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Sleep, emotional distress, and physical health in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study

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Abstract

Objective: Sleep disorders are associated with psychological and physical health, although reports in long-term survivors of childhood cancer are limited. We characterized the prevalence and risk factors for behaviors consistent with sleep disorders in survivors and examined longitudinal associations with emotional distress and physical health outcomes.

Methods: Survivors (n = 1933; median [IQR] age = 35 [30, 41]) and siblings (n = 380; age = 33 [27, 40]) from the Childhood Cancer Survivor Study completed measures of sleep quality, fatigue, and sleepiness. Emotional distress and physical health outcomes were assessed approximately 5 years before and after the sleep survey. Multivariable logistic or modified Poisson regression models examined associations with cancer diagnosis, treatment exposures, and emotional and physical health outcomes.

Results: Survivors were more likely to report poor sleep efficiency (30.8% vs 24.7%; prevalence ratio [PR] = 1.26; 95% confidence interval, 1.04-1.53), daytime sleepiness (18.7% vs 14.2%; PR = 1.31 [1.01-1.71]), and sleep supplement use (13.5% vs 8.3%; PR = 1.56 [1.09-2.22]) than siblings. Survivors who developed emotional distress were more likely to report poor sleep efficiency (PR = 1.70 [1.40-2.07]), restricted sleep time (PR = 1.35 [1.12-1.62]), fatigue (PR = 2.11 [1.92-2.32]), daytime sleepiness (PR = 2.19 [1.71-2.82]), snoring (PR = 1.85 [1.08-3.16]), and more sleep medication (PR = 2.86 [2.00-4.09]) and supplement use (PR = 1.89[1.33-2.69]). Survivors reporting symptoms of insomnia (PR = 1.46 [1.02-2.08]), fatigue (PR = 1.31 [1.01-1.72]), and using sleep medications (PR = 2.16 [1.13-4.12]) were more likely to develop migraines/headaches.

Conclusions: Survivors report more sleep difficulties and efforts to manage sleep than siblings. These sleep behaviors are related to worsening or persistently elevated emotional distress and may result in increased risk for migraines. Behavioral interventions targeting sleep may be important for improving health outcomes.

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KEYWORDS
cancer, childhood cancer survivors, emotional distress, late effects, oncology, sleep

1 | BACKGROUND

Over 80% of children diagnosed with cancer reach 5-year survival[1]; yet survivors are at high risk for medical and psychosocial late effects.[2] Approximately 70% of childhood cancer survivors develop at least one chronic health condition,[3] and survivors have an 80% greater risk for clinically significant mental health symptoms relative to siblings.[4] Sleep, which is closely related to reduced quality of life, mental health, and physical health in the general population,[5] is negatively related to psychosocial functioning in survivors.[6-8] However, the relationship between sleep and mental and physical health over time has not been thoroughly explored.

Compared with siblings, childhood cancer survivors are at higher risk for poor mental health and reduced health-related quality of life,[9] and a subgroup are at risk for persistent emotional distress.[10] Short sleep duration and symptoms of insomnia predict the onset, recurrence, and persistence of depression in the general population.[11-13] Similarly, survivors reporting poor sleep quality are five times more likely to be depressed.[7,14] Sleep and fatigue predict late depression in survivors but not controls, suggesting a greater sensitivity to the psychological impact of sleep and fatigue in cancer survivors,[15] which may contribute to the differential risk for poor psychosocial outcomes in survivors.

Sleep is also a risk factor for poor physical health. Short sleep duration predicts hypertension,[16] headache severity,[17] breast cancer,[18] and all-cause mortality[19] in the general population. Findings related to sleep and physical health in cancer survivors are limited to two studies, where poor sleep efficiency was related to lower physical health-related quality of life[8] and symptoms of insomnia were associated with prior history of migraine headaches.[20] Sleep disorders coupled with cancer treatment history may increase risk for some physical health outcomes in survivors.

The current study, utilizing the Childhood Cancer Survivor Study (CCSS) cohort, examined sleep behaviors consistent with sleep disorders (insomnia, obstructive sleep apnea, and delayed sleep phase) and sleep management strategies in survivors compared with siblings to better understand what areas of sleep are impacted in childhood cancer survivors and the demographic and treatment correlates of these sleep behaviors. Additional prospective analysis tested the association between sleep behaviors and subsequent emotional and physical health outcomes.

2 | METHODS

2.1 | Participants and procedures

The CCSS is a retrospective cohort of childhood cancer survivors, at least five years from diagnosis, diagnosed prior to 21 years of age. The CCSS was approved by the 31 member institutions' IRBs (IRB Protocol # CR00007578) and participants provided informed consent for medical record abstraction and data collection. Baseline physical and mental health were collected beginning in 1994, sleep behaviors were collected beginning in 2002, and follow-up physical and mental health outcomes were collected from the full survivor cohort beginning in 2007.

