Qual Life Res (2013) 22:781–789
DOI 10.1007/s11136-012-0208-5

Sleep disturbances in adult survivors of childhood brain tumors

Vikki G. Nolan · Roxanna Gapstur · Cynthia R. Gross · Lauren A. DeSain · Joseph P. Neglia · Amar Gajjar · James L. Klosky · Thomas E. Merchant · Marilyn Stovall · Kirsten K. Ness

Accepted: 17 May 2012 / Published online: 6 June 2012

Abstract
Purpose The aims of this study are to compare self-reported sleep quality in adult survivors of childhood brain tumors and a population-based comparison group, to identify treatment-related factors associated with sleep disturbances, and to identify the impact of post-treatment obesity and depression on sleep scores in adult survivors of childhood brain tumors.
Methods Randomly selected adult survivors of childhood brain tumors ($n = 78$) and age-, sex-, and zip code-matched population-group members ($n = 78$) completed the Pittsburgh Sleep Quality Index and the Brief Symptom Inventory. Sleep quality and the effect of demographic, treatment, and post-treatment characteristics were evaluated with linear and logistic regression analyses.
Results Brain tumor survivors were 2.7 (95 % CI, 1.1, 6.5) times more likely than the comparison group to take greater than 30 min to fall asleep. Females in both groups reported worse sleep quality and impaired daytime functioning. Among survivors, post-treatment obesity was associated with daytime dysfunction.
Conclusions These results agree with previous studies associating sleep, sex, and obesity and identified longer sleep latency as being a problem among childhood brain tumor survivors. Further study identifying factors contributing to sleep latency, and its impact on quality of life among adult survivors of childhood brain tumors is needed.

Keywords Sleep quality · Sleep latency · Adult survivors · Childhood brain tumors

Abbreviations

CNS	Central nervous system
QoL	Quality of life

V. G. Nolan (✉)
Department of Epidemiology and Biostatistics, University of Memphis, School of Public Health, 3820 Desoto Avenue, Browning Hall Room 227, Memphis, TN 38152, USA
e-mail: vgnolan@memphis.edu

R. Gapstur · C. R. Gross
School of Nursing, University of Minnesota Medical School, Minneapolis, MN, USA

C. R. Gross
College of Pharmacy, University of Minnesota Medical School, Minneapolis, MN, USA

L. A. DeSain
School of Public Health, University of Memphis, Memphis, TN, USA

J. P. Neglia
Department of Pediatrics, University of Minnesota Medical School, Minneapolis, MN, USA

A. Gajjar
Departments of Oncology, St. Jude Children's Research, Memphis, TN, USA

J. L. Klosky
Department of Psychology, St. Jude Children's Research, Memphis, TN, USA

T. E. Merchant
Department of Radiological Sciences, St. Jude Children's Research, Memphis, TN, USA

M. Stovall
Department of Radiation Physics, MD Anderson Cancer Center, Houston, TX, USA

K. K. Ness
Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN, USA

BMI	Body mass index
CCSS	Childhood Cancer Survivor Study
PSQI	Pittsburgh Sleep Quality Index
POMS	Profile of mood states
BSI-18	Brief Symptom Inventory
kg	Kilograms
m	Meter
SAS	Statistical analysis software
95 % CI	95 % Confidence interval

Introduction

Brain tumors comprise 15–20 % of cancers in children aged 0–19 years [1]. Although advances in radiation and chemotherapy treatments have improved the 5-year survival rate to 72 % central nervous system (CNS), tumors remain the second leading cause of death in children with cancer [1]. As more survivors live to adulthood, late effects of disease and treatment negatively impact quality of life [2–5]. Poor sleep quality and its effects, such as daytime sleepiness, are often reported late effect of brain tumor survivors [6–9] and may affect quality of life by decreasing participation in life events such as school, athletics, and/or social activities. A recent study by van der Klaauw et al. [9] reported that increased sleepiness (as measured by the Epworth Sleepiness Scale) in survivors of non-functioning pituitary adenomas was associated with 15 of 21 quality of life (QoL) subscores from four validated QoL questionnaires. Poor sleep quality and daytime sleepiness in childhood cancer survivors are also associated with neurocognitive deficits such as impaired task efficiency, diminished organization and impaired memory [6]. Clanton et al. [6] reported that the effect of sleepiness and poor sleep quality on neurocognitive outcomes is evident even after adjusting for cranial radiation therapy, steroids and antimetabolite chemotherapy, sex, and current age.

