Childhood Cancer Survivor Study

Analysis of Concept Proposal

Study Title: Sleep behaviors and patterns and their relationship to health and mental health outcomes in adult survivors of childhood cancers

Working groups: Psychology (primary); Chronic Disease and Second Malignancy (secondary)

Investigators:

Lauren Daniel	daniell@email.chop.edu
Lisa Schwartz	schwartzl@email.chop.edu
Tara Brinkman	tara.brinkman@stjude.org
Kim Edelstein	kim.edelstein@uhn.ca
Daniel Mulrooney	Daniel.mulrooney@stjude.org
Eric Zhou	eric_zhou@dfci.harvard.edu
Tod Gibson	todd.gibson@stjude.org
Wendy Leisenring	wleisenr@fhcrc.org
Kevin Oeffinger	oeffingk@mskcc.org
Joe Neglia	jneglia@umn.edu
Greg Armstrong	greg.armstrong@stjude.org
Kevin Krull	kevin.krull@stjude.org

Background and Rationale

Sleep disturbances are common across the continuum of cancer treatment[1,2], posing a significant threat to health and quality of life for long-term survivors. Sleep is closely related to quality of life, psychological status, and overall health in the general population[3,4], but we have a limited understanding of the role of sleep in childhood cancer survivors. Common sleep disorders such as insomnia (indicated by more than 30 minutes to fall asleep and/or frequent/protracted night awakenings[5]) and obstructive sleep apnea (snoring resulting in pauses in breathing that affect sleep continuity[6]) can reduce both the quantity and quality of sleep. Furthermore, subclinical symptoms of these conditions may also have an effect on health and quality of life in patients, and potentially more so for cancer survivors[1]. Further study of specific sleep factors in this vulnerable population is warranted to inform tailored treatment of sleep problems, as these interventions may reduce distress and improve health outcomes for survivors.

Sleep disturbances in childhood cancer survivors are highly related to fatigue[7], quality of life[8], and anxiety[9]. Furthermore, survivors reporting poor sleep quality are almost 5 times more likely to be depressed[7,10]. In the general population short sleep duration and symptoms of insomnia have been found to predict the onset, recurrence, and persistence of depression[11-13]. Our prior research has demonstrated similar sleep parameters (total sleep time, sleep onset latency, sleep quality, sleep medication use) in adolescent and young adult survivors compared to controls without chronic health conditions[14]. However, participant perceived sleep and fatigue problems predicted later depression in survivors but not controls suggesting that sleep and fatigue disturbances pose greater risk for poor mental health in cancer survivors than in healthy adolescents and young adults.

Childhood cancer survivors are resilient, evidencing similar physical and mental health to siblings as a group[15,16]. There is, however, a subgroup of survivors who demonstrate poor mental health and reduced health-related quality of life[17], and for some of these survivors, distress can be persistent[18]. Such risk for poor psychosocial outcomes suggests a need to identify predictors and correlates of distress to facilitate early detection and interventions. Because sleep disturbances pose a risk for poor mental health, especially in survivors, understanding and intervening on sleep may also improve mental health and quality of life.

Less research has examined the relation between sleep and health outcomes in childhood cancer survivors. Poor sleep efficiency (the percentage of the time in bed spent asleep) is related to self-reports of poor physical health in childhood cancer survivors[9]. In brain tumor survivors, symptoms of insomnia are strongly related to migraine headaches[19]. In the general population, health outcomes research has primarily focused on sleep duration as a predictor of morbidity. For example, short sleep duration is predictive of poor cardiovascular outcomes[20], headache severity[21], obesity[22], and all-cause mortality[23]. The role of sleep duration and other sleep parameters in the health outcomes of childhood cancer survivors is unknown. At the very least, survivors receiving insufficient sleep face the same risk for poor health outcomes as the general population, although the risk may be heightened due to their cancer history.

