Bentler & Bonett, 1980), the Comparative Fit Index (CFI) which is less biased in small samples (Bentler, 1990), the Tucker Lewis Index (TLI) (Tucker & Lewis, 1973), Hoelter's N (Hoelter, 1983) and the Root Mean Square Error of Approximation (RMSEA) (Table 4). The model is considered a good fit when there is a non-significant chi-square, a CFI and NFI of 0.90 or greater, and a Root Mean Square Error of Association (RMSEA) of 0.05 or less (Hatcher, 1994). Model modification is acceptable in order to obtain a better fit. Modification indices (statistical tests) were not used to revise models in this analysis, given the small sample size (MacCallum, 1986).

Factors Associated with Sleep Disturbances

Model comparison between nested models is performed using Akaike's Information Criterion (AIC). The AIC is used to compare two or more nested models, with smaller values representing a better fit of the hypothesized model (Akaike, 1987).

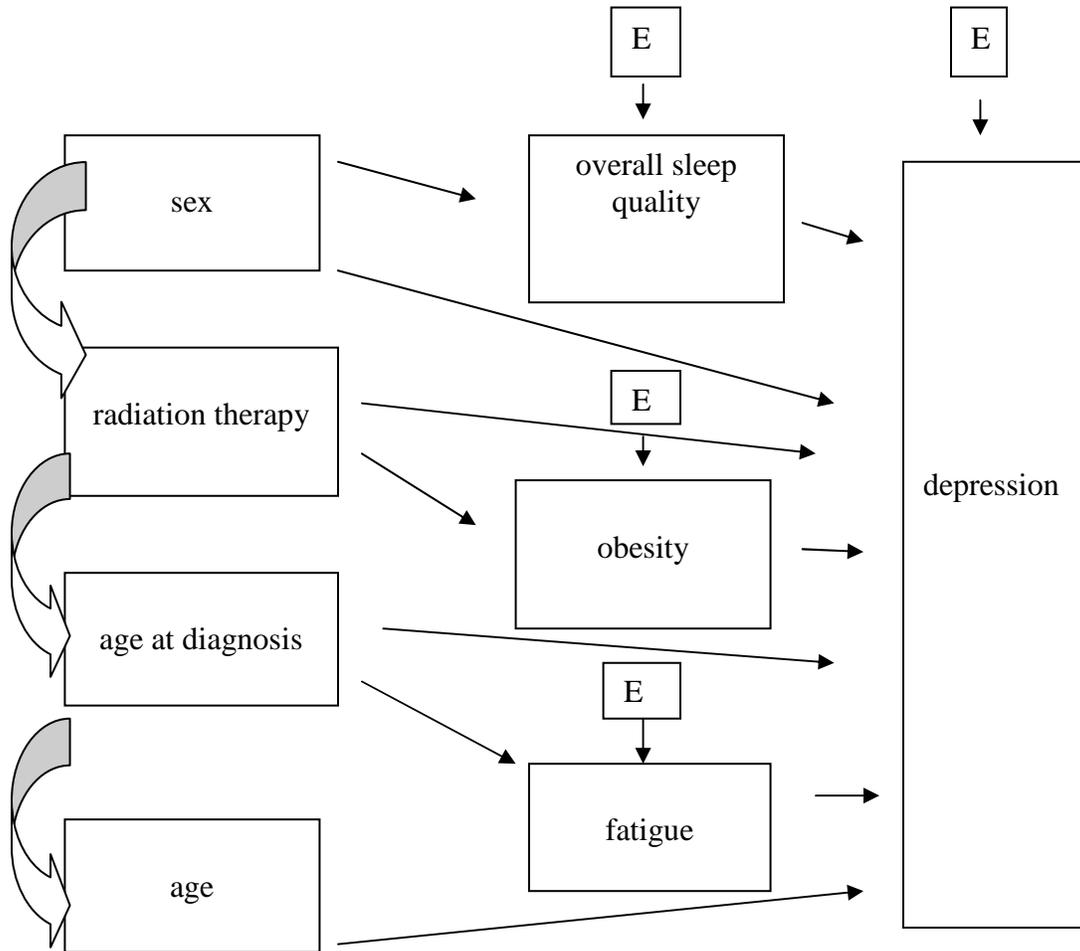
Table 4.
Path Analysis Fit Indices

Fit Indices	Good to Excellent Fit Criteria
Chi Square/degrees of freedom	< 2 excellent fit 3-5 adequate fit >5 poor fit
Normed Fit Index (NFI)	Greater than 0.90
Comparative Fit Index (CFI)	Greater than 0.90
Root Mean Square Error of Approximation (RMSEA)	0.05 Excellent Fit 0.08 Adequate Fit
Hoelter's N	N > 200
Tucker Lewis Index (TLI)	Greater than 0.90

There are several necessary conditions which were satisfied for this path analysis. These include all endogenous variables should be assessed on an interval or ratio level of measurement. A multivariate normal distribution is assumed. Relationships between variables should be linear and additive. Variables should be free of multi-collinearity. All antecedent (independent) variables should be measured without error. This assumption is often not possible in the social sciences and this problem can be minimized. Inclusions of all known causes of the model's endogenous variables should be included in the model as independent variables (Schumacher & Lomax, 2004).

Factors Associated with Sleep Disturbances

Figure 4. Second Path Model indicating Depression as the Outcome Variable.



V. RESULTS

A) Aim 1. Global Sleep Quality-All Subjects

i. Descriptive Statistics

The participants in the brain tumor survivor group included 78 of the first 132 survivors randomly selected. The non-participants included 19 (14.4%) survivors who were lost to follow-up and 35 (26.5%) survivors who declined participation in the study. Brain tumor survivor participants did not differ from non-participants by sex, current age, age at diagnosis, survival time or tumor type (Table 5). The comparison group consisted of 78 of 99 individuals who responded to the mailed invite to randomly selected names/addresses from Melissa Database based on the survivors' age, gender, and zip codes. There were a total of 78 survivors and 78 comparison group members with completed data for this analysis (Figure 5).

Factors Associated with Sleep Disturbances

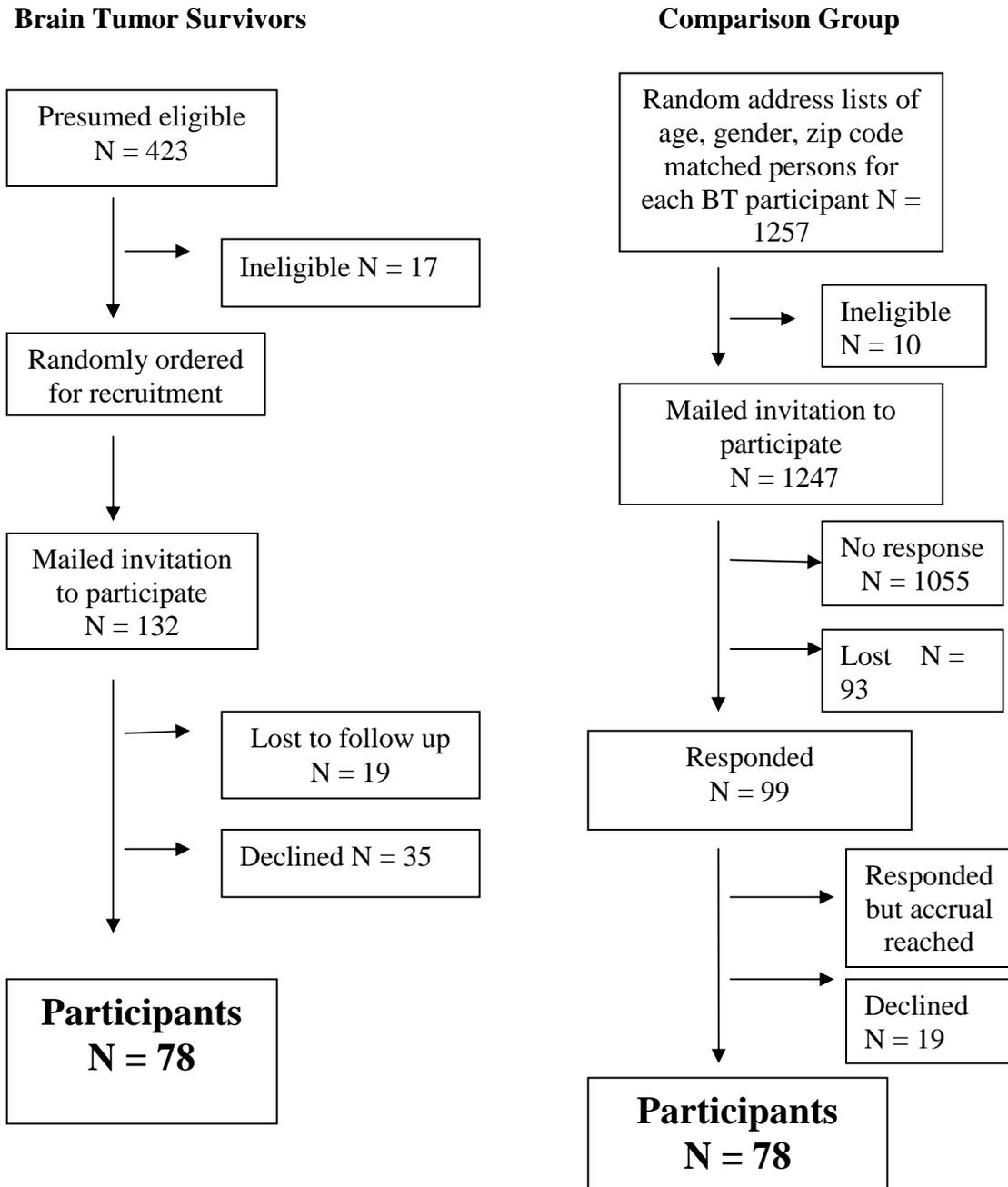
Table 5.
Participant vs. Non-Participant Characteristics of Brain Tumor Survivors

Characteristic	Participant		Non-Participant		p-value
	N = 78		N = 58		
	N	%	N	%	
Sex					
Female	36	46	28	52	0.52
Male	42	54	26	8	
Age at Questionnaire					
18-29	69	88	46	85	0.64
30-39	8	10	6	11	
40+	1	1	2	4	
Diagnosis					
Medulloblastoma/Ependymoma	22	28	11	28	0.49
Astroglial	40	52	34	63	
Craniopharyngioma	6	8	2	4	
Other	10	13	7	13	
Age at Diagnosis					
0-4	22	28	18	33	0.68
5-9	26	33	18	33	
10-14	21	27	10	19	
15+	9	12	8	15	
Time since diagnosis					
< 10	12	15	9	17	0.26
10-14	30	38	12	22	
15-19	22	28	20	37	
20+	14	18	13	24	

Factors Associated with Sleep Disturbances

Treating Institution					
St. Jude	45	58	21	39	0.03
University of Minnesota	33	42	33	61	

Figure 5. Study Recruitment and Participation



Factors Associated with Sleep Disturbances

The sample was predominantly white (86%) and average age at questionnaire for the brain tumor survivors was 24 years (range 18.4-58.3 years), and for the comparison group 24.5 years (18-54 years). Because all participants were frequency matched on age and gender, there were 36 females and 42 males in each group. Fisher's exact tests compared the two groups and found significant differences in educational, living, marital status, and employment status between survivors and the comparison group (Fisher, 1922) (Table 6).

Factors Associated with Sleep Disturbances

Table 6.
Education, Employment, Marital Status and Living Situation Characteristics

Characteristic	Survivors		Comparison Group		p-value
	N	%	N	%	
Level of Education					
< High school	4	5.10	2	2.60	<0.001
High school grad	27	34.6	8	10.3	
More than high school	47	60.3	68	87.2	
Living Situation					
Independent	58	74.4	78	100	<0.001
Family support	18	23.10	0	0.00	
Custodial care	2	2.60	0	0.00	
Marital Status					
Married/living as married	13	17.0	35	45.0	<0.001
Not married	65	83.0	43	55.0	
Employment Status					
Employed/student	51	65.4	73	93.6	<0.001
Sheltered employment	4	5.10	0	0.00	
Unemployed	23	29.5	5	6.50	

Factors Associated with Sleep Disturbances

Obesity was present in 35.9% of the survivors and 26.9% of the healthy controls, although the mean BMI for both groups was the same (Table 7).

Table 7.
Body Mass Index-All Subjects

Body Mass Index (kg/m²)	Survivor		Comparison Group	
	N	%	N	%
Not Obese	50	64.1	57	73.1
Obese (BMI \geq30)	28	35.9	21	26.9
Mean BMI	28.4		28.4	

Note. BMI = Body Mass Index. Kg = kilogram. m²= meters squared

Factors Associated with Sleep Disturbances

Medications for sleep were rare in both groups, with only three individuals using medications to assist with sleep and/or insomnia (Table 8).

Table 8.
Sleep Medication Use-All Subjects

Medication	Survivors		Comparison Group	
	N	%	N	%
Sleep*	2	2.5	1	1.2
Insomnia**	2	2.5	1	1.2

Note. *Medications for sleep-Melatonin ** insomnia-Xanax, Ativan

For the analysis of research hypotheses HA-1a-c, global and component sleep quality were compared between brain tumor survivors and the comparison group.

ii. Analysis of research hypotheses HA-1

Hypothesis HA-1a addressed the differences in global sleep quality scores between adult survivors of childhood brain tumors and the comparison group. The results from the bivariate analysis of all subjects using two-sample t-tests did not support a difference in global sleep quality scores on the PSQI between the two groups ($p=0.54$). Female participants demonstrated higher mean PSQI global scores, indicating significantly worse sleep quality when compared to their male counterparts ($p=0.04$). Obesity was not significant in the all subjects bivariate analysis and therefore, was not retained for the final multivariate model ($p=0.31$) (Table 9).

Table 9.
Bivariate Associations – PSQI Global and Subscale Scores – All Subjects

	PSQI Global			P Value	Sleep Efficiency			Sleep Latency			Daytime Dysfunction			Minutes before falling asleep		
	N	Mean	(SD)		Mean	(SD)	P Value	Mean	(SD)	P value	Mean	(SD)	P value	Mean	(SD)	P value
ALL SUBJECTS																
Comparison Group	78	6.6	(3.2)	0.54	2.1	(1.3)	0.07	0.9	(0.9)	0.08	0.7	(0.7)	0.79	23.5	(28.4)	0.07
Brain Tumor Survivor	78	6.9	(3.8)		1.7	(1.5)		1.2	(1.1)		0.7	(0.7)		33.4	(37.1)	
Current Age																
18-24	100	6.5	(3.6)	0.44	1.8	(1.4)	0.14	1.1	(1.1)	0.70	0.6	(0.7)	0.14	30.6	(35.8)	0.50
25-29	39	7.3	(3.5)		2.2	(1.3)		1.1	(1.0)		0.9	(0.7)		23.2	(19.3)	
30+	17	7.0	(3.0)		2.3	(1.3)		0.9	(0.9)		0.6	(0.6)		27.4	(41.8)	
Obese																
Yes	49	7.1	(3.3)	0.31	2.0	(1.3)	0.92	1.2	(1.0)	0.22	0.7	(0.7)	0.99	27.1	(23.2)	0.75
No	106	6.5	(3.6)		1.9	(1.4)		1.0	(1.0)		0.7	(0.7)		29.0	(37.0)	
Gender																
Male	83	6.2	(3.3)	0.04	2.1	(1.3)	0.08	1.0	(0.9)	0.10	0.6	(0.6)	0.03	27.0	(33.0)	0.56
Female	72	7.3	(3.7)		1.7	(1.4)		1.2	(1.1)		0.8	(0.7)		30.1	(33.7)	

Note: On all scales, a higher mean score = poor sleep quality. SD = standard deviation. PSQI = Pittsburgh Sleep Quality Index

Factors Associated with Sleep Disturbances

The results from the all subjects bivariate logistic regression did not demonstrate a difference for the categorical outcome of the global PSQI score (cut off ≥ 10) between the survivor and comparison groups (Table 10). However, female gender was significant for all subjects with an odds ratio indicating females were 2.6 (95%CI: 1.2, 5.7) times more likely to score ≥ 10 on the PSQI global scale, indicating poor sleep quality.