Sleep disturbances reported by brain tumor survivors include insomnia, limb movement disorders, sleep apnea, increased nighttime awakenings, and excessive daytime sleepiness [10–14]. A key contributor to sleep disturbance is damage to the hypothalamus, a region of the brain highly susceptible to radiation injury [15, 16]. Damage to hypocretin cells, which regulate arousal within the hypothalamus, is associated with excessive daytime sleepiness [17–20]. Multiple studies have found daytime sleepiness to be a significant problem among childhood brain tumor survivors [7, 11, 21–23]. One such study evaluated 14 children with brain tumors at a sleep clinic [23]. All were found to have excessive daytime sleepiness exhibited by one or more of the following: (1) increase in total sleep time per 24 h; (2) increased daytime naps previously discontinued at a younger age; (3) inability to arouse in the morning to begin usual activities; and (4) inability to sustain a wakened state during daytime activities such as school. Children with the most severe sleepiness had evidence of hypothalamic-pituitary injury with deficiencies in both the production of anterior and posterior pituitary hormones [23].

Another more recent study describes a series of CNS tumor survivors who were referred for sleep evaluations [11]. The most common reason for referral was excessive daytime sleepiness. Researchers found that a majority of the subjects were overweight/obese and had a mean sleep latency of 3.16 min, which is consistent with excessive sleepiness [11]. These results are similar to those from an earlier study that reported that higher body mass index (BMI) in some survivors may aggravate impaired daytime alertness. Researchers from St. Jude Children's Research Hospital identified age at diagnosis, radiation dose to the hypothalamus, and tumor location as risk factors for obesity following brain tumor treatment [22]. In a heterogeneous sample of 921 brain tumor survivors, researchers discovered females with younger age at diagnosis and radiation to the hypothalamus were more likely to experience obesity as long-term sequelae [21]. A recent report from the Childhood Cancer Survivor Study (CCSS) with a large sample of 2,645 childhood cancer survivors, including 398 with a variety of childhood brain tumors, identified that 16.7 % of the total sample self-reported disrupted sleep on the Pittsburgh Sleep Quality Index (PSQI), with 14 % reporting increased daytime sleepiness. Obese survivors with any cancer diagnosis were more likely to experience daytime sleepiness and sleep disruptions [7].

Sleep dysfunction is experienced by 40–60 % of outpatients with major depressive disorder[24] and is part of the diagnostic criteria for depression [25]. Gender differences in depression are genuine, with females in the general population reporting more fatigue and sleep disturbances than males [26]. Between 10 and 20 % of patients with Major Depressive Disorder, especially the atypical form, have excessive daytime sleepiness [27]. 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 sibling controls, even after accounting for other risk factors, such as gender, socioeconomic status, and physical health [28].

The links between treatment, post-treatment obesity and depression, and sleep quality are not well described in childhood brain tumor survivors. No study has compared sleep quality in brain tumor survivors with a population-based (non-sibling) comparison group. Thus, the aims of this study were to (1) compare self-reported sleep quality in adult survivors of childhood brain tumors and a population-based comparison group, (2) to identify treatment-related and demographic factors associated with sleep disturbances

in adult survivors of childhood brain tumors, and (3) identify the impact of post-treatment obesity and depression on sleep scores in brain tumor survivors.

Methods

Participants and procedures

The study population for these analyses included 78 adult survivors of childhood brain tumors aged 18 years or older, 5 or more years from their original diagnosis of a brain tumor, treated between 1970 and 2000 at the University of Minnesota Amplatz Children's Hospital or St. Jude Children's Research Hospital at less than 21 years of age. These survivors were randomly recruited from a population of 423 potentially eligible participants treated at the two institutions. The comparison group included 78 of 1,247 randomly selected individuals frequency-matched to tumor survivor's ages (18–29, 30–39, 40–49, 50–59 years), gender, and zip code. Non-English speakers, pregnant women, and persons with an active malignancy were not eligible. Recruitment of the survivors and population based comparison group has been previously described [29].

