Published in final edited form as:
Cancer. 2011 June 1; 117(11): 2559–2568. doi:10.1002/cncr.25797.

Fatigue, vitality, sleep and neurocognitive functioning in adult survivors of childhood cancer: A Report from the Childhood Cancer Survivor Study

Nancy R. Clanton, PhD[1], **James L. Klosky, PhD**[1], **Chenghong Li, PhD**[2], **Neelam Jain, PhD**[3], **Deo Kumar Srivastava, PhD**[2], **Daniel Mulrooney, MD**[4], **Lonnie Zeltzer, MD**[6], **Marilyn Stovall, PhD**[6], **Leslie L. Robison, PhD**[3], and **Kevin R. Krull, PhD**[3]

[1]Department of Psychology, St. Jude Children's Research Hospital

[2]Department of Biostatistics, St. Jude Children's Research Hospital

[3]Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital

[4]Department of Pediatrics, University of Minnesota School of Medicine

[5]Departments of Pediatrics, Anesthesiology, and Psychiatry, David Geffen School of Medicine, University of California, Los Angeles

[6]Department of Radiation Physics, The University of Texas MD Anderson Cancer Center

Abstract

Background—Long-term survivors of childhood cancer are at risk for fatigue, sleep problems, and neurocognitive impairment, though the association between these outcomes has not been previously examined.

Methods—Outcomes were evaluated in 1426 survivors from the Childhood Cancer Survivor Study using a validated Neurocognitive Questionnaire. Relative risks for neurocognitive impairment were calculated using demographic and treatment factors, and survivors' report on the FACIT-Fatigue, the Short Form-36 Vitality Scale (SF-36-V), the Pittsburgh Sleep Quality Index (PSQI), and the Epworth Sleepiness Scale (ESS).

Results—Neurocognitive impairment was identified in over 20% of survivors, using sibling-based norms for comparison. Multivariable logistic regression models revealed that fatigue (RR=1.34, 1.13–1.59), daytime sleepiness (RR=1.68, 1.55–1.83), poor sleep quality (RR=1.23, 1.01–1.49) and decreased vitality (RR=1.75, 95% CI 1.33–2.30) were all associated with impaired task efficiency. Likewise, fatigue (RR=1.77, 1.23–2.55), sleepiness (RR=1.38, 1.14–1.67) and decreased vitality (RR=3.08, 1.98–4.79) were predictive of emotional regulation problems. Diminished organization was associated with increased sleepiness (RR=1.80, 1.31–2.48) and decreased vitality (RR=1.90, 1.37–2.63). Impaired memory was associated with poor sleep quality (RR=1.45, 1.19–1.76), increased sleepiness (RR=2.05, 1.63–2.58), and decreased vitality (RR=2.01, 1.42–2.86). The impact of fatigue, sleepiness, sleep quality and vitality on neurocognitive outcomes was independent of the effects of cranial radiation therapy, steroids and antimetabolite chemotherapy, sex, and current age.

Conclusions—Neurocognitive function in long-term survivors of childhood cancer appears particularly vulnerable to the effects of fatigue and sleep disruption. These findings suggest sleep

Address correspondence to: Kevin R. Krull, Ph.D., Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, 262 Danny Thomas Place, MS 735, Memphis, TN 38105-3678; (v) 901.595.5891; (f) 901.595.5845; kevin.krull@stjude.org.

hygiene should be emphasized among survivors, as it may provide an additional mechanism for intervention to improve neurocognitive outcomes.

Keywords

Childhood Cancer Survivor Study; CCSS; neurocognitive; sleep; fatigue; vitality

As enhanced medical treatments have contributed to an increase in the number of adult survivors of childhood cancer, research has focused on the medical and functional late effects of cancer therapy.1–4 Common functional late effects that significantly impact quality of life includes neurocognitive impairment and fatigue.

Survivors of childhood cancer are at increased risk for neurocognitive impairment, either as a direct or indirect result of central nervous system (CNS) treatment. Cranial radiation treatment (CRT) has long been associated with neurocognitive late effects,1–3 though antimetabolite chemotherapy and corticosteroids have also been implicated as potential contributors to poor outcomes.5 Neurocognitive impairment is one of the most common late effects experienced by long-term survivors of pediatric acute lymphoblastic leukemia (ALL), with 20% – 40% of patients exhibiting deficits in one or more areas of function.3, 4 Adult survivors of pediatric CNS tumors also experience high rates of neurocognitive difficulties, which frequently include slow processing speed, inattention, and memory impairment.6

Reduced sleep quality and fatigue are also reported to impact neurocognitive functioning. Specifically, fatigue is associated with impairments in processing speed, attention and memory functions.7 Among adults diagnosed with chronic fatigue syndrome, slow processing speed, impaired working memory, and poor memory and learning of new information has been reported.8, 9 Similarly, the presence of significant fatigue has been associated with poor neuropsychological functioning in adults with acute medical conditions.10–13

Fatigue and reduced sleep quality are common late effects experienced by long-term survivors of childhood cancer.14 It is estimated that up to 45% of the general population report symptoms of fatigue,15 while rates as high as 90% have been reported in cancer survivors.16–19 For example, ALL survivors typically report significant fatigue many years after completion of treatment,20, 21 whereas survivors of Hodgkin lymphoma (HL) report more fatigue than their siblings and population-based controls.14, 22, 23 Survivors of childhood brain tumor report more physical health difficulties than other pediatric cancer survivors, with poorer physical functioning associating with greater fatigue.24 In a comprehensive assessment of fatigue, sleepiness and sleep quality, slightly higher rates of fatigue were reported among adult survivors of childhood cancer compared to a sibling cohort, though no significant differences were reported between siblings and survivors in regard to sleepiness or sleep quality.14