Of the 14,355 survivors who completed the baseline survey, 2,645 survivors were randomly selected to complete the sleep survey (73% participated, 25% refused, 1.5% died, and 0.5% were lost to follow-up). Hodgkin lymphoma survivors were over-sampled given their higher rates of reported fatigue. A random sample of survivors who participated in the baseline survey (n = 4022) was selected to enroll their nearest aged siblings; 500 of these siblings were randomly selected to complete the sleep survey (380 participated; 76%). All participants were over 18 at the time of the sleep survey and completed self-report measures of sleep, sleepiness, and fatigue. CCSS methodology, participant characteristics, and sleep survey methodology have been described previously.[14,21,22]

2.2 | Measures

2.2.1 | Treatment variables

Cancer diagnosis, treatment history, and radiation dose were abstracted from medical records at the treating institution. Radiation dose was defined as the maximum prescribed dose within each region (brain, neck, chest, and abdomen), which is taken as the total prescribed dose from all overlapping fields within the treated region. Dosing for each region was separated into moderate (less than 20 Gray for cranial radiation, less than 30 Gray for other body regions) or high doses (greater than or equal to 20 Gray for cranial radiation, greater than or equal to 30 Gray for other body regions) based on examination of the frequency distributions of the radiation data and the Children's Oncology Group Long-Term Follow-up Guidelines.[23]

2.2.2 | Sleep behaviors consistent with sleep disorders

The Pittsburgh Sleep Quality Index (PSQI) is a 19-item self-report measure, which describes sleep characteristics over the past month.[24] For the current study, prolonged sleep onset latency (greater than or equal to 30 minutes to fall asleep greater than or equal to three times per week), poor sleep efficiency (less than 85% time in bed spent asleep), and frequent night/early morning awakenings (greater than or equal to three times per week) were used to indicate clinically significant insomnia symptoms.[25] Self-report of snoring greater than or equal to three times per week or bed partner report of pauses in breathing greater than or equal to one time per week were used to

indicate sleep-disordered breathing.[26] Self-report and bed partner report were both included because of the difference in availability of bed partner data between the groups: 65% of survivors compared with 73% of controls. Delayed bedtimes (after 1 AM) were used as a proxy for delayed sleep phase, which manifests as bedtimes and wake times that are significantly later than social norms.[26]

2.2.3 | Sleep management strategies

Participants reported frequency of sleep medication and supplement use over the past month. Supplement use included melatonin, valerian root, tryptophan, and herbal teas. Participants were also asked about sleep management strategies by an open-ended question ("Do you use anything to help you stay asleep?"). Responses were coded as behavioral (eg, exercise, yoga, and hot bath) or nonbehavioral (eg, medication, supplements, alcohol, and marijuana).

2.2.4 | Daytime sleepiness

The Epworth Sleepiness Scale (ESS) is an eight-item questionnaire assessing the likelihood of falling asleep in different situations; higher scores indicate greater sleepiness. Epworth scores greater than 10 were used to indicate clinically significant daytime sleepiness.[27]

2.2.5 | Fatigue

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) is a 13-item scale validated in patients with cancer to assess the physical and functional impact of fatigue.[28] FACIT-F scores less than or equal to 43 were used to indicate clinically significant fatigue.[29]

2.3 | Outcomes

2.3.1 | Emotional distress

To examine the association between sleep and change in emotional distress, baseline distress was assessed with the Behavior Problems Index (BPI)[30] for participants less than 18 years old at baseline (BPI, n = 254) or the Brief Symptom Inventory (BSI)–18[31] for participants greater than or equal to 18 years old at baseline (BSI, n = 1628). At follow-up, all participants were over 18 and therefore completed the BSI. Psychological distress in survivors was defined as a score on either the BPI of greater than or equal to 90th percentile of the sibling sample[32] or a *t* score greater than or equal to 90th percentile on the BSI depression or anxiety subscale. Participants were classified within one of four categories of psychological distress: (a) low distress at baseline and follow-up, (b) high distress at baseline and follow-up, (c) high distress at baseline and low distress at follow-up, and (d) low distress at baseline and high distress at follow-up.

2.3.2 | Physical health outcomes

To examine the association between sleep and health outcomes, new-onset (occurring between CCSS baseline and follow-up) hypertension, migraines/other headaches, and subsequent neoplasms were examined. These physical health conditions were collected through self-report at baseline and follow-up, with age at onset provided. Subsequent neoplasms were confirmed though medical records.

2.4 | Statistical methods

Demographic characteristics for survivors and siblings were compared using χ^2 or *t* tests. Sleep behaviors were dichotomized based on clinically significant cut-points and compared between survivors and siblings using multivariable generalized linear regression models with robust sandwich variance estimates and adjusting for significant demographic variables. For common outcomes, modified Poisson[33] models were used to directly estimate prevalence ratios (PR). For rare outcomes (less than 10%), logistic regression models estimated odds ratios as an approximation to PRs. All models were adjusted for age at survey completion. There were more minority race/ethnicity survivors than siblings, but adjustment was not possible given the relatively small sample size of siblings.