The University of Minnesota and St. Jude Institutional Review Boards for the protection of human subjects approved this study.

Measures

Sleep

Sleep Quality was evaluated with the Pittsburgh Sleep Quality Index (PSQI). The PSQI includes 19 self-report items designed to discriminate between "poor" and "good" sleepers. 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 to 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 [30]. This instrument has been previously used in a study of adult survivors of childhood cancer that included 398 childhood brain tumor survivors. Since normative data for the PSQI include populations with higher mean ages, Mulrooney et al. [7] determined that a global score cutoff of 10 was appropriate for adult survivors of childhood cancer based on data from a large sibling control group. A global PSQI score of 10 corresponded to the highest 10th percentile of scores among the controls and adequately identified poor sleepers; therefore, the same cutoff was used in these analyses.

To reduce the number of statistical tests performed, we limited our analyses to only those components of the PSQI that have previously been found to be associated with cancer treatment [7, 23] and those that we hypothesized were most likely to occur as a result of damage to the hypothalamus. In addition to overall sleep quality, the components studied include sleep efficiency, sleep latency, and daytime dysfunction.

Emotional health

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). Raw scores on this instrument are converted to T-scores (mean = 50, standard deviation = 10). A T-score greater than or equal to 63 indicates poor emotional health or emotional distress. The BSI-18 has been validated in both childhood cancer survivors, including those with brain tumors, and population controls [31–33].

History and assessment

Examiners reviewed participants' current prescription medications and conducted a comprehensive history, collecting demographic information, current and past medical history, review of systems, and family history. Body weight and standing height to the nearest centimeter were measured with a portable electronic scale and tape measure. BMI was calculated as weight in kilograms (kg) divided by height in meters (m) squared. For the purposes of this analysis, obesity was defined as a BMI $\geq$ 30 kg/m^2.

Cancer treatment variables

Participants were asked for consent to release their medical records. Trained abstractors determined tumor type and location, surgery or biopsies, radiation dosage, and chemotherapy drugs and doses. Radiation therapy dosage was determined from the medical record, treatment diagrams, 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. [34].

Statistical analyses

Descriptive statistics were generated, and survivors and comparison group members compared. Continuous

variables were compared with two-sample t tests, and categorical variables were compared with Fisher's exact tests [35]. Sociodemographic variables that were significantly different between the two groups were tested as covariates in linear and logistic regression models. We used the change-in-estimate method to identify additional confounding variables to be included in the model. In short, the parameter estimates and odds ratios obtained from the adjusted models were compared to those obtained from the crude models, and those variables that changed the measure of association by ten percent or more, along with the matched variables age and sex, were retained in the final model. Differences in continuous sleep quality scores between childhood brain tumor survivors and the population-based comparison group were evaluated using linear regression analyses, adjusted for age (18–24, 25–29, and 30+) and sex.

The same change-in-estimate method was used to build the final model associating treatment and post-treatment-related factors, and sleep quality. In these analyses of survivors only, linear regression analyses adjusted for age (18–24, 25–29, and 30+), sex, age at diagnosis (0–4, 5–9, 10–14 and 15+), and radiation to the hypothalamus were used to study the association between treatment and post-treatment-related factors and sleep quality scores. To identify factors associated with poor sleep quality overall (PSQI global score $\geq$10 vs. <10) and sleep onset latency (minutes before falling asleep $\leq$30 vs. >30 min) [36], a multiple variable logistic model was used. Statistical analyses were performed using SAS 9.2 (Cary, NC) and AMOS 7.2 (Chicago, IL). Two-sided p values are reported with significance determined at the 0.05 level.

Results

Characteristics of the study population

The participants in the brain tumor survivor group included 78 of the first 132 survivors randomly selected. Brain tumor survivor participants did not differ from non-participants by sex, current age, age at diagnosis, survival time, or tumor type [29]. The comparison group consisted of 78 of 1247 individuals who responded to the mailed invitation sent to randomly selected names and addresses from Melissa Data Resource (available at: http://www.melissadata.com accessed on March 23, 2010).