Although the differences between rates of fatigue and sleep problems among cancer survivors and siblings may be small, differential sensitivity of fatigue and poor sleep quality on neurocognitive functions within the different cohorts may exist. Sleep is important for neural recovery following brain injury.25 Furthermore, sleep deprivation among individuals with brain injury exacerbates the degree of neurocognitive impairment.26 Thus, although the rate of fatigue and poor sleep quality in survivors of childhood cancer may or may not be clinically significant, the impact of fatigue and sleep loss on neurocognitive performance may be more salient in the survivors who are at risk for brain injury following neurotoxic cancer therapy. Little is known of the association between fatigue or sleep quality and

neurocognitive outcomes among adult survivors of childhood cancer. The primary objective of the current study is to elucidate this association. It was hypothesized that survivors with higher ratings of fatigue and sleepiness will report more problems with processing speed, attention, and memory functions, independent of the known effect of cranial radiation therapy on these neurocognitive outcomes.

Method

Participants

Participants for these analyses included 1,426 adult survivors from the Childhood Cancer Survivor Study (CCSS) and 384 sibling controls. The CCSS is a retrospective cohort study designed to investigate long-term medical, psychosocial, and functional outcomes of survivors of childhood cancer. Details of this study have been previously reported.27, 28 Briefly, eligible participants were treated for one of eight childhood cancer diagnoses at 26 institutions between 1970 and 1986 when younger than 21 years of age. Cohort entry was limited to those individuals who survived for at least five years after their original diagnosis. The human subjects committee at each of the collaborating institutions approved the study protocol before participant enrollment. Participants provided informed consent for questionnaires and medical record abstraction. Study participants have completed multiple questionnaires since their original enrollment (the full survey questionnaires are available at http://ccss.stjude.org). The study population for the current analyses included all cancer survivors and cohort of randomly selected sibling controls who completed both the 2003 Follow-Up survey (conducted between 2002 and 2006) and the Fatigue and Sleep Survey (conducted between 2002 and 2004). The 2003 Follow-Up survey was collected from 6739 survivors and 384 randomly select siblings between 2002 and 2006. The fatigue/sleep survey involved a separate mailing to 2645 randomly selected survivors and the siblings, and was collected between 2002 and 2004. 1426 survivors and 384 siblings completed both surveys. Consistent with a prior published report on the prevalence of fatigue and sleep problems in the CCSS cohort,14 survivors diagnosed with and treated for Hodgkin Lymphoma were over-represented in the current sample, given their apparently higher rates of reported fatigue and sleep problems.

In addition to the specific measures described below, the 2003 Follow-Up survey included report of the following categories of information: medical care over the prior two years; medical screening tests; health behaviors; insurance coverage; family history of cancer, birth complication, and hereditary conditions; pregnancy and offspring; dental and bone health; current medication use; cancer relapse or recurrence; and current income.

Measures

CCSS Neurocognitive Questionnaire (CCSS-NCQ)—Self-report of neurocognitive skills was assessed using the CCSS-NCQ, a measure that has been previously validated in adult survivors of childhood cancer.29 This 25 item questionnaire requires ratings of neurocognitive problems on a three –point Likert scale (0 = “Never a problem” to 2 = “Often a problem”), and has been identified as comprising four primary factors of neurocognitive outcome: Task Efficiency, Emotional Regulation, Organization, and Memory. These factors provide measures of executive functioning (i.e., Emotional Regulation and Organization factors), attention and processing speed (i.e., Task Efficiency factor), and working and long-term memory (i.e., Memory factor). Impaired performance was defined as a score falling ≤ 10^{th} percentile based on sibling age and sex-adjusted norms.

Vitality—Survivors also completed the Medical Outcomes Short Form-36 (SF-36) to evaluate health related quality of life.30 Within the SF-36, items comprising the Vitality

Scale were used as a primary predictor. The four items comprising this measure are rated on a six-point Likert scale (0 = “All of the time” to 5 = “None of the time”), and measure the degree of feeling energetic and full of life versus feeling tired and worn out. Poor vitality was defined as a T-score falling ≤ 40 based on a national standardization sample.

Fatigue—The fatigue subscale of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) was also used as a primary predictor. This is a measure of the physical and functional consequences associated with fatigue.31 The 13-items comprising this measure are scored on a reverse four-point Likert scale (4 = “Not at all” to 0 = “Very much”). Greater fatigue is represented by lower scores.

Sleep Quality—The Pittsburgh Sleep Quality Index (PSQI) was administered to assess sleep quality over the month prior to survey completion.32 A number of sleep quality components are measured by the PSQI, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medications, and daytime dysfunction. For current analyses, the overall score comprised of all 19 items on the PSQI, which are scored on a four-point Likert scale (0 = “Not during the past month” to 3 = “Three or more times a week”) was used as a measure of sleep quality, with higher scores indicating poorer quality of sleep.

Daytime Sleepiness—Symptoms of daytime sleepiness were measured using the Epworth Sleepiness Scale (ESS).33 Using a four-point Likert scale (0 = “Would never doze” to 3 = “High chance of dozing”), participants rated the likelihood of falling asleep during routine situations, with higher scores indicative of greater daytime sleepiness.