Table 10.
Bivariate Logistic Regression – PSQI ≥ 10 -All Subjects

	PSQI Global Score ≥ 10	
	Odds Ratio	95% CI
ALL SUBJECTS		
Comparison Group	1.0	
Brain Tumor Survivor	1.4	(0.6, 3.0)
Current Age		
18-24	1.5	(0.4, 5.6)
25-29	1.1	(0.2, 4.7)
30+	1.0	
Gender		
Male	1.0	
Female	2.6	(1.2, 5.7)*

Note. *p = < 0.05. PSQI = Pittsburgh Sleep Quality Index. CI = Confidence Interval

Factors Associated with Sleep Disturbances

In a multiple variable linear regression model of all subjects, adjusted for age and gender, the PSQI global score was not significantly different between survivors and the comparison group ($p = 0.34$). However, female gender remained a significant predictor of higher global scores on the PSQI, indicating poor sleep quality ($p = 0.03$) (Table 11). Female gender was also significant in the multiple variable logistic regression model for the categorical outcome $PSQI \geq 10$ with an odds ratio of 2.8 (95% CI: 1.2, 6.5) ($p = 0.02$) indicating females were almost three times more likely than males to score ≥ 10 on the PSQI global scale and experience poor sleep quality (Table 12).

Table 11.
Multiple Variable Linear Model – PSQI Global Score and Subscales-All Subjects

Predictors	Outcomes														
	PSQI Global			Sleep efficiency			Sleep latency			Daytime dysfunction			Minutes before falling asleep		
	β	(SE)	P Value	β	(SE)	P Value	β	(SE)	value	β	(SE)	P value	β	(SE)	P value
All Subjects															
Comparison Group	Reference Category														
Brain Tumor Survivor	0.5	(0.6)	0.34	-0.3	(0.20)	0.17	0.3	(0.2)	0.08	0.03	(0.1)	0.79	8.6	(5.6)	0.12
Current age															
18-24	-1.1	(0.9)		-0.3	(0.4)		0.1	(0.3)	0.88	-0.1	(0.2)		1.3	(9.5)	
			0.26			0.34						0.16			0.77
25-29	-0.2	(1.1)		0.01	(0.4)		0.2	(0.3)		0.1	(0.2)		-3.4	(10.3)	
30+	Reference Category														
Gender															
Male	Reference Category														
Female	1.3	(0.6)	0.03	-0.4	(0.2)	0.11	0.2	(0.2)	0.15	0.2	(0.1)	0.03	3.3	(5.6)	0.56
R ²	0.046			0.053			0.038			0.053			0.027		

Note. PSQI = Pittsburgh Sleep Quality Index. β = beta. SE = standard error.

Table 12.
Multiple Variable Logistic Regression – PSQI \geq 10 – All Subjects

ALL SUBJECTS	PSQI Global Score \geq 10 Odds Ratio	95% CI	p value
Comparison Group	1.0		
Brain Tumor Survivor	1.3	(0.6, 2.9)	0.56
Current age 18-24	0.9	(0.2, 3.7)	0.88
Current age 25-29	0.6	(0.1, 3.2)	0.57
Current age 30+	1.0		
Male	1.0		
Female	2.8	(1.2, 6.5)	0.02

Note. PSQI = Pittsburgh Sleep Quality Index. CI = Confidence Interval

iii. Analysis of research hypotheses H1-a

The difference in sleep latency between survivors and comparison group members was examined in hypotheses HA-1a. The sleep latency variable is measured on the PSQI as a continuous variable on a scored subscale and as a categorical variable Minutes before falling asleep > 30 or ≤ 30 . Bivariate analysis revealed the sleep latency means approached significance ($p = 0.08$) between survivors and the comparison group (Table 9). The bivariate logistic regression analysis for the categorical outcome Minutes before falling asleep demonstrated brain tumor survivors were 2.6 (95% CI: 1.1, 6.0) ($p = 0.03$) times more likely than comparison group members to take > 30 minutes to fall asleep (Table 13). In a multiple variable linear model, adjusting for age and gender, sleep latency continued to approach significance between the survivors and the comparison group ($p = 0.08$) (Table 11) with survivors reporting higher scores on the subscale indicating they take longer to fall asleep at night. This was sustained in the multiple variable logistic regression analysis of Minutes before falling asleep where survivors were 2.7 (95% CI: 1.1, 6.5) ($p = 0.03$) times more likely than the comparison group to take longer than 30 minutes to fall asleep (Table 14). Interaction terms were not investigated in this analysis due to small sample size.

Factors Associated with Sleep Disturbances

Table 13.
Bivariate Logistic Regression – Minutes Before Falling Asleep – All Subjects

	Minutes before falling asleep > 30	95% CI
	Odds Ratio	
ALL SUBJECTS		
Comparison Group	1.0	
Brain Tumor Survivor	2.6	(1.1, 6.0)*
Current Age		
18-24	2.1	(0.5, 10.1)
25-29	1.7	(0.3, 9.2)
30+	1.0	
Gender		
Male	1.0	
Female	2.1	(0.9, 4.7)

Note. *p = <0.05. CI = Confidence Interval

Factors Associated with Sleep Disturbances

Table 14.

Multiple Variable Logistic Regression – Minutes Before Falling Asleep – All Subjects

	Minutes before falling asleep >30 Odds Ratio	95% CI	p value
All Subjects			
Comparison Group	1.0		
Brain Tumor Survivor	2.7	(1.1, 6.5)	0.03
Current Age			
18-24	1.5	(0.3, 7.8)	0.60
25-29	1.6	(0.3, 9.9)	0.62
30+	1.0		
Gender			
Male	1.0		
Female	2.0	(0.8, 4.6)	0.12

Note. CI = Confidence Interval

iv. Analysis of research hypotheses HA- 1b

Sleep efficiency differences between brain tumor survivors and the comparison group were examined in hypotheses HA-1b. Sleep efficiency is measured as a component subscale on the PSQI and is a continuous variable. The bivariate analysis of all subjects on PSQI subscales indicated the p values approached significance for sleep efficiency ($p=0.07$) (Table 9). In a multiple variable linear model, adjusted for age and gender, comparing survivors and comparison group members, there was no significant difference in sleep efficiency ($p = 0.17$) (Table 11).

v. Analysis of research hypotheses HA-1c

The daytime dysfunction subscale did not demonstrate a significant difference between survivors and the comparison group in a bivariate comparison ($p = 0.79$). However, a difference was noted between male and female study participants, with females reporting significantly more daytime dysfunction ($p = 0.03$) (Table 9). In a multiple variable linear model, adjusted for age and gender, the daytime dysfunction subscale was non-significant ($p = 0.79$) between the two groups. However, female gender remained significantly associated with higher scores on the daytime dysfunction subscale, indicating females experience more sleepiness during the day ($p = 0.03$) (Table 11).

B) Aim 2. Treatment factors and sleep-Survivors only

i. Descriptive statistics of survivors

For the analysis of research hypothesis HA-2, tumor location, treatment effects, and age at diagnosis were evaluated for their effect on sleep quality among childhood brain tumor survivors. Most of the survivors in this sample were under age 10 at initial diagnosis. More than 60% of the survivors received cranial radiation therapy as part of their treatment plan, and nearly 90% had some type of surgical resection prior to beginning their radiation therapy. About 60% of the study participants were treated at St. Jude, with the others traveling to the University of Minnesota for their original cancer therapy (Table 15).

Factors Associated with Sleep Disturbances

Table 15.
Disease and Treatment Characteristics of Survivors

Characteristic	Survivors Total N = 78	
	N	%
Age at Diagnosis		
< 5 years	22	28.2
5-9 years	26	33.3
10-14 years	21	26.9
15-20 years	9	11.5
Diagnosis		
Cerebrum	11	14.1
Thalamus	5	6.4
Hypothalamic/sellar/parasellar	18	23.1
Pineal	4	5.1
Brainstem	8	10.3
Brainstem and spine	2	2.6
Cerebellum	25	32.1
Optic nerve	5	6.4
Obesity		
Body Mass Index ≥ 30	28	35.8
Tumor location		
Posterior fossa	36	46.1
Supratentorial (non-hypothalamic)	24	30.7
Hypothalamic	18	23.0
Chemotherapy		
Yes	24	30.8
No	54	69.2
Radiation to Hypothalamus		
None	29	37.1
Hypothalamus	49	62.8
Surgery		
Yes	68	87.1
No	10	12.8

Factors Associated with Sleep Disturbances

Treating Institution		
St. Jude	45	57.6
University of Minnesota	33	42.3

ii. Analysis of research hypotheses HA-2a

Hypothesis HA-2 along with sub-hypotheses HA-2a addressed the association between tumor location and sleep quality in brain tumor survivors. The bivariate analysis demonstrated tumor location was not significant for the global PSQI score among survivors ($p = 0.66$), or PSQI subscale scores including sleep latency ($p = 0.62$), daytime dysfunction ($p = 0.30$), or minutes before falling asleep ($p = 0.14$). However, current age among survivors approached significance for a higher global PSQI score among those in the 25-29 year old age group ($p = 0.08$) (Table 16). The sleep efficiency subscale of the PSQI approached significance ($p = 0.07$) for hypothalamic tumor location supporting the hypothesis that these survivors spend less time asleep while in bed compared to other survivors. Bivariate logistic regression for tumor location did not predict a PSQI ≥ 10 (poor sleep) or Minutes before falling asleep > 30 for the categorical dependent variables (Table 17). Since tumor location was not significant in the bivariate analysis, it was not retained for the final model.

Table 16.

Bivariate Associations-PSQI Global Score and Subscales-Survivors Only

	PSQI Global			Sleep Efficiency			Sleep Latency			Daytime Dysfunction			Minutes before falling asleep		
	Mean	(SD)	P Value	Mean	(SD)	P Value	Mean	(SD)	P value	Mean	(SD)	P value	Mean	(SD)	P value
Age 18-24	6.5	(3.8)	0.08	1.7	(1.5)	0.44	1.2	(1.1)	0.31	0.6	(0.7)	0.04	33.3	(35.9)	0.97
Age 25-29	9.4	(3.6)		1.7	(1.6)		1.7	(1.2)		1.2	(0.7)		31.7	(21.5)	
Age 30+	7.2	(3.3)		2.3	(1.3)		0.9	(1.1)		0.7	(0.7)		35.8	(56.9)	
Male	6.7	(3.7)	0.69	2.1	(1.4)	0.03	1.1	(1.0)	0.52	0.6	(0.7)	0.32	32.5	(37.8)	0.82
Female	7.1	(3.9)		1.4	(1.5)		1.3	(1.2)		0.8	(0.7)		34.4	(36.8)	
Obese	7.4	(3.1)	0.19	2.1	(1.4)	0.14	1.1	(1.0)	0.64	0.8	(0.7)	0.15	26.1	(22.2)	0.13
Not obese	6.6	(4.1)		1.6	(1.5)		1.3	(1.2)		0.6	(0.7)		37.7	(43.1)	
No Surgery	6.9	(4.7)	0.99	1.7	(1.5)	0.95	1.2	(1.2)	0.81	0.9	(0.9)	0.06	29.6	(27.9)	0.62
Surgery	6.9	(3.5)		1.7	(1.5)		1.2	(1.1)		0.6	(0.7)		34.6	(39.6)	
No chemo-therapy	6.9	(3.7)	0.97	1.9	(1.4)	0.24	1.1	(1.0)	0.04	0.6	(0.7)	0.80	30.13	(34.5)	0.22
Any chemo-therapy	6.9	(4.1)		1.4	(1.5)		1.6	(1.2)		0.7	(0.8)		41.7	(42.4)	

Radiation to hypothalamus	7.0	(4.0)	0.71	1.6	(1.5)	0.29	1.4	(1.1)	0.10	0.7	(0.8)	0.25	36.4	(36.5)	0.37
No radiation to hypothalamus	6.7	(3.4)		2.0	(1.5)		1.0	(1.0)		0.6	(0.6)		28.6	(38.0)	
Hypothalamic tumor	6.9	(3.5)	0.66	2.1	(1.4)	0.07	1.0	(1.0)	0.62	0.9	(0.8)	0.30	23.7	(27.9)	0.14
Posterior fossa tumor	7.3	(3.9)		2.0	(1.4)		1.3	(1.1)		0.6	(0.7)		30.2	(27.9)	
Supratentorial tumor	6.3	(3.9)		1.2	(1.5)		1.3	(1.2)		0.6	(0.7)		45.3	(50.6)	
<5 years old at diagnosis	6.2	(1.0)	0.30	1.1	(0.3)	0.01	1.2	(0.2)	0.84	0.7	(0.2)	0.62	29.2	(6.1)	0.53
≥5 years old at diagnosis	7.2	(0.5)		2.0	(0.2)		1.2	(0.1)		0.6	(0.1)		35.1	(5.5)	

Note. PSQI = Pittsburgh Sleep Quality Index. SD = standard deviation

Factors Associated with Sleep Disturbances

Table 17.
Bivariate Logistic Regression-PSQI \geq 10 and Minutes Before Falling Asleep $>$ 30 – Survivors Only

	PSQI \geq 10	(95% CI)	Minutes $>$ 30	(95% CI)
	Odds Ratio		Odds Ratio	
Age 18-24	1.2	(0.2, 6.5)	1.1	(0.2, 5.9)
Age 25-29	2.8	(0.4, 21.7)	1.8	(0.2, 14.2)
Age 30+	1.0		1.0	
Male	1.0		1.0	
Female	1.7	(0.6, 4.8)	1.4	(0.5, 3.9)
No surgery	1.0		1.0	
Resection	1.5	(0.4, 5.0)	0.8	(0.3, 2.7)
No chemotherapy	1.0		1.0	
Any chemotherapy	1.8	(0.6, 5.3)	0.8	(0.3, 2.5)
Radiation to hypothalamus	1.2	(0.6, 2.8)	2.6	(1.2, 6)*
No radiation to hypothalamus	1.0		1.0	
Hypothalamic tumor location	0.4	(0.1, 1.8)	0.4	(0.1, 2.1)
Posterior Fossa tumor location	0.8	(0.3, 2.6)	1.4	(0.4, 4.4)
Supratentorial tumor location	1.0		1.0	
$<$ 5 years old at diagnosis	1.0		1.0	
\geq 5 years old at diagnosis	2.1	(0.6, 7.0)	1.7	(0.5, 5.8)

Note. *p = $<$ 0.05. PSQI = Pittsburgh Sleep Quality Index. CI = Confidence Interval

iii. Analysis of Hypothesis HA-2b

Hypothesis HA-2b addressed the association between surgery and sleep quality. Only 10 survivors did not experience surgery as part of their treatment plan. In the bivariate analysis, surgery was not significant for the global PSQI score ($p = 0.99$), sleep efficiency ($p = 0.95$), sleep latency ($p = 0.81$), or minutes before falling asleep ($p = 0.62$). Surgery approached significance on the daytime dysfunction subscale ($p = 0.06$) (Table 16), but did not predict the categorical outcomes of a global PSQI score ≥ 10 or Minutes before falling asleep > 30 on the bivariate logistic regression analysis (Table 17). Surgery was included in an initial multiple variable model and was not a significant predictor, therefore, it was not retained for the final multivariate model.

iv. Analysis of Hypothesis HA-2c

Hypothesis 2c addressed the association between radiation treatment to the hypothalamus and sleep quality. Radiation to the hypothalamus was not significant in the bivariate analysis for the global PSQI score ($p = 0.71$), sleep efficiency ($p = 0.29$), sleep latency subscale ($p = 0.10$), daytime dysfunction ($p = 0.25$) or minutes before falling asleep ($p = 0.37$) (Table 16). However, this variable was significant on the dichotomous outcome in the bivariate logistic regression for Minutes before falling asleep indicating survivors who received radiation to the hypothalamus are 2.6 (95%CI: 1.2, 6.0) ($p = 0.02$) times more likely to take longer than 30 minutes to fall asleep (Table 17).

Factors Associated with Sleep Disturbances

In a multiple variable linear model of survivors only, adjusted for age, gender, radiation to the hypothalamus, and age at diagnosis, females ($p = 0.04$) had significantly better sleep efficiency (lower scores) and survivors diagnosed before age 5 ($p = 0.04$) were significantly more likely to have better sleep efficiency (spend more time in bed asleep) than other survivors. In addition, survivors with radiation to the hypothalamus approached significance for longer sleep latency ($p = 0.07$) indicating it takes them longer to fall asleep once they are in bed (Table 18).