The study population was predominantly white (86 %) with a mean age at evaluation of 24.0 years (range, 18.4–58.3) for the survivors and 26.0 years (range, 18.0–53.9) for the comparison group. Because comparison group members were matched to survivors, there were 36 females and 42 males in each group (Table 1). Race distribution was identical in the two groups; however, survivors differed from comparison group members with respect to education level, marital status, and employment status. Survivors were less likely to attend school past high school, be married, and to be employed full time (Table 1).

Sleep quality

Sleep outcomes among survivors and the comparison group are shown in Tables 2 and 3. After adjusting for age and gender, there were no differences between survivors and members of the comparison group in mean PSQI global scores ($p = 0.35$), in mean sleep efficiency scores ($p = 0.17$), or in daytime dysfunction ($p = 0.79$). However, survivors did report slightly longer sleep onset latency than did comparison group members ($p = 0.08$; minutes before falling asleep 32.2 vs. 23.5 min, $p = 0.12$). In logistic regression models adjusted for age and gender, survivors were 2.7 (95 % CI, 1.1, 6.5) times more likely than the comparison group to take longer than 30 min to fall asleep. Females were 2.8 (95 %CI, 1.2, 6.5) times more likely than males to report poor sleep (score 10 or higher on the PSQI). Though significantly different between the survivors and comparison group members, education level, marital status, and employment status were not significant confounders of the associations between survivor status and sleep quality.

In addition to sociodemographic variables, age at diagnosis, radiation to the hypothalamic-pituitary axis, extent of surgical resection, tumor location, chemotherapy administration, obesity, and depressive symptoms as determined by the BSI-18 were examined as predictors of PSQI component scores and of poor sleep quality. In age- and sex-adjusted linear and logistic models, there were no significant associations between sleep quality and depressive symptoms when comparing survivors to comparison group members. Similarly, there were no associations between sleep quality and depressive symptoms among cancer survivors in models adjusted for current age, sex, age at diagnosis and radiation to the hypothalamus. We did, however, find evidence of an association between obesity and daytime dysfunction and between radiation to the hypothalamus and sleep onset latency. Obese survivors had significantly worse daytime dysfunction scores than non-obese survivors (adjusted mean scores, 1.05 vs. 0.70; $p = 0.04$), and those survivors that received radiation to the hypothalamus were 2.9 (95 % CI, 1.2, 6.8; $p = 0.02$) times more likely to report taking greater than 30 min to fall asleep.

Discussion

This study evaluated self-reported sleep quality among brain tumor survivors and a population-based comparison

Table 1 Subject characteristics

	Survivors $N = 78$ n (%)	Healthy controls $N = 78$ n (%)	p value
Sex			
Female	36 (46)	36 (46)	1.000
Male	42 (54)	42 (54)	
Race			
White	67 (86)	67 (86)	1.000
Black	11 (14)	11 (14)	
Age at questionnaire[a] (years)			
Mean ± S.D.	24.0 ± 6.1	26.0 ± 5.7	0.039
Highest Level of Education			
<High school	4 (5)	1 (1)	<0.001
High school grad	25 (32)	6 (8)	
>High school	49 (63)	71 (91)	
Marital status			
Married or living as married	13 (17)	35 (45)	<0.001
Not married	65 (83)	43 (55)	
Employment status			
Working full time	38 (49)	58 (75)	<0.001
Student	17 (22)	15 (19)	
Unemployed	23 (29)	5 (6)	
BMI[a]			
Mean ± S.D.	28.4 ± 6.4	28.4 ± 5.7	0.979
Obese	28 (36)	21 (27)	0.227
Poor Sleep Quality (PSQI ≥10)	19 (25)	15 (19)	0.413
Report >30 min to fall asleep	21 (28)	10 (13)	0.022
BSI-18: depression T-score[a]			
Mean ± S.D.	49.2 ± 10.2	47.0 ± 8.3	0.129
Diagnosis			
Medulloblastoma	22 (28)	NA	
Astroglial	40 (52)		
Craniopharyngioma	6 (8)		
Other	10 (13)		
Tumor location			
Posterior fossa	36 (46)	NA	
Supratentorial (non-hypothalamic)	24 (31)		
Hypothalamic	18 (23)		
Age at diagnosis			
0–4	22 (28)	NA	
5–9	26 (33)		
10–14	21 (27)		
15+	9 (12)		
Time since diagnosis (years)			
<10	12 (15)	NA	
10–14	30 (38)		
15–19	22 (28)		
20+	14 (18)		
Chemotherapy			
Yes	24 (31)	NA	
No	54 (69)		