The PSQI and FACIT-Fatigue were originally standardized using a sample that was older on average than the age of the current survivor cohort (i.e. 59.9 years for the PSQI and 45.7 for the FACIT control samples, respectively, 35.9 years for the current cancer survivor cohort). In addition, the sample size for the control groups used in development of the PSQI (n=52) and Epworth (n=30) were relatively small. Thus, in order to dichotomize the scales and identify levels of clinical problems, we compared survivors to an age and sex matched sibling cohort group (n=384). Survivors falling ≤ 10^{th} percentile on the FACIT-fatigue or ≥ 10^{th} percentile on the PSQI and ESS were classified as having significant fatigue, poor sleep quality or daytime sleepiness, respectively. These cutoffs are consistent with the procedure used in a prior published report.14

Covariates—The Brief Symptom Inventory-18 (BSI-18) was used as a measure of global distress.34 Given the association between fatigue and emotional distress, subscales for anxiety, depression, and somatization were used as covariates. Gender-specific scores were calculated based on standardized normative values, and scores ≤ 10^{th} percentile were classified as demonstrating clinical level of emotional distress. Only 48.2% of those survivors reporting significant depressive symptoms reported using antidepressant medication. Given the impact use of this medication has on fatigue and neurocognitive function,35 and its limited multicollinearity with depressive symptoms, antidepressant medication use was included as a covariate in modeling outcomes. Cancer treatment was also utilized as a covariate. Cranial radiation therapy was categorized by radiation dose intensity resulting in three groups: None, Low (0 to <20 Gy), or High (> 20 Gy). The Low dose radiation exposure group included those with scatter exposure from radiation treatment of adjacent body areas. Treatment with CNS chemotherapy was included using dichotomous variables (yes/no) for Antimetabolites and for Corticosteroids. Additional covariates included age, sex, household income (<20,000, ≥20,000), and body mass index (non-obese [BMI <30], and obese [BMI >30]).

For the primary predictors of fatigue, sleepiness, and sleep quality and for the neurocognitive outcomes, where higher ratings are suggestive of pathology, we used a cut-off score ≥ that seen in the highest 10% of siblings. This is consistent with cut-offs used in the current literature.14 For the SF-36 Vitality score, where lower ratings are suggestive of pathology, we used a cut-off score ≤ one standard deviation from the population mean. This cut-off is also consistent with current reports in the literature and with the recommendation in the test manual and interpretation guide.30, 36

Statistical Analyses

Descriptive statistics were calculated to evaluate frequency, percent, mean, standard deviation, and range of all outcomes, predictors, and covariates used in the analyses. Pearson correlations were conducted to evaluate associations between each variable included in the analyses. To address clinical implications for each of the four outcome variables on the CCSS-NCQ (Task Efficiency, Emotional Regulation, Organization, and Memory), performance was classified into yes/no impairment based on comparison to sibling norms, and a multivariable logistic regression model was then constructed. Fatigue, vitality, and sleep variables were also classified into yes/no problem level, as described above. Backward selection was performed for each of the models using PROC GENMOD with binomial distribution and log link. These analyses began with the full model, which included all of the predictors (vitality, fatigue, sleep quality, and daytime sleepiness) and covariates (anxiety, depression, somatization, cranial radiation therapy, antimetabolite chemotherapy, corticosteroid therapy, antidepressant medication, current age, age at diagnosis, sex, household income, and BMI). Then the least significant variables (largest p-value) were excluded one at a time until all the variables left in the model were significant (p-value <0.05). Factors having more than 2 levels were kept or removed based on the p-value of the Likelihood Ratio Test. Given the association between current age and fatigue, current age was left in each model regardless of its significance. Finally, Relative Risks and 95% confidence intervals of predictors and covariates left in the final model for each outcome were calculated. Given the large sample size, this approach was perceived as appropriate for demonstrating increased risk of neurocognitive impairment associated with the primary predictors and covariates. Analyses were conducted separately for type of cancer diagnosis (e.g., ALL, CNS brain tumor, HD, other) and type of treatment (e.g., CNS radiation, CNS chemotherapy) due to multicolinearity between these variables. Because prior research has focused on treatment-related late effects associated with cancer, results from the models including treatment effects will be discussed in the following sections.

Results

Table 1 presents descriptive statistics for survivor and sibling demographics and survivor treatment characteristics. As indicated above, survivors of Hodgkin Lymphoma were oversampled to represent a majority of the cohort, given the increased rates of fatigue reported in this group. Roughly 78% of the survivor cohort received some level of cranial exposure to radiation, including 54.6% who received low dose exposure such as scatter from radiation applied to adjacent body areas.

The frequency and rates of impairment on the four factors from the CCSS-NCQ are presented by cancer diagnosis in Table 2. Survivors of CNS tumors demonstrated the highest rates of neurocognitive problems, though rates of task efficiency problems were also elevated in survivors of leukemia and Hodgkin Lymphoma.

Descriptive statistics for the neurocognitive outcome measures stratified by primary predictors and covariates are provided in Table 3. As evident in this table, problems in task efficiency, emotional regulation, organization, and memory were more common in those

survivors reporting higher fatigue, poor sleep quality, daytime sleepiness, and low vitality. Survivors reporting use of antidepressant or displaying emotional distress (i.e. depression, anxiety, somatization) were more likely to demonstrate neurocognitive problems.