Taken together, sleep is an essential component of psychosocial adjustment post-cancer and disrupted sleep may be an early marker of affective disorder diagnosis and other chronic health concerns. Previous findings from the Childhood Cancer Survivor Study (CCSS) have described the occurrence of poor sleep quality, daytime sleepiness, and fatigue relative to sibling controls, and the treatment, demographic, and psychological correlates of sleep quality, sleepiness, and fatigue[10]. For that publication, the authors utilized total scores of the Pittsburg Sleep Quality Index, Epworth Sleepiness Scale, and Functional Assessment of Chronic Illness Therapy-Fatigue to classify sleep quality, sleepiness, and fatigue respectively. These measures and the accompanying survey given as part of the CCSS Sleep Survey contain additional detail about sleep duration, sleep behaviors, symptoms of sleep problems, and sleep management strategies of survivors and sibling controls important to characterize sleep and to inform interventions. Building upon the work of Mulrooney and colleagues[10], the current proposal will characterize sleep parameters, factors contributing to poor sleep quality, and sleep management behaviors in survivors relative to sibling controls. Additionally, examining sleep duration, symptoms of insomnia, and symptoms of sleep disorders including sleep disordered breathing and delayed/advanced sleep phase disorder is important as such sleep parameters and diagnoses have been described as risk factors for poor mental and physical health outcomes[3,11,13,19-22].

In addition to characterizing the specific sleep concerns of survivors relative to siblings, the CCSS dataset offers the opportunity to test the prospective relation between sleep behaviors and symptoms of sleep disorders with mental and physical health outcomes. Sleep can be modifiable through highly efficacious behavioral interventions and medications[24]. Garnering a greater understanding of how sleep affects health over time is important to inform comprehensive survivorship care that includes regular sleep assessment and treatment of sleep disturbances.

Specific aims/objectives/research hypotheses:

Aim 1: Characterize patterns of poor sleep quality and altered sleep timing consistent with sleep disorders (insomnia, obstructive sleep apnea, delayed/advanced sleep phase onset) and sleep management strategies (sedative/stimulant medication use, complementary and alternative medicine use) in cancer survivors relative to sibling controls.

HYP 1a: Survivors will evidence similar sleep durations but greater symptoms of insomnia (delayed sleep onset latency, poor sleep efficiency), altered sleep timing (, and more symptoms of sleep disordered breathing (snoring, pauses in breathing) than sibling controls.

HYP 1b: Survivors will be more likely to endorse the use of medication, supplements, caffeine and behavioral strategies to manage sleep/wakefulness relative to sibling controls.

Aim 2: Within the survivor group, identify treatment-related predictors of specific sleep behaviors [Sleep onset latency (>30 minutes), sleep efficiency <85%, >1 nocturnal awakening, frequent snoring, frequent pauses in breathing, and delayed or advanced sleep phase onset (i.e., sleep onset after 1 am, wake time after 8 am, or a bedtime before 9 pm, wake time before 5 am)].

HYP 2a: Survivors treated with cranial irradiation will be at higher risk for delayed sleep onset latency and poor sleep efficiency compared to survivors treated without cranial radiation.

HYP 2b: Survivors treated with thoracic radiation will be at higher risk for sleep disordered breathing compared to survivors treated without thoracic radiation.

HYP 2c: Survivors treated with cranial radiation will be at higher risk for sleep timing disorders (i.e., delayed or advanced sleep phase onset) compared to survivors treated without cranial radiation.

Aim 3: Examine the prospective relationship between specific sleep problems or altered sleep timing with subsequent psychological functioning (BSI-18) in cancer survivors relative to sibling controls.

HYP 3a: Sleep onset latency (>30 minutes), sleep efficiency <85%, high daytime sleepiness (total score >8), >1 nocturnal awakening, frequent snoring, frequent pauses in breathing, high fatigue, and delayed sleep phase onset (i.e., sleep onset after 1 am) will be related to poorer psychological functioning in cancer survivors but not sibling controls.

HYP 3b: Survivors evidencing sleep concerns will be more likely to develop later psychological distress than survivors without sleep concerns.

