

Relationship between sleep problems and psychological outcomes in adolescent and young adult cancer survivors and controls

Lauren Daniel¹ · Anne E. Kazak^{2,3} · Yimei Li^{1,4} · Wendy Hobbie^{1,4} · Jill Ginsberg^{1,4} · Eliana Butler¹ · Lisa Schwartz^{1,4}

Received: 6 March 2015 / Accepted: 2 June 2015 / Published online: 1 July 2015
© Springer-Verlag Berlin Heidelberg 2015

Abstract

Purpose How cancer history and distress relate to sleep outcomes of adolescents and young adults (AYAs) is unclear. The current study compares AYA cancer survivors to controls on indicators of sleep and fatigue; examines the concurrent association between psychological status, sleep, and fatigue; and investigates the lagged relationship between sleep and fatigue problems with psychological functioning.

Methods AYA cancer survivors ($n=167$) and controls ($n=170$), ages 16 to 30, completed measures at a survivorship clinic/primary care visit (time 1) and 2 months later (time 2). Participants completed questions about sleep quality, quantity, sleep medication use, self-reports of sleep problems, and fatigue in addition to measures of depression, anxiety, and post-traumatic stress symptoms (PTSS).

Results There were no differences in sleep quantity or quality between survivors and controls, but survivors reported significantly more fatigue. Within groups, AYAs with self-reported sleep and fatigue problems reported significantly higher depression, anxiety, and PTS symptoms. Controlling for baseline depression, sleep, and fatigue problems at time 1 significantly predicted depression at time 2 in survivors but not in controls.

Conclusion This study offers important insight into the psychological functioning of childhood cancer survivors and prospectively describes sleep and fatigue as risk factors for poor psychological functioning in survivors. These findings support screening for sleep problems in AYA survivors as these difficulties are closely related to mental health functioning.

Support: National Cancer Institute CA106928

✉ Lauren Daniel
daniell@email.chop.edu
Anne E. Kazak
Anne.kazak@nemours.org
Yimei Li
LiY3@email.chop.edu
Wendy Hobbie
Hobbie@email.chop.edu
Jill Ginsberg
GinsbergJi@email.chop.edu
Eliana Butler
ButlerE@email.chop.edu
Lisa Schwartz
SchwartzL@email.chop.edu

¹ Division of Oncology, The Children's Hospital of Philadelphia, 3501 Civic Center Blvd, Philadelphia, PA 19104, USA

² Nemours Children's Health System, 1600 Rockland Road, Wilmington, DE 19803, USA

³ Sidney Kimmel Medical School of Thomas Jefferson University, 1025 Walnut St., Philadelphia, PA 19107, USA

⁴ The Perelman School of Medicine of the University of Pennsylvania, 3400 Civic Center Blvd., Philadelphia, PA 19104, USA

Keywords AYA · Sleep · Fatigue · Cancer · Psychosocial

Sleep disturbances and fatigue occur across the continuum of cancer treatment into survivorship [1] and are closely related to quality of life, psychological status, and overall health behaviors in childhood cancer survivors [2–4]. Fatigue is also a significant concern in both adolescents on treatment [5] and long-term childhood cancer survivors [3]. Fatigue is differentiated from sleepiness as a low-energy state that persists despite adequate rest [6]. Sleep and fatigue are related but distinct constructs. Increased fatigue can lead to more sporadic sleep, which can significantly impact sleep and the regularity

of the sleep/wake cycle, especially in patients with cancer [7]. Although more widely studied in adult oncology [1], few studies have examined sleep and fatigue and their relationship to psychological outcomes in adolescent and young adult (AYA) survivors of childhood cancer. Thus, the current study describes sleep, fatigue, and psychological outcomes in AYA survivors compared to a control group.

AYAs face biological and behavioral risk for sleep and fatigue difficulties [8, 9]. Hormonal shifts, greater sleep needs than adults, environmental factors not conducive to AYA schedules (e.g., early school start times), and social demands that delay bedtimes for AYA affect sleep in this age group [10]. Despite the risk for poor sleep habits, research focusing specifically on sleep in AYA survivors is sparse. Studies including AYA have done so as part of a larger age range (either childhood or adulthood) without specific subgroup analyses. Such research has described higher instances of disrupted sleep among survivors ages 5–17 relative to norms [11], sleep disturbances in 49 % of acute lymphoblastic leukemia survivors ages 18–41 [3], and sleep efficiency (percentage of time in bed asleep) below 85 % suggestive of insomnia in almost one third of 20–48-year-old survivors [12]. The Childhood Cancer Survivor Study (ages 18–50+) found slightly higher rates of sleep disturbances (16 %) in survivors relative to siblings (12 %) and that survivors were 1.9 times more likely to be fatigued than sibling controls [13]. Studies of fatigue in childhood cancer survivors have also found that survivors report higher fatigue than the general population [14] and an age-similar control group [15], with higher and more chronic fatigue in older survivors (19+) compared to younger survivors (13–18) [14].