Multivariable Prediction of Neurocognitive Impairment

Table 4 presents the relative risks for impairment on the four neurocognitive outcomes. Multivariable logistic regression models revealed significant associations between all of the primary predictors and impaired task efficiency. Specifically, decreased vitality (RR=1.75, 95% CI 1.33–2.30), increased fatigue (RR=1.34, 95% CI 1.13–1.59), increased daytime sleepiness (RR=1.68, 95% CI 1.55–1.83) and poor sleep quality (RR=1.23, 95% CI 1.01–1.49) predicted impaired task efficiency. Among treatment variables remaining in the final model, survivors in the high dose radiation group reported significantly greater impairments in task efficiency (RR=1.46, 95% CI 1.13–1.89). Decreased vitality (RR=3.08, 95% CI 1.98–4.79), increased fatigue (RR=1.77, 95% CI 1.23–2.55), and increased daytime sleepiness (RR=1.38, 95% CI 1.14–1.67) all significantly predicted impaired emotional regulation. Survivors in the high dose radiation group reported significantly more impairment in emotion regulation (RR=1.84, 95% CI 1.19–2.84). Decreased vitality (RR=1.90, 95% CI 1.37–2.63) and increased daytime sleepiness (RR=1.80, 95% CI 1.31–2.48) both predicted impaired organization. No treatment variables remained in the final model predicting organization problems. Decreased vitality (RR=2.01, 95% CI 1.42–2.86), increased daytime sleepiness (RR=2.05, 95% CI 1.63–2.58), and poor sleep quality (RR=1.45, 95% CI 1.19–1.76) all significantly predicted impaired memory. Among treatment variables, survivors in the high dose radiation group reported significantly greater memory impairments (RR=2.14, 95% CI 1.46–3.13).

Discussion

Although the relationships between fatigue, sleep and quality of life have been previously reported,14 this study is the first to extend the adverse impact of these factors to compromised neurocognitive functioning among adult survivors of childhood cancer. The relative risk for neurocognitive impairment associated with fatigue and sleep disturbance was roughly equivalent to that seen with high-dose radiation. When describing impairment observed among childhood cancer survivors, previous models of cognitive functioning have emphasized the direct insults associated with cancer treatment whereas these findings suggest the additive contributions of less direct pathways (such as poor sleep and fatigue).

It is interesting to note that more predictors were significantly associated with task efficiency than any other outcome variable. Specifically, all four of the primary variables related to fatigue, vitality, sleep quality, and daytime sleepiness predicted impaired task efficiency, as did use of antidepressant medication, high dose cranial radiation therapy, current age, and household income. Questions within this scale are generally related to attention and processing speed, which are often areas of vulnerability associated with late effects of cancer treatments, traumatic brain injury, pain, and psychological disorders such as depression. It is important to highlight that the impact of fatigue, vitality, daytime sleepiness, and poor sleep quality on task efficiency was independent of the significant effects of cranial radiation therapy, and use of antidepressant medication.

Although female sex was not a significant predictor of impaired task efficiency, organization problems or memory problems, it did contribute to the risk for problems with emotional regulation. Recent research demonstrates sex specificity to the attention problems detected in cancer survivors,37 though current measures may not be specific enough to demonstrate this differential pattern. Emotional regulation is associated with increased lability and tendencies for emotional explosiveness,38 and the current data suggests that female

survivors are more prone to report these symptoms. On the other hand, males may be less likely to acknowledge problems with emotional regulation or they may truly experience better emotional control. Of note, increased depression and anxiety were also identified risk factors for problems with emotional regulation. Problems with emotional regulation suggests increased emotional lability and/or explosiveness, and do not require the content of the lability to include either negative or positive emotions. However, the increased risk of poor emotional regulation found in those survivors reporting significant symptoms of depression and/or anxiety, suggests that the increased lability or explosiveness is likely to involve negative emotions such as sadness, frustration, and nervousness.

Poor sleep quality was identified as being significantly associated with attention and processing speed problems (Task Efficiency) and memory problems. Rapid eye movement (REM) sleep is particularly important for healthy memory functions,39 and specific disruption of REM cycles has been associated with memory impairment in aging adult populations.40 Clearly, the PSQI does not permit identification of separate REM sleep stages. However, the association between the PSQI and memory problems is consistent with the literature on REM sleep and its role in memory consolidation. As such, REM deprivation may be part of the pathway underlying this association. In addition, sleep disorder in children often mimic symptoms of attention-deficit/hyperactivity disorder, including primary problems with inattention.41 Our data would suggest that although good sleep quality may not be necessary for emotional regulation and organization skills, it is related to attention and memory functions.

Decreased vitality and increased fatigue were also strongly associated with neurocognitive impairment, even when controlling for sleep quality. Although fatigue and low vitality may result from poor sleep quality, physical and mental fatigue can also be associated with metabolic or neuroendocrine dysfunction,42, 43 as well as cardiovascular disease.44 Since survivors of childhood cancer are at increased risk for symptoms related to these medical conditions,44, 45 the role they play in neurocognitive outcomes should be examined. We are in the process of conducting just such an investigation.