Table 1 continued

	Survivors $N = 78$ n (%)	Healthy controls $N = 78$ n (%)	p value
Radiation			
None	26 (33)	NA	
Cranial only	29 (37)		
Cranial and spinal	23 (29)		
Surgery			
Yes	68 (87)	NA	
No	10 (13)		
Treating institution			
St. Jude	45 (58)	NA	
University of Minnesota	33 (42)		

This table describes the subjects included in these analyses. Data presented as n (%) or [a] mean ± standard deviation

group. There were several factors associated with poor sleep quality and daytime dysfunction in this study. These factors included survivorship status, female gender, radiation to the hypothalamic-pituitary axis, and obesity.

Brain tumor survivors were significantly more likely to have extended sleep latency (>30 min) than the population-based comparison group. In studies of the general population, sleep latencies are age dependent in a quadratic fashion, with younger children and elderly individuals taking longer to fall asleep than those between. Geisler et al. [37] reported that individuals in the general population, persons aged 20–59 who report no sleep disturbance, experience average sleep latencies of 10.1–12.9 min. This is substantially shorter than the mean reported sleep latencies of 33.6 min for brain tumor survivors and 23.5 min for our population-based comparison group. Though higher than published norms, the comparison group members in our study are within the normal range for sleep latency (<30 min). Young adult survivors of brain childhood brain tumors, however, meet at least one criterion for insomnia.

In this study, female gender was associated with both poor sleep quality (PSQI score of 10 or higher) and with significant daytime dysfunction. This is consistent with multiple studies in the general population, where daytime sleepiness in women (17.3 %) is more prevalent than in men (14.7 %) [38–42], and nearly 1 in 5 adults report intrusion of sleep during the day [43].

We found evidence of an association between hypothalamic-pituitary radiation dose and longer sleep onset latency. Inability to initiate sleep among brain tumor survivors with radiation to the hypothalamus has not been reported in the literature. Associations between radiation therapy and fatigue have been described, but not with sleep quality or daytime sleepiness in childhood brain tumor survivors [7]. Previous research of brain tumor survivors with hypothalamic damage has focused on reports of daytime sleepiness among both craniopharyngioma and other types of tumors [23, 44] but not sleep onset latency. Our results suggest a possible imbalance in the hypothalamic arousal system of adult survivors of childhood brain tumors and identify a novel pathway to study.

We hypothesized that post-treatment obesity and depression may be associated with sleep quality; however, we found no association between depressive symptoms and sleep quality and obesity is only associated with daytime dysfunction. This finding is consistent with the literature in that obesity has been linked to daytime dysfunction among childhood brain tumor survivors [7, 11, 44].

The results of this study should be interpreted in the context of several limitations. First, we had to sample over 1,000 persons to achieve an age-, gender-, and zip code-matched comparison group. It is possible that participants were healthier or more impaired than those who choose not to respond to the mailed participation request. A healthier comparison group would overestimate disordered sleep among brain tumor survivors, while a more impaired group would underestimate disordered sleep among brain tumor survivors. However, we previously reported that we did not find differences between our comparison group and the general population, so it is unlikely that low participation rates were a substantial source of bias [29]. Second, although the instruments used for this analysis have been validated in childhood cancer survivors, including those with brain tumors, self-report data are particularly subject to bias. Future studies should consider the use of polysomnography (objective) or a sleep diary ("real-time") to accurately quantify sleep quality. Finally, because our sample included only 78 adult brain tumor survivors and comparison group members, we may not be adequately powered to find an association between survivor status and treatment factors and sleep quality. Nevertheless, because