Such sleep and fatigue problems confer risk for poor psychological functioning. Internalizing symptoms and sleep are closely related in both adolescents [16] and young adults [17] without a cancer history, and longitudinally, several studies have demonstrated that disrupted sleep predicts later onset of anxiety and depression [18]. Despite the demonstrated relationship between sleep and psychological functioning in AYA without cancer, our understanding of the role that sleep plays in the psychological adjustment of AYA survivors is limited. In childhood cancer survivors, sleep disturbances are closely related to quality of life [11], and survivors reporting poor sleep quality are almost five times more likely to be depressed [3, 13]. Chronic fatigue is also related to higher reports of psychological distress in survivors who experience persistent chronic fatigue relative to survivors without a history of chronic fatigue [19]. Together with the increased risk for mood disturbances, anxiety, and poor quality of life [20, 21], AYA survivors with sleep and fatigue disturbances face high risk for poor psychosocial outcomes.

Limitations of prior studies need to be addressed to better understand sleep and fatigue. No prior study has included an unrelated control group, which is necessary to understand the

impact of cancer history and related medical concerns. This is important given the heritability, environmental, and family impact on sleep difficulties and also to demonstrate whether sleep and fatigue of AYA survivors are substantially worse than what is typical of AYAs in general. Thus, the current study extends the literature and addresses limitations with three aims: (1) compare AYA cancer survivors to controls on indicators of sleep quality, sleep quantity (total sleep time and sleep onset latency), sleep medication use, and reports of problematic sleep and fatigue; (2) understand the relationship between psychological functioning (anxiety, depression, and posttraumatic stress) and current medical concerns with sleep and fatigue in survivors and controls; and (3) understand the prospective relationship across 2 months between sleep and fatigue problems with later mental health symptoms in survivors compared to controls.

Materials and methods

Participants

The sample was recruited as part of a larger study examining the psychosocial and health outcomes of survivors [22]. Participants between the ages of 16 and 30 included 167 AYA survivors of childhood cancer recruited during cancer-related follow-up medical visits and 170 healthy AYA controls recruited at preventive or acute primary care appointments. Inclusion criteria for AYA participants were a cancer diagnosis before 18 years of age, at least 5 years since diagnosis or being followed in the Cancer Survivorship Program (CSP) as their primary oncology medical home (in some cases, patients are referred to the CSP slightly prior to 5 years posttreatment if no concerns of disease or relapse remain and their health care focus shifts to risk-based care and/or management of late effects), greater than 2 years since completion of cancer treatment, and cognitively able to complete the study. AYA survivors of brain tumors were excluded. Healthy controls with no history of chronic health conditions, injury, or psychiatric hospitalization were included. All participants were English speaking and able to read at a fifth grade level as assessed by medical providers. Rates of dropout from time 1 to time 2 were somewhat higher in the control group ($\chi^2=4.62$, $p=.031$; survivors=35; controls=57).

Procedures

After institutional review board approval, AYA participants were recruited at their annual cancer survivorship visits at a large children's hospital. The control group was recruited at primary care clinic appointments in an affiliated academic medical center. All participants provided consent/assent and completed measures at baseline (time 1) and 2 months later by mail (time 2). Participants received \$20 for completing measures at time 1 and \$30 at time 2.

Measures

Demographic information All participants completed a demographic questionnaire regarding age, gender, ethnicity/race, and family income.

Disease variables Medical records were used to confirm diagnoses, which were classified as leukemia, lymphoma, or solid tumors for sample description. For cancer survivors, information regarding cancer diagnosis, stage, and treatment (radiation, chemotherapy, surgery, and stem cell transplant) was collected through the medical record to calculate the Intensity of Treatment Rating scale 2.0 [23].

Psychological distress

Brief symptom inventory It [24] is an 18-item self-report measure assessing symptoms of psychological distress. Participants rated their distress on a 5-point Likert-type scale with higher scores indicating greater distress. The measure and individual subscales have previously demonstrated strong reliability and validity [24]. The depression subscale (six items) was used for the current analysis and reliability was acceptable (survivor $\alpha=.84$; control $\alpha=.87$).

State-trait anxiety inventory It [25] is a self-report measure, composed of a state transitory anxiety subscale (20 items) and a trait anxiety subscale (20 items). Participants responded to items on a 3-point Likert scale, with higher scores indicating greater anxiety. Total state anxiety was used for this study with higher scores indicating greater anxiety; reliability was adequate (T1, survivor $\alpha=.57$; control $\alpha=.70$; T2, survivor $\alpha=.68$; control $\alpha=.70$).