In a multiple variable logistic regression analysis, adjusted for age, gender, and age at diagnosis, survivors with radiation to the hypothalamus (OR 2.7 95%CI: 0.8, 9.3; $p=0.10$) did not demonstrate significance for predicting Minutes before falling asleep > 30 (Table 19).

Table 18.
Multiple Variable Linear Model – PSQI Global Score and Subscales – Survivors Only

	PSQI Global			Sleep Efficiency			Sleep Latency			Daytime Dysfunction			Minutes before falling asleep		
	β	(SE)	P Value	β	(SE)	P Value	β	(SE)	P value	β	(SE)	P value	β	(SE)	P value
Age 18-24	-0.5	(1.4)	0.70	-0.1	(0.5)	0.81	0.30	(0.40)	0.45	-0.18	(0.26)	0.49	-1.9	(14.4)	0.89
Age 25-29	2.3	(1.8)	0.21	-0.01	(0.7)	0.97	0.75	(0.54)	0.16	0.45	(0.35)	0.20	-4.9	(19.03)	0.79
Age 30+	Reference Category														
Male	Reference Category														
Female	0.14	(0.9)	0.87	-0.7	(0.34)	0.04	0.11	(0.26)	0.66	0.12	(0.17)	0.46	4.24	(9.29)	0.64
No Radiation	-0.7	(0.9)	0.44	0.26	(0.34)	0.44	-0.48	(0.6)	0.07	-0.20	(0.17)	0.24	-10.5	(9.36)	0.26
Radiation to hypothalamus	Reference Category														
< 5 years old at diagnosis	Reference Category														
\geq 5 years old at diagnosis	1.0	(1.0)	0.32	0.78	(0.37)	0.04	0.22	(0.28)	0.43	-0.08	(0.18)	0.66	8.9	(10.24)	0.38
R ²	0.081			0.14			0.07			0.11			0.02		

Note. *The units for the beta are the actual PSQI score. Higher scores = worse sleep quality. PSQI = Pittsburgh Sleep Quality Index. SE = standard error

Factors Associated with Sleep Disturbances

Table 19.
Multiple Variable Logistic Regression – Survivors Only

	PSQI \geq 10			Minutes before falling asleep > 30		
	Odds Ratio	(95% CI)	P Value	Odds Ratio	(95% CI)	P Value
Current age 18-24	1.0			1.0		
Current age 25-29	1.4	(0.3, 6.7)	0.65	2.0	(0.4, 8.9)	0.36
Current age 30+	0.8	(0.1, 5)	0.87	0.7	(0.1, 4.7)	0.78
Male	0.7	(0.2, 2.2)	0.59	0.5	(0.2, 1.6)	0.27
Female	1.0			1.0		
No radiation	1.0			1.0		
Radiation to Hypothalamus	1.2	(0.4, 4.0)	0.67	2.7	(0.8, 9.3)	0.10
< 5 years age at diagnosis	0.5	(0.1, 1.9)	0.35	0.3	(0.0, 1.3)	0.32
\geq 5 years age at diagnosis	1.0			1.0		

Note. PSQI = Pittsburgh Sleep Quality Index. CI = confidence interval

C) Aim 2 additional exploratory analyses

i. Tumor location and POMS vigor/fatigue subscales

Additional analyses for Aim 2 explored the relationship between tumor location and self-reported vigor/fatigue. In bivariate analyses with survivors only, there were no significant associations between tumor location and vigor ($p = 0.75$) or fatigue ($p = 0.74$) subscales of the POMS (Table 20). Therefore, tumor location was not retained for the final multivariate model.

ii. Surgery and POMS vigor/fatigue subscales

Additional analyses for Aim 2 explored the relationship between surgery and vigor/fatigue. In bivariate analyses with survivors only, there were no significant associations between surgery and vigor ($p = 0.60$) and fatigue ($p = 0.45$) (Table 20). Therefore, surgery was not retained for the final multivariate model.

iii. Radiation to the hypothalamus and POMS vigor/fatigue subscales

Additional analyses for Aim 2 explored the relationship between radiation to the hypothalamus and vigor/fatigue. Bivariate associations supported an association between radiation to the hypothalamus ($p = 0.03$) and the global POMS score, and the vigor subscale (0.007). Other associations approaching significance noted were age 25-29 ($p = 0.08$) and the global POMS score. Those aged 25-29 also had significant fatigue subscale scores ($p = 0.0002$), and vigor subscale scores ($p = 0.007$) and approached significance on the tension subscale scores ($p = 0.07$). Survivors diagnosed at less than age five reported significantly lower vigor than those diagnosed at greater than 5 years ($p = 0.008$) (Table 20).

Table 20.

Bivariate Associations-POMS Global Score and Subscales-Survivors only

	POMS Global		P	Tension		P	Depression		P	Anger		P	Vigor		P	Fatigue		P	Confusion		P
	Mean	SD		Mean	SD		Mean	SD		Mean	SD		Mean	SD		Mean	SD		Mean	SD	
Current age 18-24	9.81	16.1	0.07	36.0	7.1	0.17	40.9	7.6	0.39	43.6	7.9	0.35	55.8	11.4	0.29	40.5	9.3	0.0002	41.5	6.9	0.15
Current age 25-29	20.8	14.5		40.6	8.4		41.2	2.7		46.7	9.6		58.5	10.0		54.7	15.9		46.4	10.8	
Current age 30+	4.7	10.9		36.2	5.7		36.0	2.3		41.3	4.7		61.9	10.2		37.7	5.4		43.0	4.1	
Male	9.5	14.7	0.53	36.4	6.6	0.72	41.6	6.1	0.26	43.9	7.5	0.85	58.0	10.9	0.34	40.7	10.4	0.26	42.8	8.5	0.51
Female	11.7	17.2		36.9	8.0		39.0	7.1		43.5	8.4		55.5	11.6		43.5	11.9		41.8	5.8	
Obese	12.4	14.9	0.44	37.4	6.5	0.44	41.4	6.6	0.44	44.5	7.9	0.50	56.2	10.3	0.69	41.6	8.2	0.78	42.8	5.9	0.70
Not obese	9.4	16.4		36.1	7.6		39.6	6.8		43.2	7.8		57.3	11.8		42.2	12.6		42.1	8.1	
Surgery	9.8	14.1	0.56	36.6	6.8	0.89	40.2	5.4	0.85	43.0	7.6	0.62	57.2	11.1	0.60	41.3	10.1	0.45	42.8	7.4	0.36
No surgery	12.9	20.8		36.8	8.7		41.0	10.9		46.0	8.3		55.6	11.9		44.1	14.0		40.9	7.3	
Hypo-thalamus tumor	10.2	20.3	0.63	37.2	8.6	0.81	42.1	10.4	0.73	42.4	7.2	0.30	54.9	12.6	0.75	41.5	13.8	0.74	40.6	8.2	0.49
Post Fossa tumor	8.9	15.0		36.0	8.0		39.7	5.8		42.9	7.9		57.3	11.6		41.2	10.7		43.2	8.2	
Supraten tumor	13.0	13.4		37.0	4.8		40.1	5.5		45.8	8.1		57.5	9.9		43.5	9.7		42.5	5.3	
No radiation	6.0	12.1	0.03	35.0	5.3	0.08	39.8	5.5	0.74	42.3	5.8	0.19	61.1	8.9	0.007	40.3	9.4	0.30	42.4	5.1	0.94
Radiation to hypo-thalamus	13.3	17.3		37.6	8.0		40.6	7.4		44.6	8.8		54.1	11.8		43.0	12.0		42.3	8.5	
< 5 years old at diagnosis	15.8	20.7	0.14	37.2	9.0	0.69	43.3	10.3	0.28	45.6	9.9	0.31	51.3	9.8	0.008	44.1	12.2	0.31	41.2	7.9	0.39
≥ 5 years old at diagnosis	8.5	13.1		36.4	6.5		39.3	4.6		43.1	7.0		58.9	11.1		41.2	10.7		42.8	7.2	

Note. POMS = Profile of Mood States. SD = standard deviation. P = p value. A higher mean score is worse, except on the Vigor subscale, where a higher score is better.

Factors Associated with Sleep Disturbances

The multiple variable linear model, adjusted for age, gender, and age at diagnosis demonstrates radiation to the hypothalamus approached significance for the global POMS score ($p = 0.08$) and achieved significance on the vigor subscale ($p = 0.02$). The age group 25-29 continues to report higher global POMS scores ($p = 0.06$) and significantly higher fatigue subscale scores ($p = 0.001$). Age at diagnosis approached significance for the vigor subscale ($p = 0.06$) for those less than 5 years old (Table 21).

Table 21.
Multiple Variable Linear Model – Profile of Mood States – Survivors Only

	POMS Global Score			Tension			Depression			Anger			Vigor			Fatigue			Confusion		
	β	SE	p value	β	SE	p value	β	SE	p value	β	SE	p value	β	SE	p value	β	SE	p value	β	SE	p value
Current age 18-24	2.4	5.7	0.67	-0.78	2.7	0.77	4.43	3.7	0.24	1.7	2.9	0.56	-2.6	4.0	0.51	1.3	3.8	0.72	-0.48	2.7	0.86
Current age 25-29	14.27	7.6	0.06	3.86	3.46	0.26	5.9	4.3	0.18	5.4	3.8	0.16	-0.9	5.3	0.85	15.7	4.9	0.001	4.5	3.5	0.20
Current age 30+	Reference Category																				
Male	Reference Category																				
Female	0.8	3.73	0.81	0.5	1.73	0.77	-3.6	2.3	0.13	-0.68	1.9	0.72	-3.2	2.6	0.22	1.07	2.4	0.66	-1.5	1.8	0.38
No radiation	-6.43	3.73	0.08	-2.7	1.75	0.12	0.5	2.5	0.84	-1.75	1.93	0.36	6.2	2.6	0.02	-2.4	2.4	0.33	-0.02	1.85	0.98
Radiation to hypo-thalamus	Reference Category																				
< 5 years old at diagnosis	Reference Category																				
≥ 5 years old at diagnosis	-5.6	4.1	0.17	-0.48	1.93	0.80	-3.8	2.7	0.16	-2.1	2.2	0.33	5.4	2.9	0.06	-2.7	2.7	0.32	1.2	2.0	0.53
R ²	0.15			0.082			0.18			0.06			0.18			0.23			0.06		

Note. β = beta.. SE = standard error. POMS = Profile of Mood States. The units for the POMS beta are the actual POMS score. A higher score is worse, except on the Vigor Subscale, where a higher score is better.

Factors Associated with Sleep Disturbances

Table 22.
Bivariate Associations – Brief Symptom Inventory – All Subjects

	Global Severity Index			Somatization			Depression			Anxiety		
	Mean	SD	p value	Mean	SD	p value	Mean	SD	p value	Mean	SD	p value
Comparison Group	46.8	8.3	0.15	48.0	6.8	0.08	47.0	8.3	0.12	46.6	7.7	0.15
Brain Tumor Survivor	49.1	11.0		50.2	9.5		49.2	10.2		48.8	10.6	
Current age												
18-24	46.9	9.9	0.18	48.5	8.3	0.36	47.4	9.2	0.50	47.0	9.1	0.43
25-29	49.1	9.3		49.5	8.3		48.9	10.0		48.5	8.8	
30+	51.3	9.8		51.5	8.6		49.8	8.6		49.8	11.6	
Obese	47.8	10.4	0.86	49.1	9.1	0.99	48.1	9.4	0.93	47.08	9.4	0.57
Not obese	48.1	9.6		49.1	8.0		48.05	9.4		47.99	9.3	
Male	48.9	9.8	0.19	49.7	8.0	0.33	48.5	9.4	0.53	47.9	9.6	0.71
Female	46.9	9.7		48.4	8.7		47.6	9.3		47.4	9.0	

Note. SD = standard deviation

iv. Tumor location, treatment, and BSI depression subscale scores

Additional analyses for Aim 2 examined the relationship between tumor location, surgery, and radiation to the hypothalamus and the BSI global score and depression subscale. Upon examining bivariate associations on the BSI for all subjects, the somatization subscale approached significance ($p = 0.08$), indicating survivors had more somatization issues than the comparison group (Table 22). However, bivariate associations for the survivors alone revealed that tumor location, surgery, and radiation to the hypothalamus were not significant (Table 23). A multiple variable linear model with all subjects, adjusted for age and gender, revealed the global BSI ($p = 0.07$), somatization ($p = 0.04$), depression ($p = 0.07$), and anxiety ($p = 0.09$) subscales approached significance on three of the scales and achieved significance on the somatization subscale indicating the survivors reported higher scores on the BSI and its subscales than the comparison group (Table 24). In a multiple variable linear model, adjusting for age, gender, age at diagnosis, and radiation to the hypothalamus, with survivors only, there were no significant predictors for the BSI global or depression subscale scores (Table 25).

Table 23.
Bivariate Associations-Brief Symptom Inventory-Survivors Only

	Global Severity Index			Somatization			Depression			Anxiety		
	Mean	SD	P value	Mean	SD	p value	Mean	SD	p value	Mean	SD	p value
Current age												
18-24	47.9	10.8	0.25	49.2	9.1	0.24	48.4	10.3	0.47	48.1	10.4	0.49
25-29	51.2	10.7		53.5	10.6		51.0	9.7		49.4	9.1	
30+	54.0	12.3		53.4	10.4		52.4	10.1		52.6	13.5	
Male	50.0	11.6	0.43	50.3	8.9	0.96	50.0	10.6	0.51	49.6	11.6	0.44
Female	48.0	10.4		50.2	10.4		48.4	9.8		47.7	9.3	
Obese	50.1	11.1	0.54	51.3	10.6	0.48	50.4	10.4	0.47	48.4	10.4	0.81
Not obese	48.5	11.1		49.7	8.9		48.6	10.1		49.0	10.8	
Surgery	49.4	10.3	0.62	50.1	9.0	0.70	49.6	9.6	0.56	48.9	9.6	0.84
No surgery	47.9	13.6		51.1	11.1		48.0	12.2		48.2	13.9	
No radiation	47.0	10.8	0.19	49.1	9.7	0.40	47.3	8.8	0.19	47.2	10.6	0.33
Radiation to hypo- thalamus	50.4	11.1		51.0	9.5		50.4	10.9		49.7	10.6	
Hypo-thalamus tumor	48.4	14.0	0.93	49.9	10.6	0.94	49.5	12.8	0.66	47.6	14.4	0.87
Posterior fossa tumor	49.6	11.0		50.7	9.3		50.2	10.6		49.1	9.5	
Supratentorial tumor	48.8	8.8		50.0	9.4		47.7	7.3		49.2	9.1	

< 5 years old at diagnosis	47.2	13.3	0.37	48.0	10.4	0.19	49.6	12.7	0.86	48.6	11.9	0.92
≥ 5 years old at diagnosis	49.8	10.2		51.2	9.1		49.1	9.2		48.8	10.2	

Note. SD = standard deviation

Factors Associated with Sleep Disturbances

Table 24.
Multiple Variable Linear Model – Brief Symptom Inventory- All Subjects

	Global Severity Index			Somatization			Depression			Anxiety		
	β	SE	p value	β	SE	p value	β	SE	p value	β	SE	p value
Comparison Group	0.0			0.0			0.0			0.0		
Brain Tumor Survivor	2.9	1.6	0.07	2.7	1.4	0.04	2.8	1.6	0.07	2.6	1.6	0.09
Current age 18-24	-3.7	2.7	0.13	-2.7	2.2	0.28	-2.2	2.5	0.33	-2.7	2.6	0.29
Current age 25-29	-0.4	3.0		-0.7	2.5		0.2	2.8		-0.3	2.9	
Current age 30+	0.0			0.0			0.0			0.0		
Male	0.0			0.0			0.0			0.0		
Female	-1.7	1.6	0.28	-1.0	1.4	0.46	-0.7	1.6	0.62	-0.3	1.6	0.84
R ²	0.05			0.04			0.03			0.03		

Note. β = Beta. SE = standard error

Factors Associated with Sleep Disturbances

Table 25.
Multiple Variable Linear Regression-Brief Symptom Inventory-Survivors Only

	Global Severity Index			Somatization			Depression			Anxiety		
	β	SE	p value	β	SE	P value	β	SE	p value	β	SE	P value
Current age 18-24	-5.2	4.1	0.21	-3.5	3.6	0.32	-4.1	3.9	0.29	-4.2	4.1	0.29
Current age 25-29	-1.94	5.3	0.71	0.29	4.6	0.94	-1.2	4.9	0.80	-2.6	5.2	0.61
Current age 30+	Reference Category											
Male	Reference Category											
Female	-0.89	2.6	0.73	0.47	2.3	0.83	-0.82	2.5	0.74	-1.0	2.6	0.69
No radiation	-4.01	2.7	0.14	-2.8	2.3	0.22	-3.0	2.53	0.23	-2.5	2.6	0.35
Radiation to hypothalamus	Reference Category											
< 5 years old at diagnosis	Reference Category											
\geq 5 years old at diagnosis	2.5	2.9	0.39	3.2	2.5	0.21	-0.56	2.7	0.84	0.10	2.9	0.97
R ²	0.07			0.07			0.04			0.04		

Note. *The beta (β) is the actual Brief Symptom Inventory score. Higher scores indicate more symptoms. SE = standard error

D) Aim 3. Treatment and post-treatment factors associated with sleep quality

i. Descriptive Statistics

Among brain tumor survivors in this study, more than half had a tumor involving the hypothalamus and received radiation to this area. In addition, 36% of the survivors had a BMI > 30 indicating obesity. Those who were diagnosed at less than age 5 comprised 28% of the sample (Table 15).

ii. Analysis of research hypotheses HA-3

Analysis of research hypotheses HA-3a-d addresses the associations between post treatment variables (obesity, depression, and fatigue), and their effects on global sleep quality. Model Specification. As part of the conceptual model for this study, a path model with the PSQI global score as a continuous dependent variable was proposed a priori for examination of Aim 3 (Figure 3). The model suggests possible pathways through which sleep quality is affected after treatment for a brain tumor. It proposes that survivors who are female, were less than age 5 at diagnosis, received radiation to the hypothalamus, and are older will experience more depression, obesity, and fatigue, thereby impacting global sleep quality. A second path model proposing depression as the dependent variable indicates an alternative theory whereby a higher global score on the PSQI would yield higher BSI scores (Figure 4). Data Screening. Preliminary data screening indicated that the assumption of multivariate normality was reasonably met by the data. Prior to model testing, Pearson Correlation Coefficients were computed for all variables in the model (Table 31). In addition, the means and standard deviations of all the variables are listed in Table 26.