Table 2 Association between PSQI component scores* and survivor status

	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
Survivor status			0.35			0.17			0.08			0.79			0.12
Comparison group	Reference			Reference			Reference			Reference			Reference		
BT survivor	0.6	(0.6)		−0.3	(0.2)		0.3	(0.2)		0.03	(0.1)		8.7	(5.6)	
Current age			0.27			0.34			0.63			0.17			0.78
18–24	−1.1	(0.9)		−0.3	(0.4)		0.1	(0.3)		−0.1	(0.2)		1.3	(9.1)	
25–29	−0.2	(1.1)		0.01	(0.4)		0.2	(0.3)		0.1	(0.2)		−3.4	(10.3)	
30+	Reference			Reference			Reference			Reference			Reference		
Gender			0.03			0.12			0.16			0.03			0.56
Male	Reference			Reference			Reference			Reference			Reference		
Female	1.3	(0.6)		−0.4	(0.2)		0.2	(0.2)		0.2	(0.1)		3.3	(5.6)	

This table shows the association between PSQI components and survivor status. Differences in continuous sleep quality scores between childhood brain tumor survivors and the population-based comparison group were evaluated using linear regression, adjusted for age and sex. Parameter estimates, standard errors, and type III *p* values are reported

* Higher scores indicate poorer sleep quality

Table 3 Association between poor sleep quality and long sleep latency and survivor status

	PSQI global score ≥10			>30 min before falling asleep		
	OR	95 % CI	*p* Value	OR	95 % CI	*p* value
Survivor status			0.56			0.03
Comparison group	1.0			1.0		
Brain tumor Survivor	1.3	(0.6, 2.9)		2.7	(1.1, 6.5)	
Current age			0.76			0.87
18–24	0.9	(0.2, 3.7)		1.5	(0.8, 7.8)	
25–29	0.6	(0.1, 3.2)		1.6	(0.3, 9.9)	
30+	1.0			1.0		
Gender			0.02			0.12
Male	1.0			1.0		
Female	2.8	(1.2, 6.5)		2.0	(0.8, 4.6)	

This table shows the association between overall poor sleep quality and long sleep latency and survivor status. Factors associated with poor sleep quality overall (PSQI global score ≥10 vs. < 10) and sleep onset latency (minutes before falling asleep ≤30 vs. >30 min) were identified using a multiple variable logistic model adjusted for current age and sex. Odds ratios, 95 % confidence intervals, and type III *p* values are reported

results suggest that sleep onset latency is a problem among survivors [45–51], we believe that this novel finding warrants further study.

Implications for practice and research

It is unclear why brain tumor survivors might be at risk of longer sleep latencies, but fortunately, interventions are available. Although the FDA has approved several hypnotics for short-term insomnia and increased sleep latency, these medications can be habit forming and have potential for serious drug interaction. Furthermore, use of these medications may be particularly risky among brain tumor survivors who are often managed pharmacologically for various late effects of cancer therapy. Melatonin receptor agonists and exogenous melatonin may be useful in the treatment for delayed sleep phase syndrome and other circadian rhythm sleep disorders, but there are questions about the efficacy of this intervention in reducing sleep latency [52, 53]. In the context of treating survivors of childhood brain tumors, cognitive-behavioral therapies (utilizing stimulus–response and other sleep hygiene-related practices) may offer the safest and most efficacious intervention in reducing sleep latency, while avoiding the

risks associated with medication use [46]. Regardless of the interventions utilized, reductions in sleep latency should translate to improvements in overall sleep quality which in turn should improve overall quality of life outcomes for survivors of pediatric brain tumors.

Acknowledgments This study was funded by the American Cancer Society—RSGPB-06-210-01-CPPB and by additional funding at St. Jude Children's Research Hospital provided by ALSAC, and the University of Minnesota's Masonic Cancer Center.

Conflict of interest The authors of this manuscript have no conflicts to disclose.