Aim 4: Explore the association between specific sleep problems or altered sleep timing and relevant new onset health conditions (e.g., hypertension, migraines/headaches, second malignant neoplasms) in cancer survivors relative to sibling controls.

Methods

Study Population. CCSS Sleep Survey data will be used to describe the occurrence of specific sleep problems, behaviors, and sleep management strategies cross-sectionally in childhood cancer survivors (n=2645) and sibling controls (n=500). Additionally, to assess the prospective relationship between sleep health/mental health, survivors and sibling controls that completed the Sleep Survey (Time 1, 2002/2003), as well as the Baseline, Follow-up 2 (2003; Survivors n = 1426; Siblings n = 384) and Follow-up 4 (2007; Survivors n = 1530; Siblings n =296) surveys will be included for analyses for Aims 2 and 3.

Outcomes of Interest:

Sleep parameters and subjective report of sleep. The Pittsburg Sleep Quality Index (PSQI) describes sleep habits over the past month on a 4-point scale with higher scores indicating worse sleep[25]. Specific items that will be used from this measure are: bedtime, sleep onset latency, wake time, sleep duration, sleep efficiency (the difference between item 3 and 1 divided by item 4), sleep disturbances, sleep quality, and sleep medication use (Sleep Survey Items 1-4, 5a-j, 6, 7a-7b). PSQI items will be dichotomized to indicate clinically significant cut-points. Specifically, sleep efficiency <85%, >30 minutes sleep onset latency, and night awakenings/early morning awakenings more than 3 times per week are all suggestive of insomnia[31]. Delayed sleep phase disorders will be indicated by a bedtime after 1 am, wake time after 8 am, and at least a 1-hr delay in sleep onset 3 times per week (PSQI items 1-3, 5a). Advanced sleep phase disorder will be indicated by a bedtime before 9 pm, wake time before 5 am, and early morning wakening at least 3 times per week (PSQI items 1-3, 5b).

Daytime sleepiness. Epworth Sleepiness Scale (ESS) is an 8-item questionnaire that assesses the participant's likelihood of falling asleep in different situations on a 4-point Likert-type scale[26]. Higher scores indicate greater sleepiness. The total ESS summary score will be utilized for analyses (Sleep Survey Items 15a-15h). The ESS total score will be dichotomized based on a clinically significant cut-point of a total score greater than 10, which is indicative of significant daytime sleepiness[32].

Fatigue. Functional Assessment of Chronic Illness Therapy (FACIT) is a 13-item scale that has been validated in patients with cancer to assess the physical and functional impact of fatigue on functioning on a 4-point Likert-type scale[27]. Lower scores indicate more fatigue. The total FACIT score will be used for analyses (Sleep Survey Item 14a-14m). The FACIT total score will be dichotomized to indicate clinical significance. A FACIT score less than 40.1 suggests clinical levels of fatigue[33].

Sleep management strategies. Sleep Survey Item 9

Wakefulness management strategies. Sleep Survey Item 10

Caffeine consumption. Sleep Survey Item 11

Snoring and bedtime behaviors. Sleep Survey Item 13a-13e. Snoring/pauses in breathing more than 3 nights per week is suggestive of obstructive sleep apnea[6].

Psychosocial functioning to assess new onset psychosocial distress in survivors with and without sleep concerns.

Baseline:

- >18 y/o at baseline: Brief Symptom Inventory-18 (BSI) is an 18-item self-report questionnaire that assesses psychosocial functioning[28] using a 5-point Likert-type scale (items J16-35). Subscales indicate current symptoms (Somatization, Depression, Anxiety) and Global Severity Index (total score).
- < 18 y/o at baseline: Behavior Problem Index (BPI) is a 32-item parent report questionnaire[29] used to describe psychosocial functioning in children and adolescents on a 5-point Likert-type scale (items J19 a-w, J20 a-e, and J21 a-d on the Baseline <18 survey). Subscale scores corresponding with depression/anxiety will be used for the current analyses.