Because many quality of life outcomes are mediated by neurocognitive functions, the identification of modifiable risk factors that are associated with cognitive outcomes is a valuable and important target for intervention. In the case of childhood cancer survivors, results from this study highlight the importance of considering interventions to improve sleep hygiene and/or physical fitness as nonpharmacological mechanism for improving neurocognitive functioning. The direct relationships between poor sleep and fatigue with self-reported neurocognitive outcomes were evidenced in our study. However, the more applied consequences of insomnia and fatigue extend to specific “real world” outcomes including serious accidents, illness-related restricted activities, and psychiatric disorders, along with decreased work productivity.46 Interventions to improve sleep quality have the potential not only to enhance neurocognitive functioning, but may also have beneficial effects that extend to symptoms of depression, anxiety, and somatization, along with fatigue and vitality. Research suggests that the “first line” interventions to improve sleep in this population should be behavioral in nature as the use of hypnotics may be contraindicated due to increased risk for medical problems (including pulmonary, hepatic and renal disease) secondary to cancer treatment.47, 48

Future research examining factors impacting neurocognitive functioning in survivors could be improved by the utilization of standardized direct performance measures to supplement self-report questionnaires like the CCSS-NSQ. For example, a computerized continuous performance test would provide separate indices of processing speed and sustained attention, constructs that are combined in the CCSS-NCQ Task Efficiency scale. Although reliance on

self-report measures does not represent the “gold standard” of a comprehensive neurocognitive direct performance assessment, self-report has been shown to be a valid and convenient method of measuring neurocognitive functioning.29 Still, direct performance measures may provide additional details and identify more specific neurocognitive processes impacted by sleep disruption. For example, use of the California Verbal Learning Test would permit separation of poor memory encoding from retrieval deficits, which may suggest reduced functioning in hippocampal structures. The use of polysomnographic methods would also be advantageous and permit the characterization of sleep architecture, while at the same time, allowing for the examination of affected sleep states and their impact on neurocognitive outcomes.

In the healthy population, disrupted cycles on the sleep-wake continuum, such as rapid eye movement (REM) and slow wave sleep (SWS) adversely affect memory consolidation, perceptual and motor learning, and cognitive flexibility,49, 50 but the interaction between disrupted sleep cycles and childhood cancer treatment on neuropsychological outcomes has not yet been examined. Understanding the causal means by which factors such as reduced vitality, fatigue, daytime sleepiness, or sleep quality affect neurocognitive functioning will be important for improving the quality of life among survivors of childhood cancer. Clarity regarding the timing of neurocognitive compromise and the anatomical systems affected is also needed so that future therapies can reduce neurocognitive impairment or preserve further insult. Several of our significant findings related to covariate predictors also substantiate the need for future research to utilize comprehensive approaches which include the consideration of sociodemographic and psychological factors in predicting neurocognitive outcomes. Through this approach, we will maximize the likelihood of developing the most relevant models of cognitive functioning which will have the greatest impact on quality of life outcomes among survivors of childhood cancer.

Acknowledgments

This work was supported by the National Cancer Institute grant CA 55727 (LLR). Support to St. Jude Children’s Research Hospital also provided by the National Cancer Institute Cancer Center Support (CORE) grant (CA 21765) and by the American, Lebanese, Syrian Associated Charities (ALSAC).

REFERENCES

1. Moleski M. Neuropsychological, neuroanatomical, and neurophysiological consequences of CNS chemotherapy for acute lymphoblastic leukemia. Arch Clin Neuropsychol. 2000; 15(7):603–630. [PubMed: 14590198]
2. Mulhern RK, Fairclough D, Ochs J. A prospective comparison of neuropsychologic performance of children surviving leukemia who received 18-Gy, 24-Gy, or no cranial irradiation. J Clin Oncol. 1991; 9(8):1348–1356. [PubMed: 2072138]
3. Butler RW, Haser JK. Neurocognitive effects of treatment for childhood cancer. Ment Retard Dev Disabil Res Rev. 2006; 12(3):184–191. [PubMed: 17061287]
4. Campbell BC, Eisenberg D. Obesity, attention deficit-hyperactivity disorder and the dopaminergic reward system. Coll Antropol. 2007; 31(1):33–38. [PubMed: 17600916]
5. Peterson CC, Johnson CE, Ramirez LY, et al. A meta-analysis of the neuropsychological sequelae of chemotherapy-only treatment for pediatric acute lymphoblastic leukemia. Pediatr Blood Cancer. 2008
6. Ellenberg L, Liu Q, Gioia G, et al. Neurocognitive status in long-term survivors of childhood CNS malignancies: a report from the Childhood Cancer Survivor Study. Neuropsychology. 2009; 23(6): 705–717. [PubMed: 19899829]
7. Kahol K, Leyba MJ, Deka M, et al. Effect of fatigue on psychomotor and cognitive skills. Am J Surg. 2008; 195(2):195–204. [PubMed: 18194679]