Factors Associated with Sleep Disturbances

Table 26.

Means and standard deviations-Path model variables-Survivors only

Variable	N	Mean	Std Dev
Sex	78	1.46	0.50
Radiation to hypothalamus	78	0.314	0.46
Age at diagnosis < 5	78	0.282	0.45
Age	78	24.97	5.98
Depression subscale	78	1.92	0.26
Obesity	78	1.68	0.47
Fatigue subscale	78	41.51	10.34
PSQI global score	78	6.72	3.51

Note. PSQI = Pittsburgh Sleep Quality Index. Obesity = BMI > 30

Model testing. Path analyses were conducted using AMOS 7.2 software (Arbuckle & Wothke, 1999) and maximum likelihood estimation. Model fit was assessed with the chi-square statistic, along with degrees of freedom and p values associated with the test. The null hypothesis with AMOS 7.2 software is that the model fits the data, indicating the reproduced covariance matrix has the specified model structure, and therefore, the chi-square value for a well-fitting model should be higher than 0.05 (Arbuckle & Wothke, 1999).

The initial path analysis model with PSQI global score as a continuous dependent variable was a fully saturated (fully identified) model (Figure 6). This fully saturated model demonstrated a chi-square of 0.574, degrees of freedom = 3 and probability 0.90

Factors Associated with Sleep Disturbances

indicating the model fits the data and the null hypothesis is accepted. However, this is the expected result for a fully or just-identified model. A fully-identified model cannot be tested for goodness of fit because there are more unknown equations than known equations. In a fully-identified model, every variable is predicted to be related to every other variable in some way. Such a complex model is able to account for correlations between variables to a great degree (Hatcher, 1994).

Path model A (1) is an over-identified model with the PSQI global score as the dependent variable (Figure 7). A just-identified model becomes over-identified when you place restrictions on certain model parameters. Once these restrictions have been implemented, the model may be tested for goodness of fit. In Path model A (1), paths sex to obesity, sex to fatigue, radiation to hypothalamus to depression, diagnosis less than 5 to depression, diagnosis less than 5 to obesity, age to depression, age to obesity, and age to fatigue were fixed at zero (or eliminated) from the model prior to model testing.

The initial path analysis operations tested Path model A (1). The model revealed a chi-square of 7.751, degrees of freedom = 11, and the p value = 0.74 indicating this model could potentially fit the data. The R^2 for the model indicated 23% of the PSQI global score was explained by the variables in the model. Path model B (1) was the second hypothesized path model with depression as a continuous dependent variable instead of PSQI global score (Figure 8). The Path Model B (1) achieved a chi-square

Factors Associated with Sleep Disturbances

statistic of 63.7, degrees of freedom = 10, and a p value of < 0.0001 . This significant chi-square indicates Path model B (1) does not fit the data adequately. Fit indices were poor with an RMSEA of 0.11 (poor fit). Therefore, Path Model A (1) was accepted as a better explanation of the data and reviewed more closely.

The model covariance matrix and fit indices for Path model A (1) indicated this model could be improved. The residual covariance matrix revealed one residual over 6.0 and a second residual of over 1.2. In addition, the Normed Fit Index (NFI) was 0.82 (0.9 or higher demonstrates acceptable fit), Hoelter's N was 191 (> 200 indicates an acceptable fit). Standardized regression coefficients are reported for this analysis. A combination of statistical significance tests (t tests) and theoretical importance was used to remove or adjust paths within the model in order to determine if a better fit was possible with the current data.

After review of the path coefficients, four paths with p values > 0.60 were removed from Path model A (1) including radiation to hypothalamus to obesity ($p=0.88$), radiation to hypothalamus to fatigue ($p=0.61$), age to PSQI ($p=0.64$), and sex to PSQI ($p=0.83$). The arrows from age and sex to PSQI were replaced with arrows from age to fatigue and sex to fatigue based on the theoretical importance of age and sex and their potential impact on fatigue in the model. Removing age and sex completely from the model did not make theoretical sense despite the original high p values.

Factors Associated with Sleep Disturbances

In addition, an arrow was added from age at diagnosis < 5 to depression indicating that depression affecting sleep quality might be higher in those less than age 5 since they are likely to suffer more deficits from their treatment. Diagnosis less than 5 is important theoretically and has been an important predictor of neuro-endocrine deficits in many studies. In addition, radiation to the hypothalamus was left in the model based on its theoretical importance for sleep quality, despite a p value of 0.61 (Table 27).

Factors Associated with Sleep Disturbances

Table 27.

Standardized regression weights-Path Model (1)-Survivors Only

	Variables	Beta	SE	t	p value
Fatigue	← age at diagnosis < than 5	0.137	2.70	1.17	0.24
Depression	← sex	0.075	0.62	0.65	0.52
Obesity	← radiation to hypothalamus	0.018	0.12	0.15	0.88
Fatigue	← radiation to hypothalamus	0.059	2.50	0.51	0.61
PSQI	← age at diagnosis < than 5	-0.171	0.90	-1.57	0.12
PSQI	← obesity	-0.086	0.78	-0.85	0.40
PSQI	← depression	-0.109	1.40	-1.07	0.28
PSQI	← fatigue	0.444	0.03	4.32	0.000
PSQI	← sex	0.023	0.77	0.22	0.83
PSQI	← radiation to hypothalamus	0.053	0.80	0.50	0.62
PSQI	← age	0.049	0.06	0.46	0.64
Fatigue	← age*	NA	NA	NA	NA
Fatigue	← sex*	NA	NA	NA	NA
Depression	← age at diagnosis < than 5**	NA	NA	NA	NA

Note. Bolded paths removed. *adjusted paths. **added path. PSQI = Pittsburgh Sleep Quality Index. SE = standard error

Factors Associated with Sleep Disturbances

After removing the four paths from the model, adjusting the age and gender paths, and adding a path from age at diagnosis < 5 to depression, the Path Model A (2) was examined and revealed a chi-square of 2.728, degrees of freedom = 12, and a p value = 0.997 (Figure 10). The R² for the model indicated 22.8% of the PSQI global score was explained by the variables in the model. Although the R² was nearly the same as Path Model A (1), there were more regression weights approaching significance in the second path model (Table 28). Both depression and fatigue explained portions of the model variance, however obesity did not explain any of the variance in the PSQI global score. Age, sex, and age at diagnosis < 5 all had indirect effects on the global PSQI score. In addition, both female sex, age, radiation to the hypothalamus, and fatigue predicted a higher global PSQI score, while diagnosis less than 5, depression, and obesity actually predicted lower PSQI scores (Table 29 and 30). The residual covariance matrix revealed only one value greater than 1.2 and no values greater than 2.0. The reproduced sample correlations from the model are very close to the initial correlation matrix (Tables 31 and 32). The fit indices for this model were better, including the Normed Fit Index at 0.94, the Comparative Fit Index at 1.0 (sensitive to small samples), the RMSEA at 0.000, Hoelter's N = 579, and the AIC was 66.7, which is lower than the 73.0 achieved in Path Model A (1). The overall model met many characteristics of an ideal fit with absolute values of the normalized residual matrix not exceeding 2, the p value of the chi-square test was close to 1.00, the NFI was greater than 0.90, and the R² value explained a significant portion of the dependent variable (Hatcher, 1994). Therefore, this model was

Factors Associated with Sleep Disturbances

retained as the final model (Figure 9). A summary of the model chi-square statistics is available in Table 33.

Table 28.

Standardized regression weights for Path model A (2)-Final model

	Variables	B	SE	t	p value
Fatigue	← age at diagnosis < 5	0.184	2.67	1.59	0.11
Depression	← age at diagnosis < 5	-0.148	0.07	0.68	0.19
Depression	← sex	0.078	0.06	1.73	0.50
Fatigue	← sex	0.196	2.4	1.22	0.08
PSQI	← age at diagnosis < 5	-0.184	0.89	-1.29	0.08
PSQI	← obesity	-0.088	0.78	-1.72	0.38
PSQI	← depression	-0.110	1.40	-1.07	0.28
PSQI	← fatigue	0.453	0.03	4.41	0.00
PSQI	← radiation to hypothalamus	0.050	0.80	0.48	0.63
Fatigue	← age	0.142	0.19	-0.86	0.22

Note. PSQI = Pittsburgh Sleep Quality Index. SE = standard error. Bolded path significant < 0.001

Factors Associated with Sleep Disturbances

Table 29.
Standardized indirect effects-Final model

	age	sex	age at diagnosis < 5	obesity	radiation to hypothalam us	fatigue	depres sion
fatigue	0.000	0.000	0.000	0.000	0.000	0.000	0.000
depression	0.000	0.000	0.000	0.000	0.000	0.000	0.000
PSQI	0.064	0.080	0.100	0.000	0.000	0.000	0.000

Note. PSQI = Pittsburgh Sleep Quality Index

Table 30.
Standardized total effects-Final model

	age	sex	age at diagnosis < 5	obesity	radiation to hypothalamus	fatigue	depression
fatigue	0.142	0.196	0.184	0.000	0.000	0.000	0.000
depression	0.000	0.078	-0.148	0.000	0.000	0.000	0.000
PSQI	0.064	0.080	-0.085	-0.088	0.050	0.453	-0.110

Note. PSQI = Pittsburgh Sleep Quality Index

Factors Associated with Sleep Disturbances

Table 31.
Correlation estimates prior to path model analysis-Survivors only

	age	radiation to hypothalamus	age at diagnosis < 5	sex	obesity	fatigue	depression	PSQI
age	1.000							
radiation to hypothalamus	-0.029	1.000						
age at diagnosis < 5	-0.253	0.243	1.000					
sex	-0.150	-0.144	0.019	1.000				
obesity	-0.070	0.018	0.045	0.049	1.000			
fatigue	0.066	0.093	0.152	0.178	-0.002	1.000		
depression	-0.026	-0.130	-0.146	0.075	-0.021	-0.102	1.000	
PSQI	0.125	0.060	-0.090	0.070	-0.093	0.438	-0.133	1.000

Note. PSQI = Pittsburgh Sleep Quality Index

Table 32.

	age	radiation to hypothalamus	age at diagnosis < 5	sex	obesity	fatigue	depression	PSQI
age	1.000							
radiation to hypothalamus	-	1.000						
age at diagnosis < 5	0.023	0.246	1.000					
sex	-	-0.139	0.048	1.000				
obesity	0.153	0.033	0.053	0.049	1.000			
fatigue	0.063	0.118	0.117	0.128	0.028	1.000		
depression	0.082	-0.153	-0.111	0.107	-0.051	-0.217	1.000	
PSQI	0.045	0.043	-0.120	0.047	-0.107	0.438	-0.133	1.000

Reproduced path model correlation estimates-Survivors only

Note. PSQI = Pittsburgh Sleep Quality Index

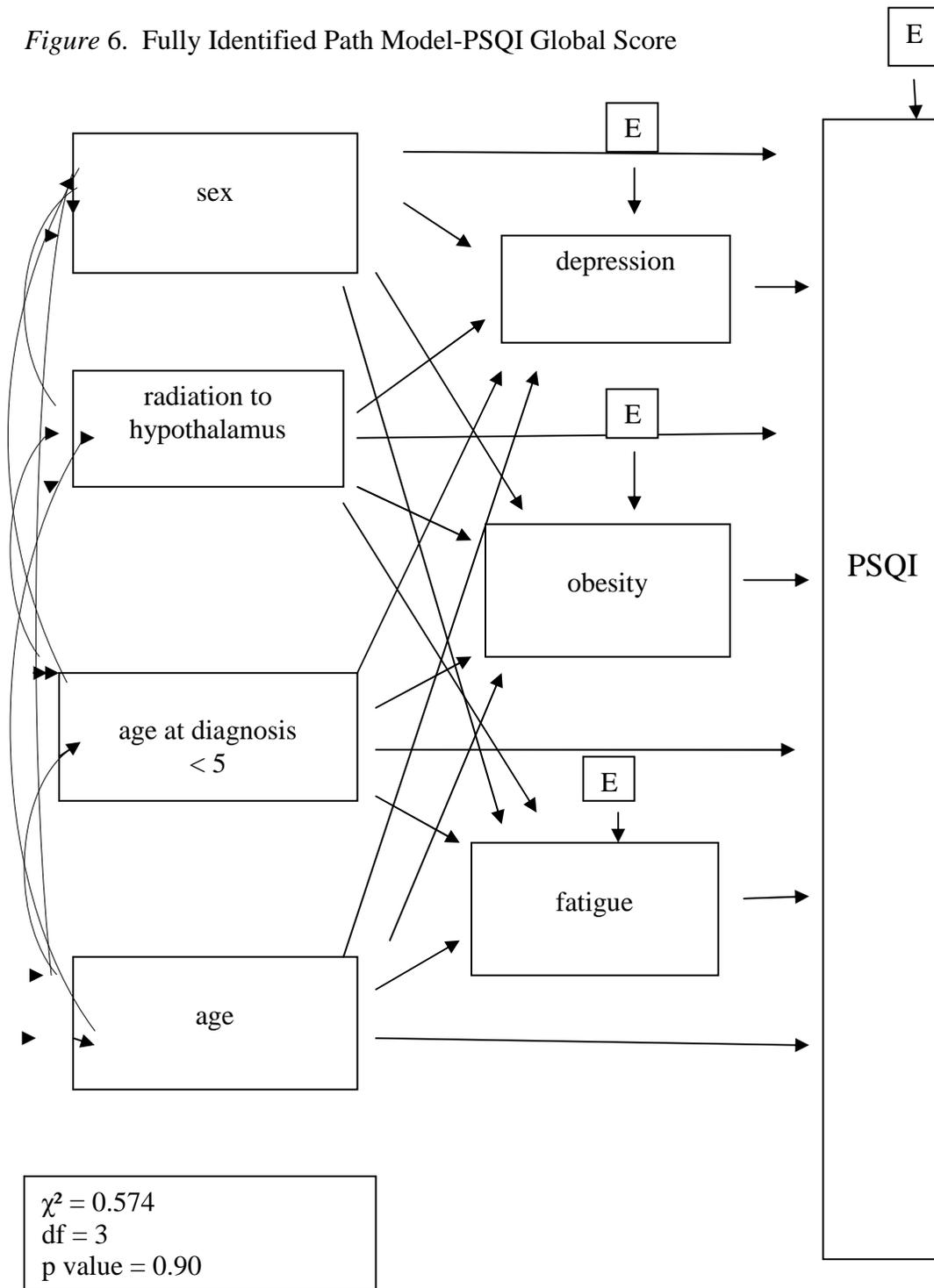
Factors Associated with Sleep Disturbances