Posttraumatic stress checklist—civilian version It [26] is a reliable and well-validated [26] 17-item self-report measure based on the DSM-IV criteria for posttraumatic stress disorder that has previously been used with childhood cancer survivors [21]. The measure is comprised of three subscales (reexperiencing, avoidance, and arousal) and a total score. The total score was used for the current analyses as an indicator of posttraumatic stress symptoms (PTSS). Participants rated distress on 5-point Likert scale, with higher scores indicating greater distress; reliability was acceptable (T1, survivor $\alpha=.92$; control $\alpha=.91$; T2, survivor $\alpha=.93$; control $\alpha=.89$).

Health problems and sleep/fatigue variables

Participants completed the *Health Knowledge Inventory* [27] regarding current health concerns. A summary score of health concerns was used as a proxy for current health. Items measuring sleep problems (“Do you have sleep problems?”) and fatigue (“Do you get tired easily?”) were not included in the

total score calculation and instead used as indicators of self-reported difficulty with sleep and fatigue.

Pittsburg sleep quality index Participants completed five items from the PSQI describing sleep habits in the past month [28]. Items assess total sleep time (TST; calculated as time between reported bedtime and wake time), sleep onset latency (SOL) in minutes, sleep quality (4-point scale ranging from poor to good sleep quality), and frequency of sleep medication use (4-point scale with higher scores indicating greater frequency). These items were dichotomized into clinically relevant categories. TST was dichotomized at above/below 8 h based on average sleep recommendations for this age group (9–10 h in adolescents [29] and 7–8 h in adults [30]). SOL was dichotomized at above/below 30 min based on clinical cut points of SOL for insomnia diagnosis [31]. Sleep medication use was dichotomized by any use versus no use. Sleep quality was dichotomized as good (very good or fairly good) and poor (fairly bad and very bad) sleep quality.

Data analysis

Data regarding psychological functioning of cancer survivors compared to controls have been presented previously [22]. Survivors and controls were compared on demographic (gender, age, ethnicity, and family income) variables at time 1 using *t* tests and chi-square analyses. For the first aim, the frequency of endorsing problematic sleep/fatigue (TST dichotomized at 8 h, SOL dichotomized at 30 min, sleep medication use yes/no, sleep quality good/poor, self-reported sleep problems yes/no, and self-reported fatigue yes/no) was compared between groups using chi-square analyses. For the second aim, within each group, those with and without sleep and fatigue problems were compared on psychological and current medical concerns using ANOVA and effect sizes were estimated using Cohen’s *d* [32]. The third aim used an analysis of covariance (ANCOVA) to examine self-reported sleep and fatigue problems at time 1 as a predictor of psychological functioning at time 2 controlling for time 1 psychological function, age, and income. To examine the difference between survivors and controls, interaction terms between groups and sleep/fatigue problems were examined.

Results

Descriptive analyses

Sample demographics are presented in Table 1. Survivors were on average 12.29 years since diagnosis (range 4–

Table 1 Sample demographics

	Survivors (<i>n</i> =154)		Control (<i>n</i> =170)		<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
Age (years)	20.08	3.17	21.08	3.43	0.007
	<i>n</i>	%	<i>n</i>	%	<i>p</i>
Female gender	80	53.33	88	51.76	0.974
Ethnicity/Race					0.457
African-American	7	4.54	16	9.41	
Asian	5	3.25	6	3.53	
Caucasian	136	88.31	139	81.76	
Hispanic	4	2.60	5	2.94	
More than one race	2	1.30	4	2.35	
Annual family income (\$)					0.014
<35,000	18	11.69	40	23.52	
35,000–74,999	48	31.17	47	27.64	
75,000–124,999	53	34.41	38	22.35	
>125,000	20	12.99	31	18.23	
Not reported	15	9.74	14	8.23	
Cancer diagnosis					
Leukemia	68	44.8	–	–	
Lymphoma	32	20.8	–	–	
Solid tumor	53	34.4	–	–	
Treatment intensity					
Least	5	4	–	–	
Moderately	72	44	–	–	
Very	57	36	–	–	
Most intense	26	16	–	–	

23 years). The survivor group was significantly younger than the control group [($F(1, 323)=7.27, p=.007$]. There were more participants from the lowest income group in the control group ($\chi^2=12.47, p=.014$). Family income and age were used as covariates for group comparison analyses.