8. Majer M, Welberg LA, Capuron L, Miller AH, Pagnoni G, Reeves WC. Neuropsychological performance in persons with chronic fatigue syndrome: results from a population-based study. Psychosom Med. 2008; 70(7):829–836. [PubMed: 18606722]
9. Michiels V, Cluydts R. Neuropsychological functioning in chronic fatigue syndrome: a review. Acta Psychiatr Scand. 2001; 103(2):84–93. [PubMed: 11167310]
10. Bruno RL, Galski T, DeLuca J. The neuropsychology of post-polio fatigue. Arch Phys Med Rehabil. 1993; 74(10):1061–1065. [PubMed: 8215857]
11. Ravdin LD, Hilton E, Primeau M, Clements C, Barr WB. Memory functioning in Lyme borreliosis. J Clin Psychiatry. 1996; 57(7):282–286. [PubMed: 8666568]
12. Archibald CJ, Fisk JD. Information processing efficiency in patients with multiple sclerosis. J Clin Exp Neuropsychol. 2000; 22(5):686–701. [PubMed: 11094403]
13. Millikin CP, Rourke SB, Halman MH, Power C. Fatigue in HIV/AIDS is associated with depression and subjective neurocognitive complaints but not neuropsychological functioning. J Clin Exp Neuropsychol. 2003; 25(2):201–215. [PubMed: 12754678]
14. 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): 271–281. [PubMed: 18274275]
15. Lewis G, Wessely S. The epidemiology of fatigue: more questions than answers. J Epidemiol Community Health. 1992; 46(2):92–97. [PubMed: 1583440]
16. Bower JE, Ganz PA, Desmond KA, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. J Clin Oncol. 2000; 18(4): 743–753. [PubMed: 10673515]
17. Servaes P, van der Werf S, Prins J, Verhagen S, Bleijenberg G. Fatigue in disease-free cancer patients compared with fatigue in patients with chronic fatigue syndrome. Support Care Cancer. 2001; 9(1):11–17. [PubMed: 11147137]
18. Loge JH, Abrahamsen AF, Ekeberg O, Kaasa S. Hodgkin's disease survivors more fatigued than the general population. J Clin Oncol. 1999; 17(1):253–261. [PubMed: 10458240]
19. Fossa SD, Dahl AA, Loge JH. Fatigue, anxiety, and depression in long-term survivors of testicular cancer. J Clin Oncol. 2003; 21(7):1249–1254. [PubMed: 12663711]
20. Meeske KA, Siegel SE, Globe DR, Mack WJ, Bernstein L. Prevalence and correlates of fatigue in long-term survivors of childhood leukemia. J Clin Oncol. 2005; 23(24):5501–5510. [PubMed: 16110010]
21. Zeltzer LK, Recklitis C, Buchbinder D, et al. Psychological status in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2009; 27(14):2396–2404. [PubMed: 19255309]
22. Joly F, Henry-Amar M, Arveux P, et al. Late psychosocial sequelae in Hodgkin's disease survivors: a French population-based case-control study. J Clin Oncol. 1996; 14(9):2444–2453. [PubMed: 8823322]
23. Loge JH, Abrahamsen AF, Ekeberg O, Kaasa S. Reduced health-related quality of life among Hodgkin's disease survivors: a comparative study with general population norms. Ann Oncol. 1999; 10(1):71–77. [PubMed: 10076725]
24. Meeske KA, Patel SK, Palmer SN, Nelson MB, Parow AM. Factors associated with health-related quality of life in pediatric cancer survivors. Pediatr Blood Cancer. 2007; 49(3):298–305. [PubMed: 16779805]
25. Orff HJ, Ayalon L, Drummond SP. Traumatic brain injury and sleep disturbance: a review of current research. J Head Trauma Rehabil. 2009; 24(3):155–165. [PubMed: 19461363]
26. Bloomfield IL, Espie CA, Evans JJ. Do sleep difficulties exacerbate deficits in sustained attention following traumatic brain injury? J Int Neuropsychol Soc. 2010; 16(1):17–25. [PubMed: 19796442]
27. Robison LL. The Childhood Cancer Survivor Study: a resource for research of long-term outcomes among adult survivors of childhood cancer. Minn Med. 2005; 88(4):45–49. [PubMed: 15942996]
28. Robison LL, Armstrong GT, Boice JD, et al. The Childhood Cancer Survivor Study: A National Cancer Institute-Supported Resource for Outcome and Intervention Research. J Clin Oncol. 2009

29. Krull KR, Gioia G, Ness KK, et al. Reliability and validity of the Childhood Cancer Survivor Study Neurocognitive Questionnaire. Cancer. 2008; 113(8):2188–2197. [PubMed: 18792068]
30. Ware, JE.; Kosinski, M.; Gandek, B. SF-36 Health Survey: Manual and Interpretation Guide. Lincoln, RI: Quality Metric Incorporated; 2003.
31. 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. J Pain Symptom Manage. 1997; 13(2):63–74. [PubMed: 9095563]
32. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989; 28(2):193–213. [PubMed: 2748771]
33. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991; 14(6):540–545. [PubMed: 1798888]
34. Derogatis, LR. Minneapolis, MN: NCS Pearson; 2000. Brief Symptom Inventory (BSI): Administration, scoring, and procedures manual.
35. Wingo AP, Wingo TS, Harvey PD, Baldessarini RJ. Effects of lithium on cognitive performance: a meta-analysis. J Clin Psychiatry. 2009; 70(11):1588–1597. [PubMed: 19689922]
36. 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 Epidemiol Biomarkers Prev. 2008; 17(2):435–446. [PubMed: 18268128]
37. Jain N, Brouwers P, Okcu MF, Cirino PT, Krull KR. Sex-specific attention problems in long-term survivors of pediatric acute lymphoblastic leukemia. Cancer. 2009; 115(18):4238–4245. [PubMed: 19536898]
38. Roth, RM.; Isquith, PK.; Gioia, GA. Behavior Rating Inventory of Executive Function - Adult Version. Lutz, FL: Psychological Assessment Resources, Inc.; 2005.
39. Dobbin CJ, Bartlett D, Melehan K, Grunstein RR, Bye PT. The effect of infective exacerbations on sleep and neurobehavioral function in cystic fibrosis. Am J Respir Crit Care Med. 2005; 172(1): 99–104. [PubMed: 15831839]
40. Bombois S, Derambure P, Pasquier F, Monaca C. Sleep disorders in aging and dementia. J Nutr Health Aging. 2010; 14(3):212–217. [PubMed: 20191256]
41. Tsai MH, Huang YS. Attention-deficit/hyperactivity disorder and sleep disorders in children. Med Clin North Am. 2010; 94(3):615–632. [PubMed: 20451036]
42. Maloney EM, Boneva RS, Lin JM, Reeves WC. Chronic fatigue syndrome is associated with metabolic syndrome: results from a case-control study in Georgia. Metabolism. 2010; 59(9):1351–1357. [PubMed: 20102774]
43. Sarzi-Puttini P, Atzeni F, Cazzola M. Neuroendocrine therapy of fibromyalgia syndrome: an update. Ann N Y Acad Sci. 2010; 1193(1):91–97. [PubMed: 20398013]
44. Wolin KY, Ruiz JR, Tuchman H, Lucia A. Exercise in adult and pediatric hematological cancer survivors: an intervention review. Leukemia. 2010; 24(6):1113–1120. [PubMed: 20410923]
45. Gurney JG, Ness KK, Sibley SD, et al. Metabolic syndrome and growth hormone deficiency in adult survivors of childhood acute lymphoblastic leukemia. Cancer. 2006; 107(6):1303–1132. [PubMed: 16894525]
46. Daley M, Morin CM, LeBlanc M, Gregoire JP, Savard J, Baillargeon L. Insomnia and its relationship to health-care utilization, work absenteeism, productivity and accidents. Sleep Med. 2009; 10(4):427–438. [PubMed: 18753000]
47. Diller L, Chow EJ, Gurney JG, et al. Chronic Disease in the Childhood Cancer Survivor Study Cohort: A Review of Published Findings. J Clin Oncol. 2009
48. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006; 355(15):1572–1582. [PubMed: 17035650]
49. Cantero JL, Atienza M. The role of neural synchronization in the emergence of cognition across the wake-sleep cycle. Rev Neurosci. 2005; 16(1):69–83. [PubMed: 15810655]
50. Walker MP, Liston C, Hobson JA, Stickgold R. Cognitive flexibility across the sleep-wake cycle: REM-sleep enhancement of anagram problem solving. Brain Res Cogn Brain Res. 2002; 14(3): 317–324. [PubMed: 12421655]