Table 33.
Summary of path model results-All models

Model	Chi-square	Degrees of Freedom	p value
Fully Identified Model	0.574	3	0.90
Path Model A (1)	7.751	11	0.74
Path Model B (1)	63.70	10	0.0001
Path Model A (2)-Final	2.728	12	0.99

Factors Associated with Sleep Disturbances

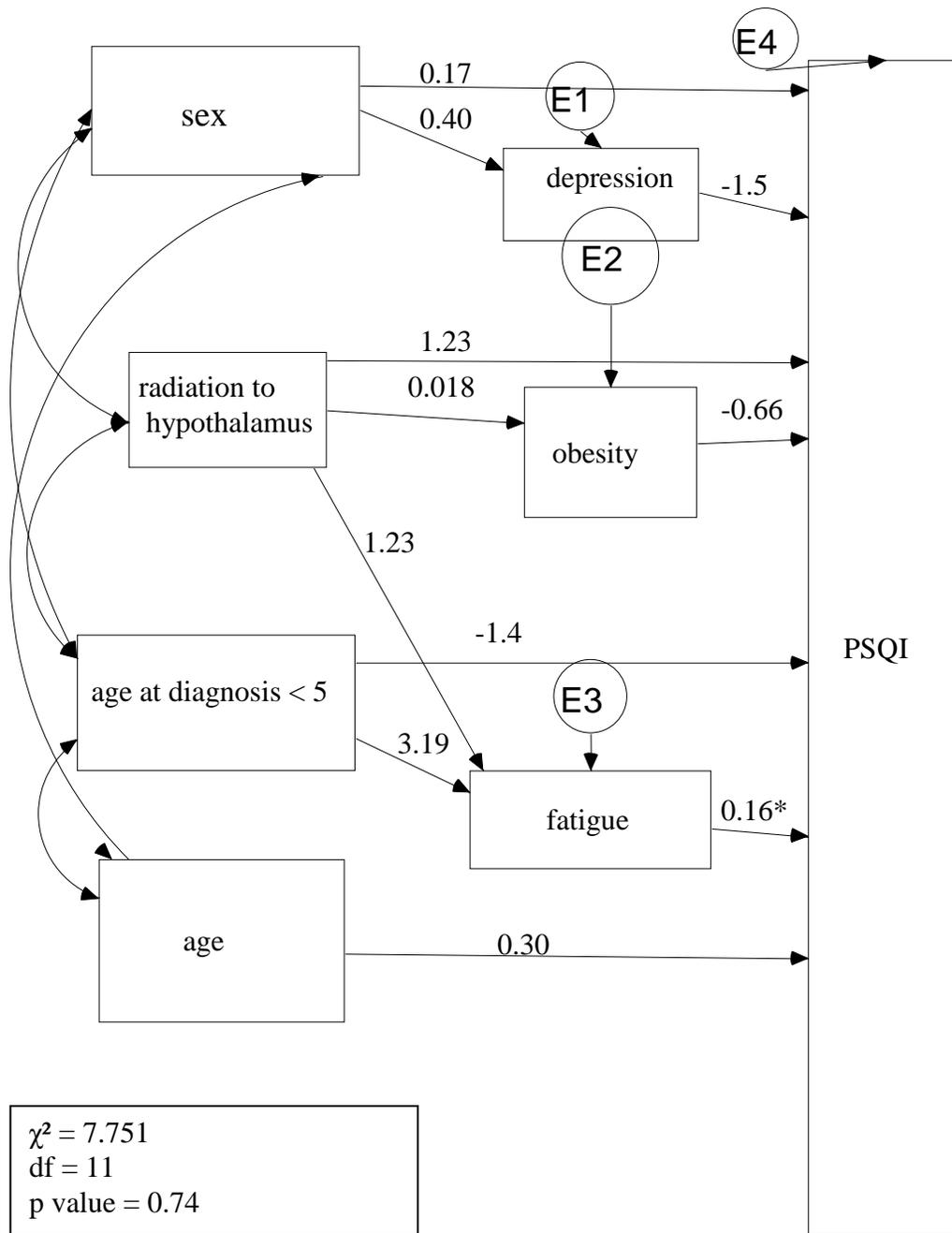
Figure 6. Fully Identified Path Model-PSQI Global Score



Note. PSQI = Pittsburgh Sleep Quality Index. Df = degrees of freedom.

Factors Associated with Sleep Disturbances

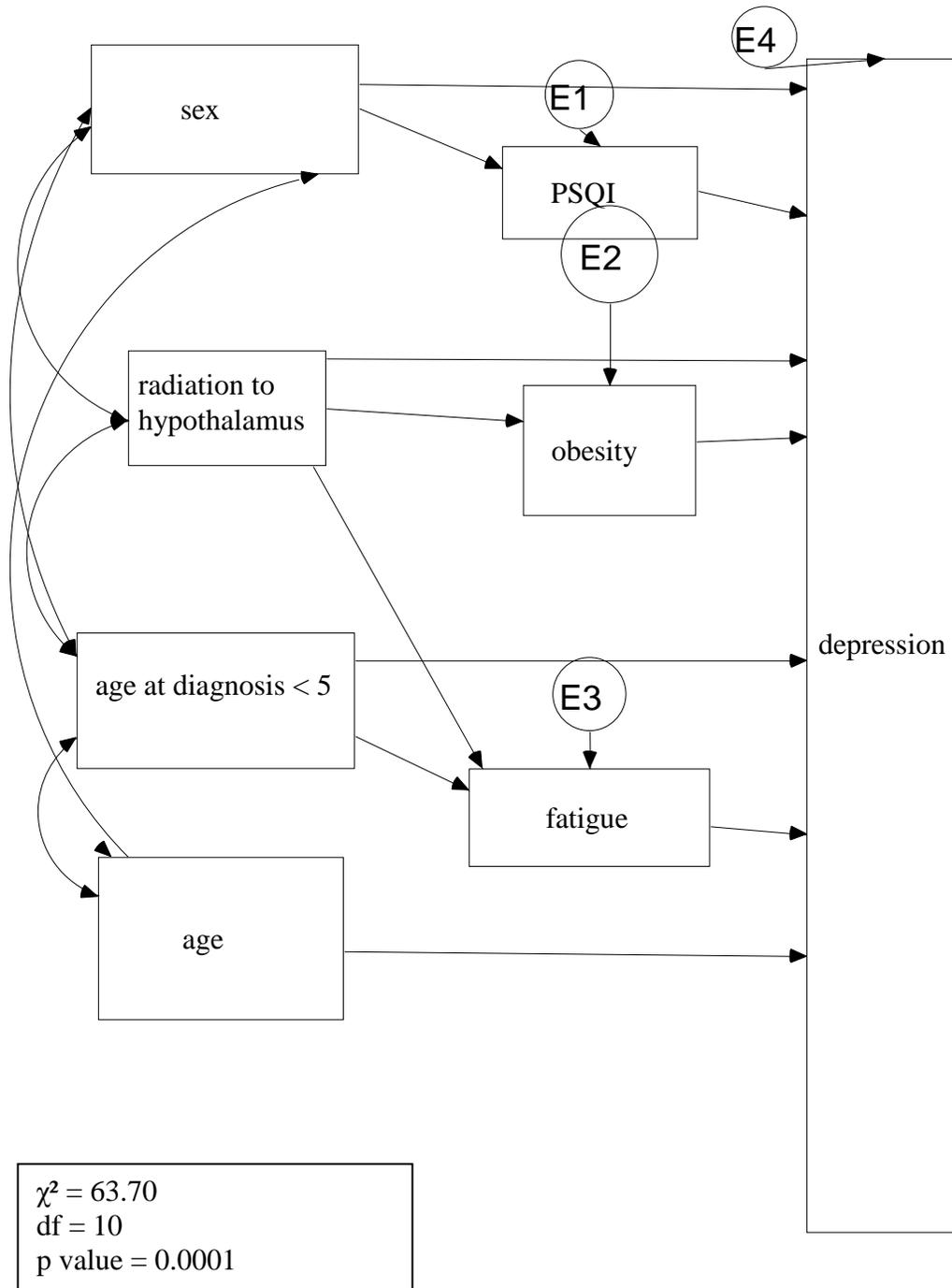
Figure 7. Path Model A (1)



Note. PSQI = Pittsburgh Sleep Quality Index. Df = degrees of freedom. * = $p < 0.001$

Factors Associated with Sleep Disturbances

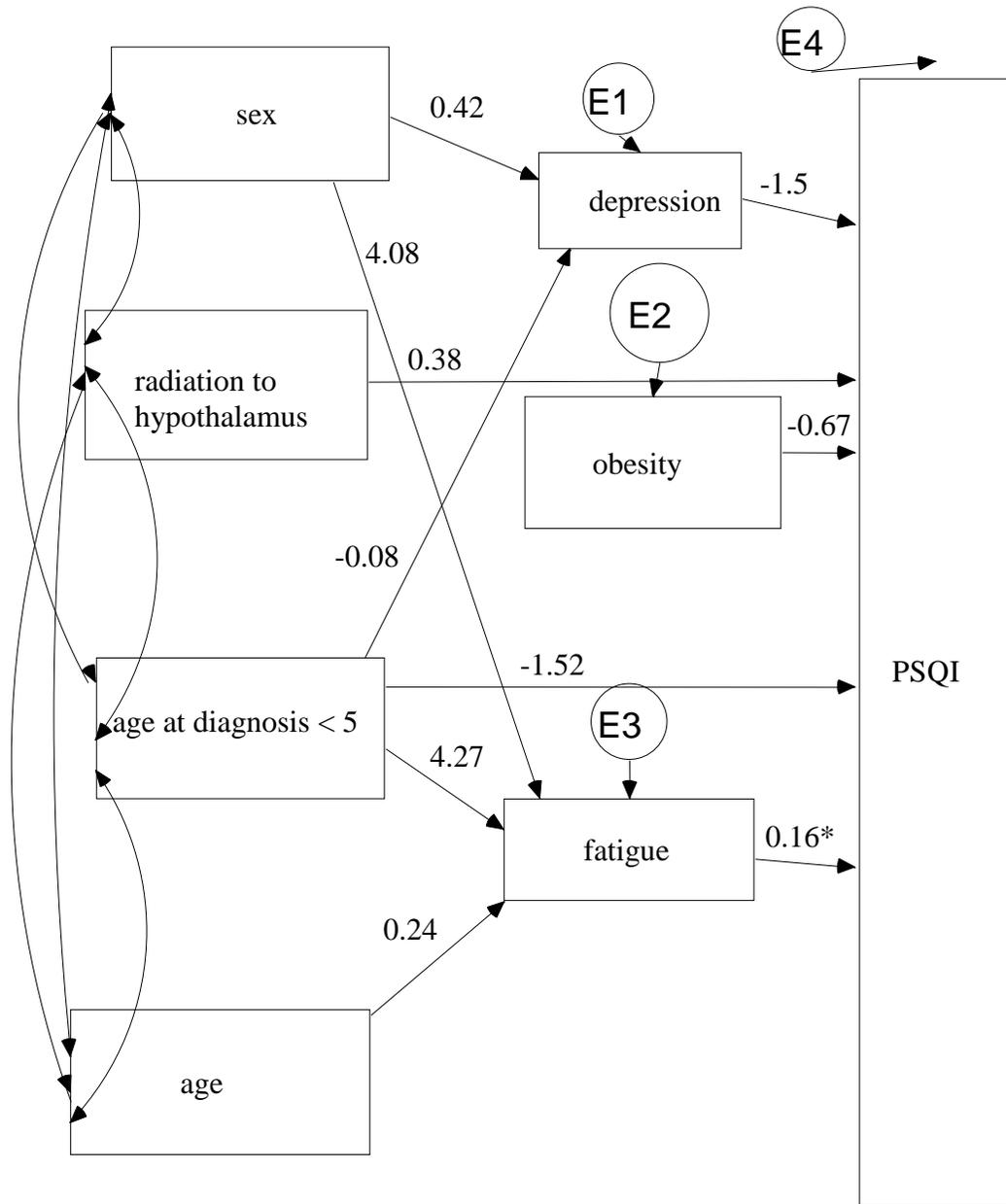
Figure 8. Path Model B (1)



Note. PSQI = Pittsburgh Sleep Quality Index. Df = degrees of freedom

Factors Associated with Sleep Disturbances

Figure 9. Path Model A (2)-Final Model



$\chi^2 = 2.728$
 df = 12
 p value = 0.99

Note. PSQI = Pittsburgh Sleep Quality Index. Df = degrees of freedom. * = $p < 0.001$

CHAPTER VI. DISCUSSION AND CONCLUSIONS

A) Aim 1: Global sleep quality comparisons in all subjects

Factors associated with sleep disturbances in patients undergoing active cancer treatment are well described. These include pain, decreased daytime activity, interruption of environmental sleep cues (e.g., decreased exposure to light), irregular sleep patterns, altered circadian rhythm, side effects of chemotherapy and radiation therapy, and use of medications which affect sleep (Berger & Farr, 1999; Berger & Higginbotham, 2000; Miaskowski & Lee, 1999; Mormont et al., 2000; Tamburini, Selmi, DeConno, & Ventafridda, 1987). Less information about sleep patterns after treatment is available on childhood cancer survivors, especially those with cancers affecting the central nervous system. Previous studies have been focused on daytime sleepiness, secondary narcolepsy, and obesity in survivors of childhood craniopharyngiomas (Muller, Handwerker, Wollny et al., 2002).

This study evaluated self-reported sleep quality among brain tumor survivors and a population-based comparison group. Vena's model of cancer-related factors affecting sleep was used as the conceptual framework in this study to examine which factors might be associated with sleep disturbance. Specifically, it was hypothesized that female gender, age less than five at diagnosis, tumor location, surgery, or radiation to the hypothalamus would be associated with poor sleep quality. Each of these characteristics was hypothesized as a contributor to understanding sleep quality in childhood survivors of brain tumors. It was also hypothesized that the post-treatment factors obesity,

Factors Associated with Sleep Disturbances

depression, and fatigue would be mediators impacting global sleep quality, thereby contributing to the understanding of why sleep is impaired in these survivors.

For this secondary analysis, the given sample size of 78 per group afforded 80% power to detect survivor vs. comparison group differences with effect sizes of 0.65 or greater, based on a two-sided t-test. Within the survivor group, effect sizes of 0.6 or greater could be detected by paired t-tests.

There were several factors associated with poor sleep quality in this study. First, survivors had significantly longer sleep latencies than the comparison group. This indicates survivors have difficulty initiating sleep once they go to bed. Those survivors who completed radiation to the hypothalamus had longer sleep latencies than other survivors. In addition, women in both the survivor and comparison groups had significantly worse global sleep quality scores and more daytime dysfunction. Survivors who were female and diagnosed before age five had improved sleep efficiency, or tended to spend most of their time in bed asleep. In a path model with the PSQI global score as the dependent variable, obesity, depression, and fatigue were not strong mediators of sleep quality, however fatigue explained more of the variance in the PSQI global score than the other two variables. These findings contribute to the current state of the knowledge on childhood cancer survivors and sleep disturbances.

Factors Associated with Sleep Disturbances

Brain tumor survivors in this study had significantly longer sleep latencies than the comparison group. In studies of the general population, sleep latencies are age-dependent in a quadratic fashion, with younger children (Nixon, Thompson, Han, Becroft, Clark, Robinson, et al., 2009) and elderly individuals taking longer to fall asleep than those in middle age. Individuals in the general population aged 20-59 experience average sleep latencies of 10.1-12.9 minutes (Geisler, Tracik, Cronlein, Fulda, Wichniak, Popp et al., 2006). This is significantly shorter than the mean reported sleep latencies of 33.6 minutes for brain tumor survivors in this study, which meet one of the criteria for the insomnia syndrome (Judd & Sateia, 2005).