References

1. American Brain Tumor. (2008). Association, *Facts and Statistics*.
2. Anderson, D. M., et al. (2001). Medical and neurocognitive late effects among survivors of childhood central nervous system tumors. *Cancer, 92*(10), 2709–2719.
3. Hudson, M. M., et al. (2003). Health status of adult long-term survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *JAMA: The Journal of the American Medical Association, 290*(12), 1583–1592.
4. Mostow, E. N., et al. (1991). Quality of life in long-term survivors of CNS tumors of childhood and adolescence. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 9*(4), 592–599.
5. Pelletier, G., et al. (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.
6. Clanton, N. R. et al. (2011). Fatigue, vitality, sleep, and neurocognitive functioning in adult survivors of childhood cancer: A report from the childhood cancer survivor study. *Cancer*, *117*(11), 2559–2568.
7. Mulrooney, D. A., et al. (2008). Fatigue and sleep disturbance in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *Sleep, 31*(2), 271–281.
8. Poretti, A., et al. (2004). Outcome of craniopharyngioma in children: Long-term complications and quality of life. *Developmental Medicine and Child Neurology, 46*(4), 220–229.
9. van der Klaauw, A. A., et al. (2007). Increased daytime somnolence despite normal sleep patterns in patients treated for non-functioning pituitary macroadenoma. *The Journal of Clinical Endocrinology and Metabolism, 92*(10), 3898–3903.
10. Di Gennaro, G., et al. (2004). Night terrors associated with thalamic lesion. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 115*(11), 2489–2492.
11. Mandrell, B. N. et al. (2012). Excessive daytime sleepiness and sleep-disordered breathing disturbances in survivors of childhood central nervous system tumors. *Pediatric blood and cancer*, *58*(5), 746–751.
12. Marcus, C. L., et al. (2002). Secondary narcolepsy in children with brain tumors. *Sleep, 25*(4), 435–439.
13. Szucs, A., et al. (2001). Insomnia and fronto-basal tumor: A case report. *European Neurology, 46*(1), 54–56.
14. Zambelis, T., Paparrigopoulos, T., & Soldatos, C. R. (2002). REM sleep behaviour disorder associated with a neurinoma of the left pontocerebellar angle. *Journal of Neurology, Neurosurgery and Psychiatry, 72*(6), 821–822.
15. Constine, L. S., et al. (1993). Hypothalamic-pituitary dysfunction after radiation for brain tumors. *The New England Journal of Medicine, 328*(2), 87–94.
16. Heikens, J., et al. (1998). Long-term neuro-endocrine sequelae after treatment for childhood medulloblastoma. *European Journal of Cancer, 34*(10), 1592–1597.
17. Arii, J., et al. (2001). A hypersomnolent girl with decreased CSF hypocretin level after removal of a hypothalamic tumor. *Neurology, 56*(12), 1775–1776.
18. Nishino, S., et al. (2000). Hypocretin (orexin) deficiency in human narcolepsy. *Lancet, 355*(9197), 39–40.
19. Selbach, O., & Haas, H. L. (2006). Hypocretins: The timing of sleep and waking. *Chronobiology International, 23*(1–2), 63–70.
20. Taheri, S., Zeitzer, J. M., & Mignot, E. (2002). The role of hypocretins (orexins) in sleep regulation and narcolepsy. *Annual Review of Neuroscience, 25*, 283–313.
21. Gurney, J. G., et al. (2003). Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. *Cancer, 97*(3), 663–673.
22. Lustig, R. H., et al. (2003). Risk factors for the development of obesity in children surviving brain tumors. *The Journal of Clinical Endocrinology and Metabolism, 88*(2), 611–616.
23. Rosen, G. M., et al. (2003). Sleep in children with neoplasms of the central nervous system: Case review of 14 children. *Pediatrics, 112*(1 Pt 1), e46–e54.
24. Armitage, R. (2000). The effects of antidepressants on sleep in patients with depression. *Canadian Journal of Psychiatry. Revue canadienne de psychiatrie, 45*(9), 803–809.
25. American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders* (4th ed.) text rev. Washington, American Psychiatric Association.
26. Piccinelli, M., & Wilkinson, G. (2000). Gender differences in depression. Critical review. *The British Journal of Psychiatry: The Journal of Mental science, 177*, 486–492.
27. Baldwin, D. S., & Papakostas, G. I. (2006). Symptoms of fatigue and sleepiness in major depressive disorder. *The Journal of Clinical Psychiatry, 67*(Suppl 6), 9–15.
28. Zebrack, B. J., 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: Official Journal of the American Society of Clinical Oncology, 22*(6), 999–1006.
29. Ness, K. K., et al. (2010). Physical performance limitations among adult survivors of childhood brain tumors. *Cancer, 116*(12), 3034–3044.
30. Buysse, D. J., et al. (1991). Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). *Sleep, 14*(4), 331–338.
31. Derogatis, L. (2000). *BSI-18, administration, scoring and procedures manual.* Mineappolis: National Computer Systems.
32. Derogatis, L. R., & Melisaratos, N. (1983). The Brief Symptom Inventory: An introductory report. *Psychological Medicine, 13*(3), 595–605.
33. Recklitis, C. J., et al. (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*(1), 22–32.
34. Packer, R. J., 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: Official Journal of the American Society of Clinical Oncology, 21*(17), 3255–3261.
35. Fisher, R. (1922). On the interpretation of X^2 from contingency tables, and the calculation of P. *Journal of the Royal Statistical Society, 85*(1), 87–94.
36. Lichstein, K. L., et al. (2003). Quantitative criteria for insomnia. *Behaviour Research and Therapy, 41*(4), 427–445.