Table 2 Unadjusted average sleep variables, unadjusted proportions, and adjusted odds ratios (ORs) comparing dichotomous sleep variables between survivors and controls

	SOL (min)	TST (h)	Sleep quality	Sleep med use		
Control M (SD)	28.94 (25.81)	7.56 (1.36)	1.91 (0.62)	1.23 (0.63)		
Survivor M (SD)	31.75 (41.84)	7.72 (1.39)	1.84 (0.63)	1.19 (0.63)		
	SOL >30	TST <8	Poor sleep quality	Sleep med use	Sleep problems	Fatigue problems
Unadjusted proportion						
Control (<i>n</i> =170)	75	87	24	26	31	22
Survivors (<i>n</i> =154)	66	77	18	17	34	40
OR (95 % CI) ^a	0.92 (0.6–1.4)	1.05 (0.6–1.6)	0.84 (0.4–1.6)	0.72 (0.4–1.4)	1.40 (0.8–2.4)	2.50 (1.4–4.4)*

^aOdds ratio adjusted for age and income. Control group is the reference

* $p<.01$

Comparing sleep by group (aim 1)

On average, survivors reported taking 31.75 min to fall asleep and sleeping for 7.72 h, rated sleep quality as good, and used sleep medication less than once per week. Similarly, controls reported taking 28.94 min to fall asleep, sleeping 7.56 h, good sleep quality, and using medication less than once per week. Contrary to hypotheses, there were no differences between survivors and controls in the occurrence of problematic sleep when controlling for age and income (Table 2). The distribution of the number of sleep problems reported was similar between groups ($\chi^2(4)=3.72, p=.445$). When controlling for age and income, survivors reported significantly more fatigue compared to controls (Wald statistic=9.18, $p=.002$, odds ratio=2.47).

Within-group analyses among participants with and without sleep and fatigue problems (aim 2)

Survivors Effect sizes for the comparisons of health problems and psychological symptoms by dichotomous sleep variables are presented in Table 3. Total health problems as reported on the HKI were higher in survivors who slept more than 8 h ($F(1, 152)=12.02, p=.001$), reported sleep problems ($F(1, 152)=11.67, p=.001$), and reported fatigue ($F(1, 152)=50.36, p<.001$). Total health concerns did not differ by SOL, sleep quality, or sleep medication use. Anxiety, depression, and PTSS were significantly higher in survivors with poor sleep quality (anxiety $F(1, 153)=4.56, p=.034$; depression $F(1, 153)=4.89, p=.028$; PTSS $F(1, 153)=10.96, p=.001$), those who used sleep medication (anxiety $F(1, 153)=14.44, p<.001$; depression $F(1, 153)=21.20, p<.001$; PTSS $F(1, 153)=27.93, p<.001$), those who reported sleep problems (anxiety $F(1, 153)=11.17, p=.001$; depression $F(1, 153)=14.35, p<.001$; PTSS $F(1, 153)=32.91, p<.001$), and those who reported fatigue problems (anxiety $F(1, 153)=17.10, p<.001$; depression $F(1, 153)=11.83, p<.001$; PTSS $F(1,$

Table 3 Cohen's *d* for comparison of health problems and psychological variables by dichotomous sleep variables

Dichotomous sleep variables	Survivor				Control			
	Health problems	Anxiety	Depression	PTSS	Health problems	Anxiety	Depression	PTSS
SOL >30 min	0.25	0.04	0.02	0.22	0.16	0.16	0.32*	0.31*
TST <8 h	0.56***	0.18	0.03	0.10	0.11	0.29	0.10	0.21
Poor sleep quality	0.36	0.49*	0.52*	0.77***	0.54**	0.30	0.17	0.49*
Sleep med use	0.38	1.11***	1.03***	1.09***	0.19	0.35	0.47*	0.63**
Sleep problems	0.65***	0.61***	0.70***	1.00***	1.10***	0.77***	1.14***	1.33***
Fatigue problems	1.27***	0.72***	0.62***	0.82***	1.09***	0.72**	0.85***	0.8***

Effect sizes are generally interpreted at 0.2 = small effect, 0.5 = medium effect, 0.8 = large effect [33]

* $p < .05$, ** $p < .01$, *** $p < .001$

153)=23.90, $p < .001$). There were no differences in psychological symptoms by SOL or TST.

Controls Total health problems were higher in those with poor sleep quality ($F(1, 167)=6.21, p=.014$), those who reported sleep problems ($F(1, 167)=36.29, p<.001$), and those who reported fatigue ($F(1, 167)=26.73, p<.001$). The total health problems did not differ by SOL, TST, or sleep medication use. Depression ($F(1, 169)=4.33, p=.039$) and PTSS ($F(1, 167)=3.95, p=.048$) were significantly higher in controls reporting SOL >30 min. Depression ($F(1, 169)=6.18, p=.014$) and PTSS ($F(1, 167)=8.81, p=.003$) were also significantly higher in controls reporting sleep medication use. PTSS was higher in controls reporting poor sleep quality ($F(1, 169)=4.97, p=.027$). Anxiety, depression, and PTSS were all significantly higher in controls reporting sleep problems [(anxiety $F(1, 169)=17.32, p<.001$; depression $F(1, 169)=39.81, p<.001$; PTSS $F(1, 169)=59.76, p<.001$) and fatigue (anxiety $F(1, 169)=10.96, p=.001$; depression $F(1, 169)=13.99, p<.001$; PTSS $F(1, 169)=18.05, p<.001$). Other comparisons by sleep variables were not significant.