Follow-up 2: BSI subscales (items G1-G18) indicating current symptoms (Somatization, Depression, Anxiety) and Global Severity Index (total score).

Follow-up 4: BSI subscales (items L1-L18) indicating current symptoms (Somatization, Depression, Anxiety) and Global Severity Index (total score).

Health outcomes/Medical conditions to assess new onset medical concerns in survivors with and without sleep concerns.

Follow-up 4: Common Terminology Criteria for Adverse Events (CTCAE) grades for chronic health conditions with age of onset occurring after completion of the Sleep Survey. Second malignant neoplasm with onset occurring after completion of the Sleep Survey.

Predictor Variables: Within the survivor group age at diagnosis (categorical), diagnostic group (acute lymphoblastic leukemia, central nervous system malignancy, Hodgkin lymphoma, soft-tissue sarcomas, bone tumors), and treatment history [received chemotherapy (yes/no), received cranial radiation (yes/no), received thoracic radiation (yes/no)] will be examined as predictors of sleep behaviors and conditions.

Exploratory Variables to be examined as Covariates. Age at questionnaire completion (categorical 18-29, 30-39, 40-49, 50+), gender, and race will be examined as covariates between groups.

Data Analysis.

Descriptive statistics of demographic (age, gender, race) and treatment variables will be calculated in both the original cohort and siblings and will be compared using χ^2 tests or t-tests. Means and standard errors will be compared between survivors and siblings using generalized linear mixed models with generalized estimating equations to address intra-family correlation[30].

Sleep/fatigue variables will be dichotomized based on clinical significance and cut-offs for measures (as defined above). For each sleep behavior, we will compare survivors and controls with the percentage of individuals exhibiting the clinically significant sleep behavior. Sleep behaviors and sleep/wake management strategies will be compared between survivors and controls using multivariable generalized linear regression models with robust sandwich variance estimates to account for intra-family correlations and adjusting for demographic confounding variables. If outcomes are rare (<10%), we will use a logistic regression models to estimate odds ratios as an approximation to prevalence ratios (PR) estimates. If not rare, we will use a log link with Poisson error structure to directly estimate PRs. PRs for clinically significant sleep behaviors will be reported with corresponding 95% confidence intervals. Similarly, generalized linear models with the appropriate link function will be used to assess the impact of treatment related factors on sleep behavior outcomes among survivors.

Multivariable generalized linear regression models will be used to examine the relationship between sleep and later psychological functioning and health outcomes, with adjustment for relevant demographic variables. Similar to above, we will select the appropriate link function dependent on prevalence of the outcome, but likely will use a log link with Poisson error structure and sandwich variance estimates. Prevalence ratios for psychological distress will be reported with corresponding 95% confidence intervals, with significant sleep behaviors and patterns as predictors of distress outcome. To examine differences between survivors with and without distress, interaction terms between sleep disturbances and demographic variables will be explored.

For the exploratory Aim 4, we will identify which chronic health conditions and second malignant neoplasms occur with enough frequency within the cohort who completed the sleep survey. We will then determine whether a sufficient number of these conditions occurred after the date of completion of the sleep survey to evaluate the association of sleep behaviors/patterns with these subsequent outcomes. Multivariable generalized linear model regressions will be used to model the chronic condition outcome and/or second malignant neoplasms with significant sleep behaviors/patterns from Aim 1 and 2 as predictors and covariates specific to the chronic condition and/or second malignancy.

Tables that may be included in the manuscript

Table 1. Sample Demographics.

	Survivor	Control	*p* value
	N (%)	N (%)	
Gender			
Male			
Female			
Race			
White			
Black			
Hispanic			
Asian			
American			
Indian/Alaska Native			
Other			
Age at Questionnaire			
18-29			
30-39			
40-49			
50+			
Body Mass Index			
Normal/underweight			
Over weight			
Obese			
Age at Diagnosis			
0-4			
5-9			
10-14			
15+			
Diagnosis			
Leukemia			
CNS malignancy			
Hodgkin lymphoma			
Soft tissue sarcoma			
Bone cancer			
Chemotherapy			
Yes			
No			
Cranial radiation			
Yes			
No			
Thoracic radiation			
Yes			
No			

Table 2. Aim 1— Generalized linear models for comparison of frequency of sleep behaviors and sleep/wake management strategies between survivors and sibling controls.