In this study, female gender was associated with both poor sleep quality (PSQI score \geq 10) and significant daytime dysfunction. This is consistent with multiple studies of the general population, where daytime sleepiness in women (17.3%) is higher than in men (14.7%) (Baldwin, Kapur, Holdberg, & Rose, 2004; Breslau, Roth, Rosenthal, & Andreski, 1996; Hara, Lopes, & Lima-Costa, 2004; Hublin, Kaprio, Partinen, Heikkila, & Koskenvui, 1996; Stradling, Barbour, Glennon, Langford, & Crosby, 2000), and nearly 1 in 5 adults report intrusion of sleep during the day (Young, 2004). Poor sleep quality and daytime dysfunction are commonly associated with sleep disorders (i.e. sleep apnea), psychiatric and mood disorders (i.e. major depressive disorder, schizophrenia, and bipolar disease), and other medical conditions (i.e. Parkinson's and cancer) (Arnulf, 2005; Baldwin & Papakostas, 2006; Benca, 2007; Liebowitz, Brooks & Black, 2006). In this sample of brain tumor survivors and comparison group members, there were not obvious

Factors Associated with Sleep Disturbances

reasons for poor sleep quality and excessive daytime sleepiness among females. Another study among childhood cancer survivors reported the presence of an infant in the home as a significant predictor of daytime dysfunction (Mulrooney et al., 2008). In addition, there were no gender differences in depression scores among the groups in this study.

B) Aim 2: Treatment impact on sleep quality in survivors

Among the hypothesized treatment variables including tumor location and surgery, only brain tumor survivors who experienced radiation to the hypothalamus as part of their treatment approached significance for longer sleep latencies than survivors without radiation to the hypothalamus. Inability to initiate sleep among brain tumor survivors with damage to the hypothalamus has not been reported in the literature. In fact, treatment with radiation therapy was associated with fatigue, but not with sleep quality or daytime sleepiness in childhood brain tumor survivors in one recent study (Mulrooney et al., 2008). Long sleep latency is an interesting and surprising finding, given that previous research findings from brain tumor survivors with hypothalamic damage have focused on reports of daytime sleepiness among both cranio-pharyngioma and other types of tumors (Muller, Handwerker, Wollny et al, 2002; Rosen et al., 2003). This could indicate an imbalance in the hypothalamic arousal system and may spark new investigations employing longitudinal analyses to identify more clearly which sleep disturbances occur most frequently among brain tumor survivors, and where they occur along the survivor trajectory.

Factors Associated with Sleep Disturbances

Finally, female survivors and those diagnosed before age five reported significantly better sleep efficiency than other survivors. This indicates that once they are in bed, these survivors spend most of their time asleep. This could indicate female survivors are sleeping longer, even if they initially have difficulty falling asleep. This should be validated in future studies of sleep quality in this population.

C) Aim 2: Exploratory analyses

Exploratory analyses for this study included the relationship of treatment variables and sleep in survivors to the POMS and BSI global and subscale scores. Tumor location and surgery were not significantly associated in multiple variable regression models with depression, fatigue, or vigor. However, radiation to the hypothalamus and age at diagnosis less than five years were associated with significantly lower scores on the vigor subscale of the POMS. This is an interesting finding and might relate to sleep quality considering the sleep latencies of > 30 minutes among those survivors with radiation to the hypothalamus. However, this finding might also reflect lower physical or cognitive functioning in those with younger age at diagnosis who received radiation therapy (Robison, Green, et al., 2005). Adjectives used for the vigor subscale of the POMS include: lively, active, energetic, full of pep, and vigorous.

Those survivors in the 25-29 year age group had significantly higher fatigue subscale scores than survivors who were either younger or older. Adjectives used for the fatigue subscale of the POMS include: worn out, fatigued, exhausted, sluggish, and weary.

These results are not striking for fatigue in this sample and diverge from other studies of

Factors Associated with Sleep Disturbances

childhood cancer survivors where significant percentages of survivors reported fatigue, but not disturbed sleep (Mulrooney, et al., 2008). In addition, other cancer survivors have reported significant fatigue which was positively associated with symptoms of insomnia (Davidson, MacLean, Brundage, & Schulze, et al., 2002).

Prior to the survivor analysis of the BSI and depression subscales, a multiple variable regression model between survivors and the comparison group demonstrated survivors had higher mean scores on the global BSI score and all subscales which were either significant (somatization subscale) or approached significance (global scale, depression subscale, anxiety subscale). In addition, 6.4% of the comparison group and 8.9% of the survivors met the cut-off score of 63 on the t-distribution indicating emotional distress. This is similar to the 8.1% of childhood brain tumor survivors reported by another author using the BSI-18 (Mulrooney, et al., 2008). In this study, analyses with survivors only demonstrated no significant associations between the BSI-18 and age, gender, radiation to the hypothalamus, or age at diagnosis less than five. This is consistent with two other larger studies by Mulrooney, et al., (2008) and Zebrack, et al., (2004) who identified no association between those who received radiation therapy and depression in childhood brain tumor survivors. In fact, no treatment-related variables appeared significantly associated with any of the BSI-18 subscales in the Zebrack study, however, female survivors reported greater somatic distress, and there was a significant interaction effect for the global scale and anxiety subscale. Interaction terms among the BSI-18 subscales were not investigated in this study due to the small sample size.

D) Aim 3: Path model

Obesity, depression, and fatigue were hypothesized in a path model as post-treatment variables of childhood cancers which might impact global sleep quality. Obesity has become more common in the U.S. population with 25.6% of the general population reporting a BMI ≥ 30 (Galuska, Gillespie, Kuester, Mokdad, Cogswell, & Philip, 2008). Obesity has been linked with fatigue, sleep disorders and daytime dysfunction in both the general population (Flegal, Carroll, Ogden, & Johnson, 2002), among patients with narcolepsy (Longstretch, Koepsell, Thanh, & Hendrickson, 2007; Schuld, Hebebrand, Geller, & Pollmacher, 2000) and among childhood brain tumor survivors (Muller, Handwerker, Wollney, et al., 2002; Mulrooney, et al., 2008). Body mass index ≥ 30 and depression were not significant variables explaining sleep quality scores in the path model for this sample of childhood brain tumor survivors. Higher fatigue subscale scores explained 7% of the variance in sleep quality and were associated with slightly higher global sleep quality scores. Survivors who were female and diagnosed before age 5 had higher fatigue subscale scores and the strongest indirect associations with higher sleep quality scores within the path model. This is consistent with others who found female sex has been associated with fatigue in childhood cancer survivors, including those with brain tumors (Mulrooney et al., 2008). There are no reported associations between age at diagnosis and fatigue reported in the literature, however, significant neuro-endocrine and neuro-cognitive effects are more common in those diagnosed at less than 5 years old (Chin & Maruyama, 1984; Fouladi et al., 2005).

E) Fit with the Vena Model

These study results demonstrated Vena's model was an appropriate framework when applied to real clinical research situations. The model can be used to 1) guide selection of important predictor variables, and 2) explain part of the variance in survivors' sleep quality. In addition, Vena's conceptual framework was a good fit for categorizing variable associations for this analysis. Because of its focus on the important demographic, treatment, and post-treatment categories which might affect sleep after a cancer diagnosis, it was easy to identify significant variables. In addition, this model poses a complex inter-relationship between multiple variables as an explanation for sleep disturbances in patients or survivors with cancer. It is likely that this complexity is a real phenomenon and a simpler model would not capture the full significance of survivorship variables.

A limitation of using the Vena Model for this analysis was the limited data available for some of the categories. For instance, lifestyle variables were not collected for these participants and medication use was often not completely elucidated. However, despite this limitation, a number of variables were identified and tested during the analysis.

Other models were evaluated for use in this analysis, but were not found to fit well for various reasons. One such model was the Two Process Model of Sleep Regulation developed by Borbely & Achermann (1999). This model explains the importance of influences on the various physiological sleep mechanisms, but does not address

Factors Associated with Sleep Disturbances

psychological or demographic factors. The Vena Model was extremely useful for determining associations between variables and sleep quality.

Summary

There are some interesting contributions from this study regarding sleep quality in childhood brain tumor survivors. This study showed no difference in global sleep quality between survivors and comparison group members. However, significant differences on the sleep latency subscales of the PSQI were identified between brain tumor survivors and comparison group members. This indicates that survivors have difficulty falling asleep and often take longer than 30 minutes to do so, once they go to bed. These results are consistent with other studies of cancer survivors two to five years after treatment, indicating 23-44% suffer from some type of insomnia symptoms, compared to 9-12% of the general population (Ford & Kamerow, 1989). This may indicate a propensity toward chronic insomnia or other clinically meaningful sleep disorders in cancer survivors (Savard & Morin, 2001).

The other interesting finding is the significant impact of female gender on global sleep quality. Females in this study were nearly three times as likely to score ≥ 10 on the PSQI, than their male counterparts. Although females in the general population tend to report more sleep disturbance, depression, and fatigue than males, reasons for poor sleep quality among females are not readily apparent within this sample, but are consistent with multiple other studies reporting this same phenomenon in different groups. In contrast, female survivors in this study and those diagnosed at age less than five years reported

Factors Associated with Sleep Disturbances

higher sleep efficiency (spend more time in bed asleep) than other survivors. These results may indicate female survivors are sleeping longer, once they do fall asleep.

Further investigation of sleep efficiency in future studies could help to identify associations between sleep latency and sleep efficiency.

An interesting finding during the exploratory analysis among survivors was the impact of age at diagnosis less than five and radiation to the hypothalamus on the vigor subscale of the POMS. These survivors reported significantly lower vigor scores than other survivors and the comparison group. Despite this, neither of these groups reported higher fatigue or global sleep scores than other survivors. This may speak to either the conceptualization of vigor, the sophistication of those reporting, or the complexity of the relationships between vigor, fatigue, and sleep.

Lastly, a path model fitted with the variables from the survivor analysis explained 23% of the variance in PSQI global sleep scores among survivors. Female gender and age at diagnosis less than five years were both associated with higher fatigue subscale scores. Fatigue had a significant association in the model for higher PSQI global sleep quality scores, indicating that survivors with higher fatigue scores would report worse sleep quality. These results are consistent with others who have reported that fatigue, disturbed sleep, and daytime sleepiness were associated in childhood cancer survivors (Mulrooney, et al., 2008).

F) Strengths and Limitations

Strengths

Sample size and complete in-home data collection were strengths of this study. Because assessments were completed in the home with trained interviewers, missing data for participants was almost non-existent and participation bias was minimized for those unable to travel to the clinic for assessment. Few sleep studies of childhood brain tumor survivors in the literature have reported sample sizes greater than 25. This sample of 78 survivors is one of the largest ever reported. In addition, the inclusion of multiple tumor types with survival of 5 years or greater were strengths of this study. The decision to recruit a comparison group allowed the possibility of generalizing the study findings. Sex, age, and geographic matching of survivors and comparison group members enhanced the study analysis.

Limitations

As with most secondary analyses, data points collected for this study were pre-defined and not specifically identified for this analysis. It would have been valuable to examine other aspects of Vena's model, such as lifestyle factors. In addition, this sample was mostly white and therefore, conclusions about other ethnic groups cannot be inferred. Participation among the brain tumor survivors was only 59%. It is possible that those who chose to participate may have had either more or fewer sleep disturbances than those who did not participate. Non-response among potential comparison group members was also high, which could potentially bias the results, as those who did not participate may have had more or fewer sleep disturbances than those who did participate. The sample

Factors Associated with Sleep Disturbances

size for the path analysis was less than 200 and this might affect the fit of the model. Finally, although the instruments used for this analysis were validated with childhood cancer survivors, including those with brain tumors, the use of self-report data is subject to measurement error. In addition, initial psychometric evaluation of the PSQI was performed on a sample with an older mean age than this sample (Buysse, Reynolds, Monk, Hoch, Yeager, & Kupfer, 1991).

Due to the nature of cross-sectional observational data, this study does not purport to establish any causal relationships. Therefore, no causal relationships between the variables tested in multivariate or path analyses and sleep quality can be proven. In addition, this study was not able to prove any causal relationships between the POMS and BSI subscales and sleep disturbances.

G) Implications for nurses and recommendations for future research

This study examined sleep quality in childhood brain tumor survivors and a comparison group. Nurses should be aware of those cancer survivors who might be at risk for late effects from their treatment. Specific risk factors for sleep disturbances should be attended to and assessed at each interaction. Sleep is an often overlooked effect of cancer treatment which can impact role functioning, participation in daily activities, and quality of life. Convenient, short surveys appropriate for the clinical setting might help nurses assess patients when they return for follow up. These assessments open the door for further conversations about sleep quality.

Factors Associated with Sleep Disturbances

It is unclear why brain tumor survivors in general, or specifically survivors with radiation to the hypothalamus, might be at risk for longer sleep latencies. This new finding should be explored in follow-up studies with adequate sample sizes and power in order to detect clinically significant differences. Any further studies should include other contributing factors such as a thorough medication history and the impact of cognitive performance on self-report of sleep quality. In addition, other factors from the Vena Model, such as lifestyle factors, should be included. Ideally, a prospective longitudinal study evaluating the multiple influences of various factors on sleep quality in brain tumor survivors would be beneficial for addressing specific interventions.

This study reports new findings about sleep quality in childhood brain tumor survivors with one of the largest samples to date. It is important because it is a unique opportunity to characterize sleep disturbances in a cross-sectional sample of these survivors. In this analysis, surprising information about survivors was presented and described. These findings will guide additional hypotheses for future studies about sleep and survivorship in survivors of brain tumors.

References

- Akaike, H. (1987). Factor analysis and AIC. *Psychometrika*, 52, 317-332.
- Akerstedt, T., Froberg, J.E., Friberg, Y., & Wetterberg, L. Melatonin excretion, body temperature, and subjective arousal during 64 H of sleep deprivation. *Psychoneuroendocrinology*, 4, 219-225
- American Brain Tumor Association. (n.d.). Retrieved on November 11, 2009, <http://www.abta.org>
- Anderson, D.M., Rennie, K.M., Ziegler, R.S., Neglia, J.P., Robison, L.R., & Gurney, J.G. (2001). Medical and neurocognitive late effects among survivors of childhood central nervous system tumors. *Cancer*, 92(10), 2709-2719.
- Anderson, K.O., Getto, C.J., Mendoza, T.R., Palmer, S.N., Wang, X.S., Reyes-Gibby, C.C., et al. (2003). Fatigue and sleep disturbance in patients with cancer, patients with clinical depression, and community-dwelling adults. *Journal of Pain and Symptom Management*, 25(4), 307-318.
- Arbuckle, J. L. & Wothke, W. (1999). AMOS 4.0 users guide. Chicago: Smallwaters.
- Armitage, R. (2000). The effects of antidepressants on sleep in patients with depression. *Canadian Journal of Psychiatry*, 45, 803-809.
- Armstrong, G.T., Liu, Q., Yusai, Y., Huang, S., Ness, K.K., Leisenring, W. et al. (2009). Long-term outcomes among adult survivors of childhood central nervous system malignancies in the childhood cancer survivor study. *Journal of the National Cancer Institute*, 101(13), 946-958.

Factors Associated with Sleep Disturbances

- Arii, J., Kanbayashi, T., Tanabe, Y., Ono, J., Nishino, S., & Kohno, Y. (2001). A hypersomnolent girl with decreased CSF hypocretin level after removal of a hypothalamic tumor. *Neurology*, *56*(12), 1775-1776.
- Arnulf, I. (2005). Excessive daytime sleepiness in parkinsonism. *Sleep Medicine Reviews*, *9*, 185-200.
- Baldwin, C.M., Kapur, V.K., Holberg, C.J., & Rose, C. (2004). Associations between gender and measures of daytime somnolence in the Sleep Heart Health Study. *Sleep*, *27*, 305-311.
- Baldwin, D.S. & Papakostas, G.I. (2006). Symptoms of fatigue and sleepiness in major depressive disorder. *Journal of Clinical Psychiatry*, *67*(supp 6), 9-15.
- Barton-Burke, M. (2006). Cancer-related fatigue and sleep disturbances. *American Journal of Nursing*, *106*(3S), 72-77.
- Benca, R.M. (2007). Narcolepsy and excessive daytime sleepiness: Diagnostic considerations, epidemiology, and comorbidities. *Journal of Clinical Psychiatry*, *68*(supp 13), 5-8.
- Bentler, P.M. (1990). Comparative fit indexes in structural models. *Psychological Bulletin*, *107*, 238-246.
- Bentler, P.M., & Bonett, D.G. (1980). Significance tests and goodness-of-fit in the analysis of covariance structures. *Psychological Bulletin*, *88*, 588-606.
- Berger, A.M. & Farr, L. (1999). The influence of daytime inactivity and nighttime restlessness on cancer-related fatigue. *Oncology Nursing Forum*, *26*, 1663-1671.