Prospective relationship between psychological functioning and sleep (aim 3)

Table 4 presents ANCOVA results of sleep/fatigue problems endorsed at time 1 predicting psychological functioning at time 2 controlling for time 1 psychological function, age, and income. The interactions between group and sleep/fatigue problem (sleep problems $\chi^2=5.96, p=.014$; 95 % confidence interval (CI) 1.05, 9.59; fatigue $\chi^2=5.06, p=.024$, 95 % CI 0.75, 10.98) were significant in the predictive model of depression, such that the effect of sleep and fatigue on time 2 depression was significant for survivors but not for controls. Interaction terms were not significant in the predictive models of anxiety and PTSS; however, there was a significant main effect of sleep and fatigue on time 2 anxiety and PTSS for survivors but not for controls.

Discussion

This study is the first to describe the relationship between sleep parameters and psychological outcomes in AYA cancer survivors and controls. Few studies have explored sleep and fatigue in AYA survivors, and none have used an unrelated control group. Understanding the risk for poor sleep and the sleep/psychological functioning relationship is important to informing clinical practice and improving health-related quality of life in AYA cancer survivors. Study strengths are examining sleep and psychological functioning cross sectionally and prospectively across the AYA age spectrum (16–30) and using an unrelated control group without a history of disease recruited in a primary care setting. Furthermore, lagged models contribute to our understanding of sleep as not only a correlate of mental health but also a potential underlying risk factor for poor psychosocial outcomes.

Survivors and controls reported similar sleep—sleeping on average between 7.5 and 8 h nightly and taking about 30 min to fall asleep, with good sleep quality, and minimal sleep

Table 4 ANCOVA models of time 1 sleep/fatigue predicting time 2 psychological functioning

	Anxiety T2	Depression T2	PTSS T2
Sleep problems endorsed T1			
Group by sleep interaction Wald χ^2	0.81	5.96*	0.40
Effect in survivor	4.80**	3.61*	4.42*
Effect in control	2.75	-1.71	2.17
Fatigue problems endorsed T1			
Group by fatigue interaction Wald χ^2	0.50	5.06*	1.61
Effect in survivor	4.07**	5.47***	6.33***
Effect in control	2.04	-0.39	2.23

All models control for corresponding time 1 psychological variable, age, and income

* $p < .05$, ** $p < .01$, *** $p < .001$

medication use. TST is similar to population norms but slightly shorter than recommendations of 8–9 h for this age group [29]. SOL is generally adequate and also similar to previously published norms for both adolescents [31] and adults [17]. Prior research is mixed as to the extent of sleep disturbances in childhood cancer survivors with some research suggesting similar sleep to those without a cancer history [13] and other studies indicating increased risk for symptoms of insomnia (long SOLs and poor sleep efficiency) [3, 12]. Because the current sample is younger than prior studies [3, 12], our sample may report lower rates of prolonged SOLs, as the prevalence of insomnia symptoms increases with age and shifts from intermittent to chronic over time [33].

Despite similar adequate sleep between survivors and controls, survivors reported significantly more fatigue. Greater fatigue in survivors is consistent with research comparing survivors to sibling controls [13] and normative values [14]. Results suggest an underlying mechanism such as treatment-related late effects as the root cause of fatigue in survivors rather than inadequate sleep. Higher fatigue in survivors is likely multifactorial and may reflect both biological mechanisms and psychological/behavioral influences on fatigue, including low physical activity and low behavioral activation. These results also validate the importance of assessing sleep problems and fatigue separately as they are differing constructs that may not co-occur [34]. Additionally, because current health problems are similarly related to sleep/fatigue problems in both groups, current health concerns not the cancer history may be more important to sleep and fatigue in AYA.

The relationship between sleep and psychological functioning was similar between groups—participants in both groups who endorsed sleep and fatigue problems also endorsed more psychological symptoms. For survivors, sleep quality and medication use were also consistently related to psychological functioning. The relationship between sleep/fatigue and psychological symptoms is consistent with prior research linking insomnia symptoms and psychological well-being in survivors [3, 12] in addition to other studies associating sleep/fatigue with psychological functioning in adult oncology and adolescents without health concerns [16]. Sleep disturbances and fatigue can be symptoms of psychological distress. However, repeated sleep disturbances and fatigue may also trigger psychological distress by limiting engagement in daily activities, impairing school and social functioning [9], and increasing engagement in risk-taking activities [35].