Sleep Domain	Sleep Variable	Control	Survivor	
		PR (95% CI)	Unadjusted PR (95% CI)	Adjusted PR (95% CI)*
Insomnia Symptoms	Sleep Onset Latency >30 minutes	Ref		
	Sleep Efficiency <85%	Ref		
	Night awakening/early morning awakening >3 times per week	Ref		
Sleep Disordered Breathing Symptoms	Snoring >3 times per week	Ref		
	Pauses in breathing >3 times per week	Ref		
Delayed Sleep/Wake Timing	Sleep onset after 1 am	Ref		
	Wake time after 8 am	Ref		
Advanced Sleep/Wake Timing	Bedtime before 9 pm	Ref		
	Wake time before 5 am	Ref		
Sleep Management Strategies	Medication Use	Ref		
	Supplement Use	Ref		
	Behavior Strategies Use	Ref		
Wake Management Strategies	Medication Use	Ref		
	Supplement Use	Ref		
	Behavior Strategies Use	Ref		

* Adjusted for significant variables from Table 1.

Table 3. Aim 2— Multivariable generalized linear models for associations between sleep outcomes and treatment characteristics in survivors only.

	Sleep Onset Latency	Sleep Efficiency	Night Awakenings	Snoring	Pauses in Breathing	Bedtime
	≥ 31 minutes PR (95% CI)	≤ 85% PR (95% CI)	> 3 times per week PR (95% CI)	> 3 times per week PR (95% CI)	> 3 times per week PR (95% CI)	After 2 am PR (95% CI)
Body Mass Index Normal/underweight Over weight Obese	Ref	Ref	Ref	Ref	Ref	Ref
Age at Diagnosis 0-4 5-9 10-14 15+	Ref	Ref	Ref	Ref	Ref	Ref
Diagnosis Leukemia CNS malignancy Hodgkin lymphoma Soft tissue sarcoma Bone cancer	Ref	Ref	Ref	Ref	Ref	Ref
Chemotherapy Yes No	Ref	Ref	Ref	Ref	Ref	Ref
Cranial radiation Yes No	Ref	Ref	Ref	Ref	Ref	Ref
Thoracic radiation* Yes No	Ref	Ref	Ref	Ref	Ref	Ref

*If thoracic radiation is confounded with diagnosis, we will run separate models for treatment and diagnosis variables.

Table 4. Aim 3—Multivariable generalized linear models examining the association between specific sleep problems or altered sleep timing with later psychological functioning (BSI-18) in cancer survivors relative to sibling controls.

	BSI Anxiety			BSI Depression			BSI Somatization		
	Survivors	Controls		Survivors	Controls		Survivors	Controls	
	PR (95% CI)	PR (95% CI)	*p*	PR (95% CI)	PR (95% CI)	*p*	PR (95% CI)	PR (95% CI)	*p*
Sleep Onset Latency									
≤ 30 minutes	Ref	Ref		Ref	Ref		Ref	Ref	
≥ 31 minutes									
Sleep Efficiency <85%									
≤ 85%	Ref	Ref		Ref	Ref		Ref	Ref	
≥ 85.1%									
Night awakenings									
< 3 times per week	Ref	Ref		Ref	Ref		Ref	Ref	
> 3 times per week									
Sleepiness > 10									
≤ 10	Ref	Ref		Ref	Ref		Ref	Ref	
≥ 10.1									
Fatigue									
≤ 40.1	Ref	Ref		Ref	Ref		Ref	Ref	
≥ 40.2									
Snoring									
< 3 times per week	Ref	Ref		Ref	Ref		Ref	Ref	
> 3 times per week									
Pauses in breathing									
< 3 times per week	Ref	Ref		Ref	Ref		Ref	Ref	
> 3 times per week									
Bedtime									
Before 1 am	Ref	Ref		Ref	Ref		Ref	Ref	
After 1 am									
Before 9 pm									
After 9 pm	Ref	Ref		Ref	Ref		Ref	Ref	
Wake Time									
Before 5 am									
After 5 am	Ref	Ref		Ref	Ref		Ref	Ref	
Before 8 am	Ref	Ref		Ref	Ref		Ref	Ref	
After 8 am									