Factors Associated with Sleep Disturbances

- Berger, A.M. & Higgenbotham, P. (2000). Correlates of fatigue during and following adjuvant breast cancer chemotherapy: A pilot study. *Oncology Nursing Forum*, 27, 1443-1448.
- Berger, A. M., Parker, K. P., Young-McCaughan, S., Mallory, G. A., Barsevick, A. M., Beck, S. L., et al. (2005). Sleep/wake disturbances in people with cancer and their caregivers: State of the science. *Oncology Nursing Forum*, 32(6), E98-E126.
- Bhopal, R. (2002). *Concepts of Epidemiology: An Integrated Introduction to the Ideas, Theories, Principles and Methods of Epidemiology*. Oxford University Press: New York.
- Borbely, A.A. & Achermann, P. (1999). Sleep homeostasis and models of sleep regulation. *Journal of Biological Rhythms*, 14(6), 559-568.
- Bower, J.E., Ganz, P.A., Desmond, K.A., Rowland, J.H., Meyerowitz, B.E., & Belin, T.R. (2000). Fatigue in breast cancer survivors: Occurrence, correlates, and impact on quality of life. *Journal of Clinical Oncology*. 18(4), 743-753.
- Breslau, N., Roth, T., Rosenthal, L., & Andreski, P. (1996). Sleep disturbances and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biological Psychiatry*, 39, 411-418.
- Broeckel, J., Jacobsen, P.B., Horton, J., Balducci, L., & Lyman, G.H. (1998). Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. *Journal of Clinical Oncology*, 16, 1689-1696.

Factors Associated with Sleep Disturbances

- Buysse, D.J., Reynolds, C.F. III, Hauri, P.J., Roth, T., Stepanski, E.J., Thorpy, J.J., et al. (1994). Diagnostic concordance for DSM-IV sleep disorders: a report from the APA/NIMH DSM-IV field trial. *American Journal of Psychiatry*, *151*, 1351-1360.
- Buysse, D.J., Reynolds, C.F., Monk, T.H., Berman, S.R., & Kupfer, D.J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research*, *28*, 193-213.
- Buysse, D.J., Reynolds, C.F., Monk, T.H., Hoch, C.C., Yeager, A.L., & Kupfer, D.J. (1991). Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). *Sleep*, *14*, 331-338.
- Buzsaki, G. (1998). Memory consolidation during sleep: A neurophysiological perspective. *Journal of Sleep Research*, *7 (Suppl)*, 17-23.
- Carpenter, J.S. & Andrykowski, M.A. (1998). Psychometric evaluation of the Pittsburgh Sleep Quality Index. *Journal of Psychosomatic Research*, *45(1)*, 5-13.
- CBTRUS, 2005. Statistical report: primary brain tumors in the United States, 1995-1999. Published by the Central Brain Tumor Registry of the United States.
- Chin, H.W. & Maruyama, Y. (1984). Age at treatment and long-term performance results in medulloblastoma. *Cancer*, *53*, 1952-1958.
- Claustrat, B., Brun, J., & Chazot, G. (2005). The basic physiology and pathophysiology of melatonin. *Sleep Medicine Reviews*, *9*, 11-24.

Factors Associated with Sleep Disturbances

- Constine, L.S., Woolf, P.D., Cann, D., Mick, G., McCormick, K., Raubertas, R.F. et al., (1993). Hypothalamic-pituitary dysfunction after radiation for brain tumors. *The New England Journal of Medicine*, 328(2), 87-94.
- Czeisler, C.A., Duffy, J.F., Shanahan, T.L., Brown, E.N., Mitchell, J.F., Rimmer, D.W., et al. (1999). Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science*, 284, 2177-2181.
- Davidson, J.R., MacLean, A.W., Brundage, M.D., & Schulze, K. (2002). Sleep disturbance in cancer patients. *Social Science & Medicine*, 54, 1309-1321.
- Derogatis, L. R. (2000). BSI-18 Administration, Scoring and Procedures Manual. National Computer Systems: Minneapolis.
- Dijk, D.J. & Czeisler, C.A. (1995). Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *Journal of Neuroscience*, 15, 3526-3538.
- Dijk, D.J., Shanahan, T.L., Duffy, J.F., Ronda, J.M., & Czeisler, C.A. (1997). Variation of electroencephalographic activity during non-rapid eye movement and rapid eye movement sleep with phase of circadian melatonin rhythm in humans. *Journal of Physiology*, 505, 851-858.
- Diller, L., Chow, E.J., Gurney, J.G., Hudson, M.M., Kadin-Lottick, N.S., Kawashima, T.I., et al., (2009). Chronic disease in the childhood cancer survivor study cohort: A review of published findings. *Journal of Clinical Oncology*, 27(14), 2339-2355.

Factors Associated with Sleep Disturbances

- Etzioni, A., Luboshitzky, R., Tiosano, D., Ben-Harush, M., Golsher, D. & Lavie, P., (1996). Melatonin replacement corrects sleep disturbances in a child with pineal tumor, *Neurology*, 46(1), 261-263.
- Faithfull, S. (1991). Patients' experiences following cranial radiotherapy: A study of the somnolence syndrome. *Journal of Advanced Nursing*, 16(8), 939-946.
- Faithful, S. & Brada, M., (1998). Somnolence syndrome in adults following cranial irradiation for primary brain tumors. *Clinical Oncology*, 10, 250-254.
- Fava, M. (2004). Daytime sleepiness and insomnia a correlates of depression. *Journal of Clinical Psychiatry*, 65(S16), 27-32.
- Finlay, J.L., Erdreich-Epstein, A., & Packer, R.J. (2007). Progress in the treatment of childhood brain tumors: No room for complacency. *Pediatric Hematology and Oncology*, 24, 79-84.
- Fisher, R. A. (1922). On the interpretation of X^2 from contingency tables, and the calculation of P. *Journal of the Royal Statistical Society*, 85, 87-94.
- Flegal, K.M., Carroll, M.D., Ogeden, C.L., & Johnson, C.L. (2002). Prevalence and trends in obesity among U.S. adults, 1999-2000. *JAMA*, 288, 1723-1727.
- Ford, D. E. & Kamerow, D. B. (1989). Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? *JAMA*, 262, 1479-1484.
- Fouladi, M., Gilger, E., Kocak, M., Wallace, D., Buchanan, G., Reeves, C. et al., (2005). Intellectual and functional outcome of children 3 years and younger who have CNS malignancies. *Journal of Clinical Oncology*, 23(28), 7152-7160.

Factors Associated with Sleep Disturbances

- Galuska, D.A., Gillespie, M.S., Kuester, M.S., Mokdad, A.H., Cogswell, M.E., & Philip, C.M. (2008). State-specific prevalence of obesity among adults-United States, 2007. *Morbidity and Mortality Weekly Report*, 57(28), 765-768.
- Geisler, P., Tracik, F., Cronlein, T., Fulda, S., Wichniak, A., Popp, R., et al. (2006). The influences of age and sex on sleep latency in the MSLT-30-A normative study. *Sleep*, 29(5), 687-692.
- di Gennaro, G.D., Autret, A., Mascia, A., Onorati, P., Sebastiano, F., & Quarato, P.P. (2004). Night terrors associated with thalamic lesion. *Clinical Neurophysiology*, 115(11), 2489-2492.
- Gurney, J.G., Ness, K.K., Stovall, M., Wolden, S., Punyko, J.A., Neglia, J.P. et al. (2003). Final height and body mass index among adult survivors of childhood brain cancer: Childhood cancer survivor study. *The Journal of Clinical Endocrinology & Metabolism*. 88(10), 4731-4739.
- Hara, C., Lopes, R.F., & Lima-Costa, M.F. (2004). Prevalence of excessive daytime sleepiness and associated factors in a Brazilian community: the Bambui study. *Sleep Medicine*, 5, 31-36.
- Hatcher, L. (1996). *A Step-by-Step Approach to using the SAS System for Factor Analysis and Structural Equation Modeling*. Cary, NC: SAS Institute, Inc.
- Heikens, J., Michiels, E.M.C., Behrendt, H., Endert, E., Bakker, P.J.M., & Fliers, E. (1998). Long-term neuro-endocrine sequelae after treatment for childhood medulloblastoma. *European Journal of Cancer*, 34(10), 1592-1597.

Factors Associated with Sleep Disturbances

Hoelter, J. W. (1983). The analysis of covariance structures: Goodness of fit indices.

Sociological Methods & Research, 11, 325-344.

Hosmer, D. W. & Lemeshow, S. (2000). *Applied Logistic Regression*. 2nd Ed. Wiley:

New York.

Howell, D. C. (2002). *Statistical Methods for Psychology*. 5th Ed. Duxbury: Pacific

Grove.

Hublin, C., Kaprio, J., Partinen, M., Heikkila, K., & Koskenvui, M. (1996). Daytime

sleepiness in adult Finnish population. *Journal of Internal Medicine*, 239, 417-

423.

Hudson, M.M., Mertens, A.C., Yasui, Y., Hobbie, W., Chen, H., Gurney, J.G., et al.

(2003). Health status of adult long-term survivors of childhood cancer: A report

from the childhood cancer survivor study. *JAMA*, 290(12), 1583-1592.

Hypothalamus location. (n.d.). In *Wikipedia*. Retrieved July 23, 2009, from

<http://en.wikipedia.org/wiki/File:Gray654.png>

Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., & Thun, M.J. (2009). Cancer Statistics

2009. *CA: A Cancer Journal for Clinicians*, 59(4), 225-249.

Joreskog, K.G. & Sorbom, D. (1989). *LISREL 7: A guide to the program and*

applications. Chicago: SPSS, Inc.

Judd, B.G. & Sateia, M.J. (2005). *International Classification of Sleep Disorders-2:*

Diagnostic and Coding Manual, 2nd ed., Westchester: American Academy of

Sleep Medicine.

Factors Associated with Sleep Disturbances

- Kunz, H. & Achermann, P. (2003). Simulation of circadian rhythm generation in the suprachiasmatic nucleus with locally coupled self-sustained oscillators. *Journal of Theoretical Biology*, 224, 63-78.
- Langeveld, N., Ubbink, M., & Smets, E. (2000). 'I don't have any energy': The experience of fatigue in young adult survivors of childhood cancer. *European Journal of Oncology Nursing*, 4, 20-28.
- Liebowitz, S.M., Brooks, S.N. & Black, J.E. (2006). Excessive daytime sleepiness: Considerations for the psychiatrist. *Psychiatric Clinics of North America*, 29, 921-945.
- Longstreth, W.T. Jr., Koepsell, T.D., Thanh, G.T., & Hendrickson, A.F. (2007). The epidemiology of narcolepsy. *Sleep*, 30(1), 13-26.
- Lustig, R. H., Post, S. R., Kleebsabai, S., Rose, S. R., Danish, R. K., Burghen, G. A., et al. (2003). Risk factors for the development of obesity in children surviving brain tumors. *The Journal of Clinical Endocrinology & Metabolism*, 88(2), 611-616.
- MacCallum, R. C. (1986). Specification searches in covariance structure modeling. *Psychological Bulletin*, 100, 107-120.
- Marcus, C., Trescher, W., Halbower, A., & Lutz, J. (2002). Secondary narcolepsy in children with brain tumors. *Sleep*, 25(4), 435-439.
- McNair, D.M., Lorr, M., & Droppleman, L.F. (1981). Profile of mood states. San Diego, CA: Educational and Industrial Testing Service.
- Meacham, L.R., Gurney, J.G., Mertens, A.C., Ness, K.K., Sklar, C.A., Robison, L.L. & Oeffinger, K.C. (2005). Body mass index in long-term adult survivors of

Factors Associated with Sleep Disturbances

childhood cancer: A report of the childhood cancer survivor study. *Cancer*, *103*(8), 1730-1739.

Miaskowski, C. & Lee, K.A. (1999). Pain, fatigue, and sleep disturbances in oncology outpatients receiving radiation therapy for bone metastasis: A pilot study. *Journal of Pain and Symptom Management*, *17*, 320-332.

Mormont, M.C., Waterhouse, J., Bleuzen, P., Giacchetti, S., Jami, A., Bogdan, A, et al. (2000). Marked 24-h rest/activity rhythms are associated with better quality of life, better response, and longer survival in patients with metastatic colorectal cancer and good performance status. *Clinical Cancer Research*, *6*, 3038-3045.

Mostow, E.N., Byrne, J., Connelly, R.R., & Mulvihill, J.J. (1991). Quality of life in long-term survivors of CNS tumors of childhood and adolescence. *Journal of Clinical Oncology*, *9*(4), 592-599.

Muller, H.L., Handwerker, G., Gebhardt, U., Faldum, A., Emser, A., Kolb, R., et al., (2006). Melatonin treatment in obese patients with childhood craniopharyngioma and increased daytime sleepiness. *Cancer Causes Control*, *17*(4), 583-589.

Muller, H.L., Handwerker, G., Wollny, B., Faldum, A., & Sorensen, N. (2002). Melatonin secretion and increased daytime sleepiness in childhood craniopharyngioma patients. *The Journal of Clinical Endocrinology & Metabolism*, *87*(8), 3993-3996.

Mulrooney, D.A., Ness, K.K., Neglia, J.P., Whitton, J.A., Green, D.A., Zeltzer, L.K., et al. (2008). Fatigue and sleep disturbances in adult survivors of childhood cancer:

Factors Associated with Sleep Disturbances

a report from the Childhood Cancer Survivor Study (CCSS). *Sleep*, 31(2), 271-281.

Nixon, G.M., Thompson, D.Y., Han, D.M.O., Becroft, P.M., Clark, E., Robinson, K.E. et al. (2009). Falling asleep: the determinants of sleep latency. *Archives of Disease in Childhood*, 94, 686-689.

Nyenhuis, D. L., Yamamoto, C., Luchetta, T., Terrien, A., & Parmentier, A. (1999). Adult and geriatric normative data and validation of the Profile of Mood States. *Journal of Clinical Psychology*, 55(1), 79-86.

Ouyang, M., Hellman, K. Abel, T., & Thomas, S.A. (2004). Adrenergic signaling plays a critical role in the maintenance of waking and in the regulation of REM sleep. *Journal of Neurophysiology*, 92, 2071-2082.

Packer, R. J., Gurney, J. G., Punyko, J.A., Donaldson, S. S., Inskip, P.D., Stovall, M., et al. (2003). Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: Childhood cancer survivor study. *Journal of Clinical Oncology*, 21(17), 3255-3261.

Packer, R.J., MacDonald, T., & Vezina, G. (2008). Central nervous system tumors. *Pediatric Clinics of North America*, 55, 121-145.

Palm, L., Nordin, V., Elmqvist, D., Blennow, G., Persson, E., & Westgren, U. (1992). Sleep and wakefulness after treatment for craniopharyngioma in childhood; influence on the quality and maturation of sleep. *Neuropediatrics*, 23(1), 39-45.

Factors Associated with Sleep Disturbances

- Parker, D., Malpas, J.S., Sandland, R., Sheaff, P.C., Freeman, J.E., & Paxton, A. (1978). Outlook following "somnolence syndrome" after prophylactic cranial irradiation. *British Medical Journal*, *1*(6112), 554.
- Pelletier, G., Verhoef, M.J., Khatri, N., & Hagen, N. (2002). Quality of life in brain tumor patients: The relative contributions of depression, fatigue, emotional distress, and existential issues. *Journal of Neuro-Oncology*, *57*(1), 41-49.
- Piccinelli, M. & Wilkinson, G. (2000). Gender differences in depression: Critical review. *British Journal of Psychiatry*. *177*, 486-492.
- Pilcher, J.J. & Huffcutt, A.I. (1996). Effects of sleep deprivation on performance: A meta-analysis. *Sleep*, *19*, 318-326.
- Poretti, A., Grotzer, M.A., Ribbi, K., Schonle, E., & Boltshauser, E. (2004). Outcome of craniopharyngioma in children: Long-term complications and quality of life. *Developmental Medicine & Child Neurology*, *46*(4), 220-229.
- Rechtschaffen, A. & Bergman, B. (2002). Sleep deprivation in the rat: An update of the 1989 paper. *Sleep*, *25*(1), 18-24.
- Rechtschaffen, A., Bergman, B.M., Everson, C.A., Kushida, C.A., & Gilliland, M.A. (2002). Sleep deprivation in the rat: X. Integration and discussion of the findings. *Sleep*, *25*, 68-87.
- Recklitis, C. J., Parsons, S. K., Shih, M. C., Mertens, A., Robison, L. L., & Zeltzer, L. (2006). Factor structure of the Brief Symptom Inventory-18 in adult survivors of childhood cancer: Results from the Childhood Cancer Survivor Study. *Psychological Assessment*, *18*, 22-32.