Lagged models predicting depression indicated that sleep and fatigue problems predicted depression in survivors but not in controls, when controlling for baseline depression. The threat to quality of life that sleep and fatigue pose for some survivors is an important finding

due to the vulnerable nature of this population and warrants further investigation. Although results did not indicate similar relationships between sleep/fatigue and later psychological problems, longitudinal studies in non-cancer AYA populations have found that insomnia [35] and sleep deprivation [36] in adolescence predict depression in adulthood. The short time frame between assessments (2 months) may contribute to the differences observed in control participants relative to prior research, which have used longer 1-year time frames [35, 36]. For survivors, it appears that depressive symptoms related to sleep and fatigue may emerge earlier than controls, although underlying mechanisms are unclear. Further longitudinal research examining sleep in survivors over time will be important to understanding the role of sleep in mental health outcomes as well as determining the most appropriate interventions for such sleep and fatigue difficulties.

Cancer history may confer a greater risk for sleep/psychological relationships through bio-behavioral pathways that place survivors at greater risk for sleep/fatigue to impact psychological functioning. The Predisposing, Precipitating, and Perpetuating Factor (PPP) Model of Insomnia [37] and its application to cancer [38] may offer insight into the behavioral contributions of cancer to the sleep/depression relationship. The PPP model categorizes etiological factors of sleep disturbances as predisposing (risk factors for insomnia such as family history or psychological diagnoses), precipitating (stressors), and perpetuating factors (thoughts/behaviors that maintain sleep disturbance). Stress, such as a cancer diagnosis, can precipitate sleep disturbances during treatment and later become a predisposing factor to insomnia in survivorship [38]. This major life stress may explain the stronger relationship between sleep/fatigue and depression for survivors relative to controls. Survivors may also have more perpetuating factors for sleep disturbances such as sleep habits and beliefs about sleep developed during treatment. Children and adolescents with cancer are in the process of developing sleep habits during treatment, and treatment-related sleep disturbances may lead to the development of poor sleep hygiene (i.e., sleeping with the television on, later bedtimes, and napping). Survivors may be more susceptible to the effects of sleep problems on psychological functioning because of poor sleep habits developed during treatment that perpetuate intermittent sleep problems, eventually impacting the survivor's mood. Alternatively, underlying neuroendocrine and immune pathways that have been proposed to explain symptom clusters of sleep disturbances, fatigue, and depression in cancer patients and survivors [39] may also play a role in the stronger relationship between sleep/fatigue and depression in survivors. A more thorough assessment of sleep habits and

sleep hygiene is needed to better understand mechanisms of the sleep-depression relationship described in this study.

The current study is limited by self-report of sleep and mental health concerns. This study did not exclude participants with a history of anxiety or depression which may have impacted results, but this practice was consistent across survivors and controls. Future studies using objective measures of sleep (i.e., actigraphy and polysomnography) are necessary due to the potential over-estimation of sleep times (by approximately 30 min) that occurs when using self-report compared to actigraphy [40]. Also, one-time reports of sleep times miss the nuances of sleep patterns over time that can be collected through use of actigraphy. Furthermore, research including a detailed account of specific medications used for sleep and a more thorough assessment of fatigue is also needed. The survivor group represents childhood cancer survivors seeking follow-up care and may not adequately represent the broader population of survivors. This study is also limited in the exclusion of AYA with brain tumors. Because the control group was recruited at primary care medical visits, it may also not be representative of all AYAs and reasons for acute medical visits (e.g., cold symptoms and headaches) may have affected sleep prior to the visit. That there were differences in prospective findings between the two groups indicates that reports of fatigue and relationships between sleep/fatigue and psychological outcomes are presumably unique to cancer survivors and not those seeking health care, in general. The use of two measurement points is a strength relative to other cross-sectional studies, but more sophisticated models with additional time points could serve to further elucidate the prospective relationship between sleep/fatigue and psychological functioning.

Assessing sleep and fatigue is essential for understanding psychosocial adjustment post-cancer given the close relationships to physical health and psychological functioning. Poor sleep may also impact survivors' medical status due to the connection between sleep and immune functioning [41] and resistance to infection [42]. Poor sleep and fatigue can be treated with cognitive-behavioral interventions [43], physical activity [44], and/or pharmacotherapy [45], though evidence for treatments specific to AYA is lacking [46]. Although treating sleep problems may be beyond the scope of a survivorship visit, assessing sleep, making recommendations to improve sleep hygiene and necessary sleep needs (<http://sleepfoundation.org/sleep-topics/teens-and-sleep>), and referrals as appropriate to sleep specialists can be an important first step in supporting survivors in improving sleep and associated psychological functioning.