Note: Models will be adjusted for relevant demographic variables.

Table 5. Aim 4—Multivariable generalized regression for associations between sleep problems/altered sleep timing and specific CTCAE health outcomes among survivors.

	Hypertension	Migraines/ Headaches	Secondary Neoplasms
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Sleep Onset Latency			
≤ 30 minutes	Ref	Ref	Ref
≥ 31 minutes			
Sleep Efficiency <85%			
≤ 85%	Ref	Ref	Ref
≥ 85.1%			
Night awakenings			
< 3 times per week	Ref	Ref	Ref
> 3 times per week			
Sleepiness > 10			
≤ 10	Ref	Ref	Ref
≥ 10.1			
Fatigue			
≤ 40.1	Ref	Ref	Ref
≥ 40.2			
Snoring			
< 3 times per week	Ref	Ref	Ref
> 3 times per week			
Pauses in breathing			
< 3 times per week	Ref	Ref	Ref
> 3 times per week			
Bedtime			
Before 1 am	Ref	Ref	Ref
After 1 am			
Before 9 pm			
After 9 pm	Ref	Ref	Ref
Wake Time			
Before 5 am			
After 5 am	Ref	Ref	Ref
Before 8 am	Ref	Ref	Ref
After 8 am			

Note: Models will be adjusted for relevant treatment variables.

REFERENCES

1. Ancoli-Israel S, Moore PJ, Jones V. The relationship between fatigue and sleep in cancer patients: A review. *European Journal of Cancer Care.* 2001;10(4):245-255.

2. Lee K, Cho M, Miaskowski C, Dodd M. Impaired sleep and rhythms in persons with cancer. *Sleep Medicine Reviews.* 2004;8(3):199-212.

3. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: A longitudinal epidemiological study of young adults. *Biological Psychiatry.* 1996;39(6):411-418.

4. Lund HG, Reider BD, Whiting AB, Prichard JR. Sleep patterns and predictors of disturbed sleep in a large population of college students. *Journal of Adolescent Health.* 2010;46(2):124-132.

5. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med.* 2008;4(5):487-504.

6. Epstein LJ, Kristo D, Strollo Jr PJ, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med.* 2009;5(3):263-276.

7. Meeske KA, Siegel SE, Globe DR, Mack WJ, Bernstein L. Prevalence and correlates of fatigue in long-term survivors of childhood leukemia. *Journal of Clinical Oncology.* 2005;23(24):5501-5510.

8. Gordijn MS, van Litsenburg RR, Gemke RJ, et al. Sleep, fatigue, depression, and quality of life in survivors of childhood acute lymphoblastic leukemia. *Pediatric Blood & Cancer.* 2013;60(3):479-485.

9. Zhou E, Recklitis C. Insomnia in adult survivors of childhood cancer: a report from project REACH. *Supportive Care in Cancer.* 2014:1-9.

10. Mulrooney DA, Ness KK, Neglia JP, et al. Fatigue and sleep disturbance in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *Sleep.* 2008;31(2):271.

11. Baglioni C, Battagliese G, Feige B, et al. Insomnia as a predictor of depression: A meta-analytic evaluation of longitudinal epidemiological studies. *Journal of Affective Disorders.* 2011;135(1–3):10-19.

12. Perlis ML, Giles D, Buysse DJ, Tu X, Kupfer D. Self-reported sleep disturbance as a prodromal symptom in recurrent depression. *Journal of Affective Disorders.* 1997;42(2-3):209-212.