Table 1

Demographic and treatment characteristics of the survivor and sibling cohorts.

	Survivors (n=1426)		Siblings (n=384)	
	Mean (SD)	**Range**	**Mean (SD)**	**Range**
Age at Diagnosis	11.9 (5.6)	0–21	---	---
Time Since Diagnosis	24.0 (4.7)	16.2– 34.3	---	---
Current Age	35.9 (7.5)	19.2–53.4	33.7 (8.4)	17.8–58.4
	Frequency	**Percent**	**Frequency**	**Percent**
Sex				
Male	684	48.0	181	47.9
Female	742	52.0	199	52.1
Income				
<20,000	135	9.5	24	6.3
20,000–39,999	250	17.5	58	15.1
≥40,000	919	64.5	271	71.9
Cancer Diagnosis				
Leukemia	200	14.0	---	---
CNS tumor	214	15.0	---	---
Hodgkin Lymphoma*	768	53.9	---	---
Other Cancer	244	17.1	---	---
Chemotherapy Treatment				
Alkylators	721	50.6	---	---
Anthracycline	407	28.5	---	---
Antimetabolite (IV)	265	18.6	---	---
Antimetabolite (IT)	795	55.8	---	---
Corticosteroids	538	38	---	---
Epipodophyllotoxin	45	3.2	---	---
Cranial Radiation Treatment (CRT)				
NO CRT	309	21.7	---	---
CRT <20Gy	779	54.6	---	---
CRT ≥ 20Gy	201	14.1	---	---

*Survivors diagnosed with and treated for Hodgkin Lymphoma were over-represented in the current sample, given the higher rates of reported fatigue and sleep problems.

Table 2

Neurocognitive problems in survivors by cancer diagnosis.

		Task Efficiency		Emotion Regulation		Organization		Memory	
Diagnosis	**N**	**n**	**Impaired***	**n**	**Impaired***	**n**	**Impaired***	**n**	**Impaired***
Leukemia	200	50	25%	21	11%	27	14%	27	14%
CNS Tumors	214	92	43%	28	13%	44	21%	50	23%
Hodgkin Lymphoma	768	120	16%	92	12%	95	12%	93	12%
Other Cancers	244	35	14%	20	8%	22	9%	16	7%
Total	**1426**	**297**	**21%**	**161**	**11%**	**188**	**13%**	**186**	**13%**

* Impairment defined as a performance ≥ a symptom level reported by the highest 10% of sibling controls.

Table 3

Descriptive statistics for primary predictors and covariates, N= 1,426.