Acknowledgments This research was supported by the National Cancer Institute (CA106928). The Principal Investigator, Dr. Kazak, was at CHOP/PENN at the time that the study was conducted. The authors thank the study participants. We also thank Claire Carlson, RN, Sue Ogle, CRNP, and Maureen Reilly, BSN, RN, for assisting with recruitment and access to patients and Andrew Gaffney, Emily Knudsen-Strong, Muhammad Monsour, Ifigenia Mougianis, Sonali Sanyal, Mary Caitlin St. Clair, Mindy Yang, and Lauren Brumley for serving as research assistants.

Compliance with ethical standards The authors have no conflicts of interest to declare.

The study was approved by the appropriate institutional review board. All procedures performed were in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

References

1. Lee K, Cho M, Miaskowski C, Dodd M (2004) Impaired sleep and rhythms in persons with cancer. *Sleep Med Rev* 8(3):199–212
2. Meeske KA, Patel SK, Palmer SN, Nelson MB, Parow AM (2007) Factors associated with health-related quality of life in pediatric cancer survivors. *Pediatr Blood Cancer* 49(3):298–305. doi:10.1002/pbc.20923
3. Meeske KA, Siegel SE, Globe DR, Mack WJ, Bernstein L (2005) Prevalence and correlates of fatigue in long-term survivors of childhood leukemia. *J Clin Oncol* 23(24):5501–5510
4. Zeltzer LK, Recklitis C, Buchbinder D, Zebrack B, Casillas J, Tsao JC et al (2009) Psychological status in childhood cancer survivors: a report from the childhood cancer survivor study. *J Clin Oncol* 27(14):2396–2404
5. Daniel LC, Brumley LD, Schwartz LA (2013) Fatigue in adolescents with cancer compared to healthy adolescents. *Pediatr Blood Cancer* 60(11):1902–1907
6. Cella D, Peterman A, Passik S, Jacobsen P, Breitbart W (1998) Progress toward guidelines for the management of fatigue. *Oncology* 12(11A):369–377
7. Ancoli-Israel S, Moore PJ, Jones V (2001) The relationship between fatigue and sleep in cancer patients: a review. *Europ J Cancer Care* 10(4):245–255
8. Carskadon MA, Mindell J, Drake C (2006) Contemporary sleep patterns of adolescents in the USA: results of the 2006 National Sleep Foundation Sleep in America Poll. *Journal of Sleep Research*. England Blackwell Publishing, Oxon, p 42
9. Millman RP (2005) Excessive sleepiness in adolescents and young adults: causes, consequences, and treatment strategies. *Pediatrics* 115(6):1774–1786
10. Carskadon MA (1990) Patterns of sleep and sleepiness in adolescents. *Pediatrician* 17(1):5–12
11. Gordijn MS, van Litsenburg RR, Gemke RJ, Huisman J, Bierings MB, Hoogerbrugge PM et al (2013) Sleep, fatigue, depression, and quality of life in survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer* 60(3):479–485
12. Zhou ES, Recklitis CJ (2014) Insomnia in adult survivors of childhood cancer: a report from project REACH. *Supportive Care Cancer*. doi: 10.1007/s00520-014-2316-y
13. Mulrooney DA, Ness KK, Neglia JP, Whitton JA, Green DM, Zeltzer LK 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