13. van Mill JG, Vogelzangs N, Van Someren EJ, Hoogendikj W, Penninx B. Sleep duration, but not insomnia, predicts the 2-year course of depressive and anxiety disorders. *Journal of Clinical Psychiatry.* 2014;75(2):119-126.

14. Daniel L, Kazak A, Li Y, et al. Relationship between sleep problems and psychological outcomes in adolescent and young adult cancer survivors and controls. *Supportive Care in Cancer.* 2015:1-8.

15. Hudson MM, Mertens AC, Yasui Y, et al. Health status of adult long-term survivors of childhood cancer: A report from the childhood cancer survivor study. *JAMA.* 2003;290(12):1583-1592.

16. Zeltzer LK, Recklitis C, Buchbinder D, et al. Psychological status in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. *Journal of Clinical Oncology.* 2009;27(14):2396-2404.

17. Zeltzer LK, Lu Q, Leisenring W, et al. Psychosocial Outcomes and Health-Related Quality of Life in Adult Childhood Cancer Survivors: A Report from the Childhood Cancer Survivor Study. *Cancer Epidemiology Biomarkers & Prevention.* 2008;17(2):435-446.

18. Brinkman TM, Zhu L, Zeltzer LK, et al. Longitudinal patterns of psychological distress in adult survivors of childhood cancer. *British Journal of Cancer.* 2013;109(5):1373-1381.

19. Zhou E, Manley P, Marcus K, Recklitis C. Medical and Psychosocial Correlates of Insomnia Symptoms in Adult Survivors of Pediatric Brain Tumors. *Journal of Pediatric Psychology.* 2015.

20. Heslop P, Smith GD, Metcalfe C, Macleod J, Hart C. Sleep duration and mortality: the effect of short or long sleep duration on cardiovascular and all-cause mortality in working men and women. *Sleep Medicine.* 2002;3(4):305-314.

21. Houle TT, Butschek RA, Turner DP, Smitherman TA, Rains JC, Penzien DB. Stress and Sleep Duration Predict Headache Severity in Chronic Headache Sufferers. *Pain.* 2012;153(12):2432-2440.

22. Hasler G, Buysse DJ, Klaghofer R, et al. The association between short sleep duration and obesity in young adults: a 13-year prospective study. *Sleep.* 2004;27(4):661-666.

23. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Sleep Duration and All-Cause Mortality: A Systematic Review and Meta-Analysis of Prospective Studies. *Sleep.* 2010;33(5):585-592.

24. Smith MT, Perlis ML, Park A, et al. Comparative Meta-Analysis of Pharmacotherapy and Behavior Therapy for Persistent Insomnia. *American Journal of Psychiatry.* 2002;159(1):5-11.

25. Buysse DJ, Angst J, Gamma A, Ajdacic V, Eich D, Rössler W. Prevalence, course, and comorbidity of insomnia and depression in young adults. *Sleep.* 2008;31(4):473.

26. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *sleep.* 1991;14(6):540-545.

27. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *Journal of Pain and Symptom Management.* 1997;13(2):63-74.

28. Derogatis LR. *The Brief Symptom Inventory: Administration, scoring, and procedure manual*. Minneapolis: National Computer Systems, Inc.; 1993.

29. Zill N. *Behavior problems index based on parent report*: Child Trends; 1990.

30. Verbeke G, Molenberghs G. *Linear mixed models for longitudinal data*: Springer Science & Business Media; 2009.

31. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults. *Journal of Clinical Sleep Medicine.* 2008;4(5):487-504.

32. Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep.* 1992;15(4):376-381.

33. Cella D, Zagari MJ, Vandoros C, Gagnon DD, Hurtz H-J, Nortier JW. Epoetin alfa treatment results in clinically significant improvements in quality of life in anemic cancer patients when referenced to the general population. *Journal of Clinical Oncology.* 2003;21(2):366-373.