Factors Associated with Sleep Disturbances

- Recklitis, C. J. & Rodriguez, P. (2007). Screening childhood cancer survivors with the Brief Symptom Inventory-18: Classification agreement with Symptom Checklist-90-Revised. *Psycho-Oncology*, *16*, 429-436.
- Reppert, S.M. & Weaver, D.R. (2002). Coordination of circadian timing in mammals. *Nature*, *418*, 935-941.
- Robison, L.L., Green, D.M., Hudson, M., Meadows, A.T., Mertens, A.C., Packer, R.J. et al. (2005). Long-term outcomes of adult survivors of childhood cancer: Results from the childhood cancer survivor study. *Cancer*, *104*(11), 2557-2564.
- Robison, L. L., Mertens, A. C., Boice, J. D., Breslow, N. E., Donaldson, S. S., Green, D. M. et al. (2002). Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. *Medical Pediatrics and Oncology*, *38*, 229-239.
- Rosen, G.M., Bendel, A.E., Neglia, J.P., Moertel, C.L., & Mahowald, M. (2003). Sleep in children with neoplasms of the central nervous system: Case review of 14 children. *Pediatrics*, *112*(1), e46-e54.
- Rothman, K.J., Greenland, S., & Lash, T.L. (2008). *Modern Epidemiology*, 3rd Ed., Lippincott, Williams, & Wilkins: New York, NY.
- Saper, C.B., Scammell, T.E., & Lu, J. (2005). Hypothalamic regulation of sleep and circadian rhythms. *Nature*, *437*, 1257-1263.
- Savard, J. & Morin, C.M. (2001). Insomnia in the context of cancer: A review of a neglected problem. *Journal of Clinical Oncology*, *19*(3), 895-908.

Factors Associated with Sleep Disturbances

Schumacker, R. E. & Lomax, R. G. (2004). *A Beginner's Guide to Structural Equation Modeling*. 2nd Ed. Psychology Press: New York.

Schuld, A., Hebebrand, J., Geller, F., & Pollmacher, T.. (2000). Increased body-mass index in patients with narcolepsy. *Lancet*, 355(9211), 1274-1275.

Selbach, O. & Haas, H. L. (2006). Hypocretins: The timing of sleep and waking. *Chronobiology International*, 23 (1&2), 63-70.

Sejnowski, T. & Destexhe, A. (2000). Why do we sleep? *Brain Research*, 886, 208-223.

Shanahan, T.L. & Czeisler, C.A. (1991). Light exposure induces equivalent phase shifts of the endogenous circadian rhythms of circulating plasma melatonin and core body temperature in men. *Journal of Clinical Endocrinology and Metabolism*, 73, 227-235.

Silber, M.H. & Rye, D.B. (2001). Solving the mysteries of narcolepsy: The hypocretin story. *Neurology*, 56(12), 1616-1618.

Spiegel, K., Leproult, R., & Van Cauter, E. (1999). Impact of sleep debt on metabolic and endocrine function. *The Lancet*, 354, 1435-1439.

Stradling, J.R., Barbour, C., Glennon, J., Langford, B.A., & Crosby, J.H. (2000). Prevalence of sleepiness and its relation to autonomic evidence of arousals and increased inspiratory effort in a community based population of men and women. *Journal of Sleep Research*, 9, 381-388.

Szucs, A., Bodizs, T., Barsi, P., & Halasz, P. (2001). Insomnia and fronto-basal tumor: A case report. *European Neurology*, 46(1), 54-56.

Factors Associated with Sleep Disturbances

- Taheri, S. Zeitzer, J.M., & Mignot, E. (2002). The role of hypocretins (orexins) in sleep regulation and narcolepsy. *Annual Reviews in Neuroscience*, 25, 283-313.
- Tamburini, M., Selmi, S., DeConno, F., & Ventafridda, V. (1987). Semantic descriptors of pain. *Pain*, 25, 187-193.
- Tucker, L.R. & Lewis, C. (1973). The reliability coefficient for maximum likelihood factor analysis. *Psychometrika*, 38, 1-10.
- Tentorium cerebelli. (n.d.). In *Wikipedia*. Retrieved July 23, 2009, from http://en.wikipedia.org/wiki/Tentorium_cerebelli
- Turek, F.W. (2004). Circadian rhythms: From the bench to the bedside and falling Asleep. *Sleep*, 27(8), 1600-1602.
- Turek, F.W., Dugovic, C., & Laposky, A. (2004) Introduction section four: Master circadian clock: The SCN; Master circadian rhythm: The sleep-wake cycle? In: Kryger, M.H., Roth, T., & Dement, W.C. (Eds.), *Principles and Practice of Sleep Medicine*, 4th Ed., New York: WB Saunders.
- Uzal, D., Ozyar, E., Hayran, M., Zorlu, F., Atahan, L., & Yetkin, S. (1998). Reduced incidence of the somnolence syndrome after prophylactic cranial irradiation in children with acute lymphoblastic leukemia. *Radiotherapy and Oncology*, 48(1), 29-32.
- Vena, C., Parker, K., Cunningham, M., Clark, J., & McMillan, S. (2004). Sleep-wake disturbances in people with cancer Part I: An overview of sleep, sleep regulation, and effects of disease and treatment. *Oncology Nursing Forum*, 31(4), 735-746.

Factors Associated with Sleep Disturbances

- Wager-Smith, K. & Kay, S.A. (2000). Circadian rhythm genetics: from flies to mice to humans. *Nature & Genetics*, 26, 23-27.
- Winningham, M.L., Nail, L.N., Barton-Burke, M., Brophy, L., Cimprich, B., Jones, L.S. et al. (1994). Fatigue and the cancer experience: the state of the knowledge. *Oncology Nursing Forum*, 21, 32-36.
- Wright, S. (1934). The method of path coefficients. *The Annals of Mathematical Statistics*, 5(3), 161-215.
- Young, T.B. (2004). Epidemiology of daytime sleepiness: Definitions, symptomatology, and prevalence. *Journal of Clinical Psychiatry*, 65(supp 16), 12-16.
- Zebrack, B.J., Gurney, J.G., Oeffinger, K., Whitton, J., Packer, R.J., Mertens, A., et al. (2004). Psychological outcomes in long-term survivors of childhood brain cancer: A report from the childhood cancer survivor study. *Journal of Clinical Oncology*. 22(6), 999-1006.
- Zembelis, T., Paparrigopoulos, T., & Soldatos, C.R. (2002). REM sleep behaviour disorder associated with a neurinoma of the left pontocerebellar angle. *Journal of Neurology, Neurosurgery, & Psychiatry*, 72(6), 821-822.

Factors Associated with Sleep Disturbances

Appendix 1: St. Jude IRB Notification

**ST. JUDE INSTITUTIONAL REVIEW BOARD #29
FWA00004775**

August 8, 2008

Kirsten Ness, PT, PhD
Epidemiology and Cancer Control

RE: Non-Human Subjects Research Determination NR08-097

Dear Dr. Ness,

This is to certify that, on August 8, 2008, the e-mail dated 7/29/08, Subject: IRB Application, and attachment, Study Title: Factors associated with Sleep-Wake Disturbances in Adult Survivors of Childhood Brain Tumors was reviewed by the OHSP Director regarding the determination of whether the activity constitutes research involving human participants. Based upon your assurance that Ms. Gapstur will not receive individually linked information, I determined that she will be unable to ascertain the identities of individual participants.

IRB Review Status:

The activity has been determined to not involve human subjects, as defined in 45CFR46.102 (f):

Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information.

This determination also is based on the Office for Human Research Protections' (OHRP) Guidance Document dated 8-10-2004, on *Research Involving Coded Private Information or Biological Specimens*, found at the following Web link:
<http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>

Please keep this letter in your files.



Mark S. Long, MPA, CIP, OHSP
Director

Appendix 2: University of Minnesota IRB Notification

Subject: [0807E41502 - PI Gapstur - IRB - Exempt Study Notification](#)

From: irb@umn.edu +

Date: Tue, 21 Oct 2008 09:51:46 -0500 (CDT)

To: boel0006@umn.edu +

The IRB: Human Subjects Committee determined that the referenced study is exempt from review under federal guidelines 45 CFR Part 46.101(b) category #4 EXISTING DATA; RECORDS REVIEW; PATHOLOGICAL SPECIMENS.

Study Number: 0807E41502

Principal Investigator: Roxanna Gapstur

Title(s):

Factors Associated with Sleep Disturbances in Adult Survivors of Childhood

Brain Tumor Survivors

This e-mail confirmation is your official University of Minnesota RSPP notification of exemption from full committee review. You will not receive a hard copy or letter. This secure electronic notification between password protected authentications has been deemed by the University of Minnesota to constitute a legal signature. The study number above is assigned to your research. That number and the title of your study must be used in all communication with the IRB office. If you requested a waiver of HIPAA Authorization and received this e-mail, the waiver was granted. Please note that under a waiver of the HIPAA Authorization, the HIPAA regulation [164.528] states that the subject has the right to request and receive an accounting of Disclosures of PHI made by the covered entity in the six years prior to the date on which the accounting is requested. If you are accessing a limited Data Set and received this email, receipt of the Data Use Agreement is acknowledged.

This exemption is valid for five years from the date of this correspondence and will be filed inactive at that time. You will receive a notification prior to inactivation. If this research will extend beyond five years, you must submit a new application to the IRB before the study's expiration date. Upon receipt of this email, you may begin your research. If you have questions, please call the IRB office at (612) 626-5654. You may go to the View Completed section of eResearch Central at <http://eresearch.umn.edu/> to view further details on your study. The IRB wishes you success with this research

Appendix 3: Medical Records Abstraction Form

UNIVERSITY OF MINNESOTA

Physical Performance, Disability and QOL in Childhood Brain Tumor Survivors
History & Physical/Treatment Information

Name: _____

Tester's initials:

Birthdate:
 / /
 m m d d y y y y

Visit date:
 / /
 m m d d y y y y

Sex:
 Male
 Female

How would you describe your race?

American Indian and Alaska Native
 Asian
 Black or African American
 Native Hawaiian and Other Pacific Islander
 White
 Other - Please Specify:

Race Cod

Ethnicity:
 Hispanic or Latino
 Not Hispanic or Latino

RESIDENCE

Single Family Home **Own?** Yes No **Rent?** Yes No

Apartment **Own?** Yes No **Rent?** Yes No

Dormitory

Assisted Living

Residential Care

Other - Describe:

Res Code

STAIRS

None

Entry **Number:** **Railing:** Right Left **Use?** Yes No

Basement **Number:** **Railing:** Right Left **Use?** Yes No

Between Floors **Number:** **Railing:** Right Left **Use?** Yes No

Appendix 3: Medical Records Abstraction Form (continued)

OTHERS WHO LIVE IN HOME

Live Alone Yes No

Spouse/Significant Other Yes No Provide Care? Yes No

Roommate Yes No Provide Care? Yes No

Parent(s) Yes No Provide Care? Yes No

Sibling(s) Yes No Provide Care? Yes No

Other Yes No Provide Care? Yes No

If Other, Specify: Other Code

OUTSIDE CARE

None Yes No

Nursing Yes No

Personal Care Attendant Yes No

Homemaker Yes No

Meals Yes No

Other Yes No

If Other, Specify: Other Code

OUTSIDE INTERVENTIONS

Physical Therapy Yes No

Occupational Therapy Yes No

Speech Therapy Yes No

Special Education Yes No

Other Yes No

If Other, Specify: Other Code

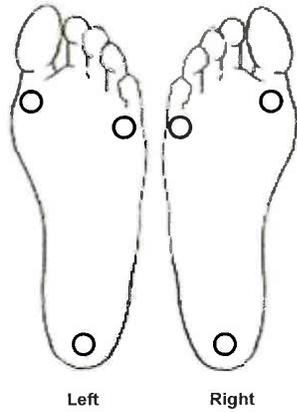
Drive? Yes No StateID? Yes No

Occupation: Accomodations:

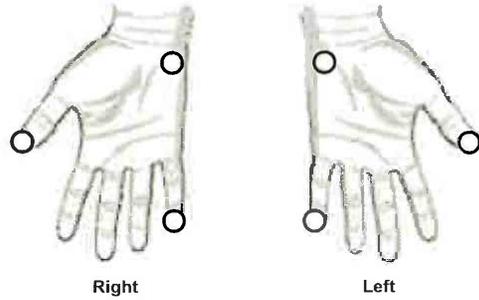
Occ Code 1 Occ Code 2 Acc. Code 1 Acc. Code 2 Acc. Code 3

Appendix 3: Medical Records Abstraction Form (continued)

PROTECTIVE SENSATION



Fill in the circles at the places where the subject has sensation.



ROM

ROM WNL Limited If Yes, Describe:

FUNCTIONAL STRENGTH

Functional Strength WNL Limited If Yes, Describe:

FORMAL STRENGTH

GRIP Right kg Left kg

KNEE EXTENSION Right N Left N

DOMINANCE Right Left

Comments:

Appendix 3: Medical Records Abstraction Form (continued)

DIAGNOSIS

Diagnosis: ICD O Code:

SURGERIES

Surgery Type: Date: / / ICD Proc Code: .
m m d d y y y y

Surgery Type: Date: / / ICD Proc Code: .
m m d d y y y y

Surgery Type: Date: / / ICD Proc Code: .
m m d d y y y y

RADIATION

Brain Total Dose to Brain: Units:
 Start Date: / / End Date: / /

Spine Total Dose to Spine: Units:
 Start Date: / / End Date: / /

TBI - Total Dose: Units:
 Start Date: / / End Date: / /
m m d d y y y y m m d d y y y y

Appendix 3: Medical Records Abstraction Form (continued)

CHEMO 1-5

1. Name: <input type="text"/>	Total Dose: <input type="text"/>	Units: <input type="text"/>	Med Code: <input type="text"/> <input type="text"/> <input type="text"/>
Start Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y	End Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y		

2. Name: <input type="text"/>	Total Dose: <input type="text"/>	Units: <input type="text"/>	Med Code: <input type="text"/> <input type="text"/> <input type="text"/>
Start Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y	End Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y		

3. Name: <input type="text"/>	Total Dose: <input type="text"/>	Units: <input type="text"/>	Med Code: <input type="text"/> <input type="text"/> <input type="text"/>
Start Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y	End Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y		

4. Name: <input type="text"/>	Total Dose: <input type="text"/>	Units: <input type="text"/>	Med Code: <input type="text"/> <input type="text"/> <input type="text"/>
Start Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y	End Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y		

5. Name: <input type="text"/>	Total Dose: <input type="text"/>	Units: <input type="text"/>	Med Code: <input type="text"/> <input type="text"/> <input type="text"/>
Start Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y	End Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y		

Appendix 3: Medical Records Abstraction Form (continued)

CHEMO 6-10

6. Name: <input type="text"/>	Total Dose: <input type="text"/>	Units: <input type="text"/>	Med Code: <input type="text"/> <input type="text"/> <input type="text"/>
Start Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y	End Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y		

7. Name: <input type="text"/>	Total Dose: <input type="text"/>	Units: <input type="text"/>	Med Code: <input type="text"/> <input type="text"/> <input type="text"/>
Start Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y	End Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y		

8. Name: <input type="text"/>	Total Dose: <input type="text"/>	Units: <input type="text"/>	Med Code: <input type="text"/> <input type="text"/> <input type="text"/>
Start Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y	End Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y		

9. Name: <input type="text"/>	Total Dose: <input type="text"/>	Units: <input type="text"/>	Med Code: <input type="text"/> <input type="text"/> <input type="text"/>
Start Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y	End Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y		

10. Name: <input type="text"/>	Total Dose: <input type="text"/>	Units: <input type="text"/>	Med Code: <input type="text"/> <input type="text"/> <input type="text"/>
Start Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y	End Date: <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> m m d d y y y y		