37. Geisler, P., et al. (2006). The influence of age and sex on sleep latency in the MSLT-30—a normative study. *Sleep, 29*(5), 687–692.
38. Baldwin, C. M., et al. (2004). Associations between gender and measures of daytime somnolence in the Sleep Heart Health Study. *Sleep, 27*(2), 305–311.
39. Breslau, N., et al. (1996). Sleep disturbance and psychiatric disorders: A longitudinal epidemiological study of young adults. *Biological Psychiatry, 39*(6), 411–418.
40. Hara, C., Lopes Rocha F., & Lima-Costa M. F. (2004). Prevalence of excessive daytime sleepiness and associated factors in a Brazilian community: The Bambui study. *Sleep Medicine*, *5*(1):31–36.
41. Hublin, C., et al. (1996). Daytime sleepiness in an adult, Finnish population. *Journal of Internal Medicine, 239*(5), 417–423.
42. Stradling, J. R., et al. (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*(4), 381–388.
43. Young, T. B. (2004). Epidemiology of daytime sleepiness: Definitions, symptomatology, and prevalence. *The Journal of Clinical Psychiatry, 65*(Suppl 16), 12–16.
44. Muller, H. L., et al. (2002). Melatonin secretion and increased daytime sleepiness in childhood craniopharyngioma patients. *The Journal of Clinical Endocrinology and Metabolism, 87*(8), 3993–3996.
45. Holbrook, A. M., et al. (2000). Meta-analysis of benzodiazepine use in the treatment of insomnia. *CMAJ: Canadian Medical Association Journal = journal de l'Association medicale canadienne*, *162*(2):225–233.
46. Morin, C. M., et al. (2006). Psychological and behavioral treatment of insomnia: Update of the recent evidence (1998–2004). *Sleep, 29*(11), 1398–1414.
47. Morin, C. M., et al. (1999). Nonpharmacologic treatment of chronic insomnia. An American Academy of Sleep Medicine review. *Sleep, 22*(8), 1134–1156.
48. National Institutes of Health. (2005). NIH State-of-the-Science conference statement on manifestations and management of chronic insomnia in adults. In *NIH consensus state sci statements*.
49. Nowell, P. D., et al. (1997). Benzodiazepines and zolpidem for chronic insomnia: A meta-analysis of treatment efficacy. *JAMA: The Journal of the American Medical Association, 278*(24), 2170–2177.
50. Ritterband, L. M., et al. (2011). Initial evaluation of an Internet intervention to improve the sleep of cancer survivors with insomnia. *Psycho-oncology*. doi:10.1002/pon.1969.
51. Wade, A. G., et al. (2010). Nightly treatment of primary insomnia with prolonged release melatonin for 6 months: A randomized placebo controlled trial on age and endogenous melatonin as predictors of efficacy and safety. *BMC Medicine, 8*, 51.
52. Buscemi, N., et al. (2005). The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. *Journal of General Internal Medicine, 20*(12), 1151–1158.
53. Buscemi, N., et al. (2006). Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: Meta-analysis. *BMJ, 332*(7538), 385–393.