		Task Efficiency		Emotional Regulation		Organization		Memory	
	N	Mean (SD)	Impaired*	Mean (SD)	Impaired*	Mean (SD)	Impaired*	Mean (SD)	Impaired*
SIBLINGS	384	2.9 (3.1)	10.0%	2.0 (1.6)	10.0%	1.6 (1.6)	10.0%	1.8 (1.8)	10.0%
SURVIVORS	1426	3.8 (3.8)	20.8%	2.2 (1.7)	11.3%	1.7 (1.6)	13.2%	2.1 (2.0)	13.0%
Primary Predictors									
Fatigued									
Yes	197	7.3 (4.6)	53.3%	3.8 (1.7)	39.6%	2.4 (1.8)	24.4%	3.7 (2.4)	37.1%
No	1229	3.2 (3.3)	15.6%	2.0 (1.6)	6.8%	1.5 (1.6)	11.4%	1.8 (1.9)	9.2%
Poor Sleep Quality									
Yes	248	5.9 (4.4)	40.7%	3.3 (1.8)	28.2%	2.2 (1.8)	23.0%	3.2 (2.4)	29.4%
No	1178	3.3 (3.5)	16.6%	2.0 (1.6)	7.7%	1.5 (1.5)	11.1%	1.9 (1.9)	9.6%
Daytime Sleepiness									
Yes	195	6.2 (4.5)	43.1%	3.2 (1.8)	26.7%	2.3 (1.8)	25.1%	3.4 (2.4)	32.3%
No	1231	3.4 (3.5)	17.3%	2.1 (1.6)	8.9%	1.5 (1.6)	11.3%	1.9 (1.9)	10.0%
Decreased Vitality									
Yes	567	5.3 (4.3)	33.2%	3.0 (1.8)	22.6%	2.0 (1.8)	19.8%	2.8 (2.3)	22.8%
No	859	2.7 (3.1)	12.7%	1.7 (1.5)	3.8%	1.3 (1.5)	8.8%	1.6 (1.8)	6.6%
Covariates									
BMI >=30 (Obese)									
Yes	281	3.9 (3.8)	22.8%	2.3 (1.7)	12.8%	1.7 (1.7)	15.3%	2.2 (2.1)	14.9%
No	1109	3.7 (3.8)	19.9%	2.2 (1.7)	11.1%	1.6 (1.6)	12.6%	2.1 (2.1)	12.4%
Antidepressant Use									
Yes	227	6.2 (4.6)	45.4%	3.4 (1.7)	28.6%	2.3 (1.9)	22.9%	3.2 (2.4)	28.2%
No	1184	3.3 (3.5)	16.1%	2.0 (1.6)	8.0%	1.5 (1.5)	11.5%	1.9 (1.9)	10.1%
Depression									
Yes	139	7.8 (4.9)	60.4%	4.1 (1.6)	45.3%	2.6 (1.9)	30.9%	3.8 (2.4)	38.1%
No	1287	3.3 (3.4)	16.6%	2.0 (1.6)	7.6%	1.5 (1.5)	11.3%	1.9 (1.9)	10.3%
Anxiety									

		Task Efficiency		Emotional Regulation		Organization		Memory	
	N	Mean (SD)	Impaired*	Mean (SD)	Impaired*	Mean (SD)	Impaired*	Mean (SD)	Impaired*
Yes	100	7.0 (4.2)	54.0%	4.3 (1.4)	50.0%	2.4 (1.8)	26.0%	3.8 (2.6)	39.0%
No	1326	3.5 (3.7)	18.3%	2.1 (1.6)	8.4%	1.5 (1.6)	12.2%	2.0 (2.0)	11.1%
Somatization									
Yes	213	6.2 (4.3)	41.3%	3.3 (1.7)	29.6%	2.3 (1.7)	24.4%	3.4 (2.3)	28.6%
No	1213	3.3 (3.6)	17.2%	2.0 (1.6)	8.1%	1.5 (1.6)	11.2%	1.9 (1.9)	10.3%

*Impairment defined as a performance ≥ a symptom level reported by the highest 10% of sibling controls.

Table 4

Relative Risk for the prediction of neurocognitive outcome comparing adult survivors of childhood cancer to national norms, N= 1,426.

	Task Efficiency			Emotional Regulation			Organization			Memory		
	RR	**95%CI**	**p-value**	**RR**	**95%CI**	**p-value**	**RR**	**95%CI**	**p-value**	**RR**	**95%CI**	**p-value**
Primary Predictors												
Vitality	1.75	1.33–2.30	<0.0001	3.08	1.98–4.79	<0.0001	1.90	1.37–2.63	0.0001	2.01	1.42–2.86	<0.0001
Fatigue	1.34	1.13–1.59	0.0009	1.77	1.23–2.55	0.002	----	----	----	----	----	----
Daytime Sleepiness	1.68	1.55–1.83	<0.0001	1.38	1.14–1.67	0.0008	1.80	1.31–2.48	0.0003	2.05	1.63–2.58	<0.0001
Sleep Quality	1.23	1.01–1.49	0.04	----	----	----	----	----	----	1.45	1.19–1.76	0.0002
Behavioral Covariates												
Depression	----	----	----	1.84	1.26–2.68	0.002	1.56	1.09–2.23	0.015	----	----	----
Anxiety	----	----	----	1.66	1.20–2.30	0.002	----	----	----	----	----	----
Somatization	----	----	----	----	----	----	----	----	----	1.43	1.17–1.75	0.0005
Antidepressant	1.56	1.46–1.67	<0.0001	----	----	----	----	----	----	1.70	1.37–2.11	<0.0001
Cranial Radiation Tx												
None	1.00			1.00			1.00			1.00		
Low Dose	0.91	0.69–1.20	0.51	1.20	0.78–1.84	0.40	----	----	----	1.02	0.69–1.52	0.91
High Dose	1.46	1.13–1.89	0.0038	1.84	1.19–2.84	0.006	----	----	----	2.14	1.46–3.13	<0.0001
Sex												
Male	1.00			1.00			1.00			1.00		
Female	----	----	----	1.45	1.22–1.73	<0.0001	----	----	----	----	----	----
Current Age	0.99	0.98–1.00	0.041	1.01	1.00–1.02	0.22	0.99	0.97–1.01	0.37	1.00	0.99–1.01	0.94
Household Income												
<$20,000/yr	1.50	1.39–1.62	<0.0001	----	----	----	1.76	1.26–2.47	0.001	----	----	----
≥$20,000/yr	1.00			1.00			1.00			1.00		

Note. Tx= Treatment, RR= Relative Risk, CI= Confidence Interval. Variables listed were included in the final model. ---- identifies variable dropped from final model through the backward selection process.