14. Jóhannsdóttir IMR, Hjermstad MJ, Moum T, Wesenberg F, Hjorth L, Schröder H et al (2012) Increased prevalence of chronic fatigue among survivors of childhood cancers: a population-based study. *Pediatr Blood Cancer* 58(3):415–420
15. Hamre H, Zeller B, Kanellopoulos A, Kiserud CE, Aakhus S, Lund MB et al (2013) High prevalence of chronic fatigue in adult long-term survivors of acute lymphoblastic leukemia and lymphoma during childhood and adolescence. *J Adolesc Young Adult Oncol* 2(1):2–9
16. Ivanenko A, McLaughlin Crabtree V, Gozal D (2005) Sleep and depression in children and adolescents. *Sleep Med Rev* 9(2):115–129
17. Breslau N, Roth T, Rosenthal L, Andreski P (1996) Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry* 39(6):411–418
18. Gregory AM, Caspi A, Eley TC, Moffitt TE, O'Connor TG, Poulton R (2005) Prospective longitudinal associations between persistent sleep problems in childhood and anxiety and depression disorders in adulthood. *J Abnorm Child Psychol* 33(2):157–163
19. Zeller B, Loge JH, Kanellopoulos A, Hamre H, Wyller VB, Ruud E (2014) Chronic fatigue in long-term survivors of childhood lymphomas and leukemia: persistence and associated clinical factors. *J Pediatr Hematol Oncol* 36(6):438–444
20. Kanellopoulos A, Hamre HM, Dahl AA, Fosså SD, Ruud E (2013) Factors associated with poor quality of life in survivors of childhood acute lymphoblastic leukemia and lymphoma. *Pediatr Blood Cancer* 60(5):849–855
21. Schwartz LA, Drotar D (2006) Posttraumatic stress and related impairment in survivors of childhood cancer in early adulthood compared to healthy peers. *J Pediatr Psychol* 31(4):356–366. doi:10.1093/jpepsy/psj018
22. Kazak AE, Derosa BW, Schwartz LA, Hobbie W, Carlson C, Ittenbach RF et al (2010) Psychological outcomes and health beliefs in adolescent and young adult survivors of childhood cancer and controls. *J Clin Oncol* 28(12):2002–2007. doi:10.1200/JCO.2009.25.9564
23. Werba B, Hobbie W, Kazak A, Ittenbach R, Reilly A, Meadows A (2007) Classifying the intensity of pediatric cancer treatment protocols: the intensity of treatment rating scale 2.0 (ITR-2). *Pediatr Blood Cancer* 48(7):673–677. doi:10.1002/pbc.21184
24. Derogatis LR, Melisaratos N (1983) The brief symptom inventory: an introductory report. *Psychol Med* 13(03):595–605
25. Spielberg CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA (1983) Manual for the state-trait anxiety inventory. Consulting Psychologists Press, Palo Alto
26. Ruggiero KJ, Del Ben K, Scotti JR, Rabalais AE (2003) Psychometric properties of the PTSD checklist-civilian version. *J Trauma Stress* 16(5):495–502. doi:10.1023/A:1025714729117
27. Schwartz LA, Mao JJ, DeRosa BW, Ginsberg JP, Hobbie WL, Carlson CA et al (2010) Self-reported health problems of young adults in clinical settings: survivors of childhood cancer and healthy controls. *J Am Board Fam Med* 23(3):306–314. doi:10.3122/jabfm.2010.03.090215
28. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh Sleep Quality Index (PSQI): a new instrument for psychiatric research and practice. *Psychiat Res* 28(2):193–213
29. Mercer PW, Merritt SL, Cowell JM (1998) Differences in reported sleep need among adolescents. *J Adolesc Health* 23(5):259–263
30. Ferrara M, De Gennaro L (2001) How much sleep do we need? *Sleep Med Rev* 5(2):155–179
31. Lichstein KL, Durrence HH, Taylor DJ, Bush AJ, Riedel BW (2003) Quantitative criteria for insomnia. *Behav Res Ther* 41(4):427–445
32. Cohen J (1988) Statistical power analysis for the behavioral sciences, 2nd edn. Lawrence Erlbaum Associates, Hillsdale
33. Buysse DJ, Angst J, Gamma A, Ajdacic V, Eich D, Rössler W (2008) Prevalence, course, and comorbidity of insomnia and depression in young adults. *Sleep* 31(4):473
34. Shen J, Barbera J, Shapiro CM (2006) Distinguishing sleepiness and fatigue: focus on definition and measurement. *Sleep Med Rev* 10(1):63–76
35. Roane BM, Taylor DJ (2008) Adolescent insomnia as a risk factor for early adult depression and substance abuse. *Sleep* 31(10):1351
36. Roberts RE, Duong HT (2014) The prospective association between sleep deprivation and depression among adolescents. *Sleep* 37(2):239–244
37. Spielman A, Glovinsky P (1991) The varied nature of insomnia. In: Hauri PJ (ed) Case studies in insomnia. Plenum, New York
38. Savard J, Morin CM (2001) Insomnia in the context of cancer: a review of a neglected problem. *J Clin Oncol* 19(3):895–908
39. Miller AH, Ancoli-Israel S, Bower JE, Capuron L, Irwin MR (2008) Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. *J Clin Oncol* 26(6):971–982
40. Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ (2008) Self-reported and measured sleep duration: how similar are they? *Epidemiology* 19(6):838–45
41. Moldofsky H (1995) Sleep and the immune system. *Int J Immunopharmacol* 17(8):649–654
42. Hui L, Hua F, Diandong H, Hong Y, Hui L, Hua F et al (2007) Effects of sleep and sleep deprivation on immunoglobulins and complement in humans. *Brain Behav Immun* 21(3):308–310
43. Langford DJ, Lee K, Miaskowski C (2012) Sleep disturbance interventions in oncology patients and family caregivers: a comprehensive review and meta-analysis. *Sleep Med Rev* 16(5):397–414
44. Brown JC, Huedo-Medina TB, Pescatello LS, Pescatello SM, Ferrer RA, Johnson BT (2011) Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: a meta-analysis. *Cancer Epidemiol Biomark Prev* 20(1):123–133
45. Minton O, Richardson A, Sharpe M, Hotopf M, Stone P (2008) A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue. *J Natl Cancer Inst* 100(16):1155–1166
46. Meltzer LJ, Mindell JA (2014) Systematic review and meta-analysis of behavioral interventions for pediatric insomnia. *J Pediatr Psychol* 39(8):932–948