Among survivors, disease and treatment-related predictors of sleep behaviors were examined in two separate models: model 1 included age, sex, body mass index (BMI), and treatment variables; model 2 included age, sex, BMI, and primary cancer diagnosis. Sleepiness and fatigue were omitted from these models because analyses with these variables have been published previously.[14] Sleep behaviors, daytime sleepiness (greater than or equal to 10), and fatigue (less than or equal to 43) were evaluated as predictors in multivariable generalized linear models of longitudinal emotional distress (assessed before and after sleep survey). Multivariable generalized regression models tested associations between sleep, daytime sleepiness, and fatigue with hypertension, subsequent neoplasms, and headaches (with age at onset before and after sleep survey).

3 | RESULTS

3.1 | Sample characteristics

No significant differences were identified between survivors and siblings on sex ($P = 0.56$), although survivors were slightly older at survey ($P < 0.001$) and had higher minority representation ($P = 0.0031$; Table 1).

3.2 | Sleep quality, sleep timing, and sleep management strategies

Survivors were more likely to report poor sleep efficiency (30.8% vs 24.7%; PR = 1.26; 95% CI, 1.04-1.53), excessive daytime sleepiness (18.7% vs 14.2%; PR = 1.31; 95% CI, 1.00-1.71), and more

TABLE 1 Demographic and treatment characteristics of survivors of childhood cancer and siblings

Characteristic	Survivors n (%)	Siblings n (%)	*P*
Total	1933	380	
Sex			
Female	981 (50.8)	199 (52.4)	0.56
Male	952 (49.2)	181 (47.6)	
Race/Ethnicity			
White	1717 (89.1)	341 (94.2)	
Black	64 (3.3)	9 (2.4)	
Hispanic	86 (4.4)	7 (1.9)	
Asian	17 (0.9)	4 (1.1)	
American Indian/ Alaska Native	16 (0.8)	1 (0.2)	
Other	27 (1.4)	0 (0.0)	
Age at questionnaire (years)			
18-29	457 (23.7)	140 (36.8)	<0.001
30-39	890 (46.2)	139 (36.6)	
40+	581 (30.1)	101 (26.6)	
Mean (SD)	35.1 (7.6)	33.4 (8.4)	<0.001
Median (IQR)	35.0 (30.0, 41.0)	33.0 (27.0, 40.0)	
Body mass index			
Normal/underweight	871 (46.7)	174 (47.8)	0.89
Overweight	597 (32.0)	116 (31.9)	
Obese	398 (21.3)	74 (20.3)	
Age at diagnosis (years)			
0-4	357 (18.5)		
5-9	395 (20.4)		
10-14	539 (27.9)		
15-21	642 (33.2)		
Mean (SD)	11.6 (5.7)		
Median (IQR)	12.5 (6.5, 16.1)		
Diagnosis			
Hodgkin lymphoma	1018 (52.7)		
CNS Tumor	303 (15.7)		
Leukemia	302 (15.6)		
Bone cancer	159 (8.2)		
Soft tissue sarcoma	151 (7.8)		
Chemotherapy			
No	597 (34.4)		
Yes	1140 (65.6)		
Alkylating agents			
No	829 (48.0)		
Yes	897 (52.0)		
Anthracyclines			
No	1252 (72.2)		
Yes	481 (27.8)		
Platinum			
No	1668 (96.1)		
Yes	68 (3.9)		
Alkylating agent cyclophosphamide-equivalent (CED)			
No	862 (49.6)		
Yes	875 (50.4)		
Radiation in the first 5 y after diagnosis			
No	393 (22.3)		
Yes	1371 (77.7)		
Cranial radiation dose			
None	1293 (73.3)		
<20 Gy	165 (9.4)		
≥20 Gy	306 (17.3)		
Neck Radiation			
None	830 (47.1)		
<30 Gy	239 (13.5)		
≥30 Gy	695 (39.4)		
Chest radiation			
None	871 (49.4)		
<30 Gy	211 (12.0)		
≥30 Gy	682 (38.7)		
Abdominal radiation			
None	1118 (63.4)		
<30 Gy	172 (9.8)		
≥30 Gy	474 (26.9)		

Abbreviations: Gy, Gray; IQR, interquartile range; SD, standard deviation.

supplement use to manage sleep (13.5% vs 8.3%; PR = 1.56; 95% CI, 1.09-2.22) compared with siblings. Unadjusted models also indicated a higher prevalence of snoring (8.4% vs 5.3%; PR = 1.64; 95% CI, 1.02-2.65) and medication use to manage sleep (10.1% vs 6.6%; PR = 1.54; 95% CI, 1.03-2.30; Table 2) among survivors.

3.3 | Predictors of sleep behaviors in survivors

Compared with females, males reported better sleep efficiency (PR = 0.79; 95% CI, 0.68-0.91), fewer nighttime awakenings (PR = 0.76; 95% CI, 0.65-0.90), and less use of sleep medications (PR = 0.58; 95% CI, 0.43-0.78) and supplements (PR = 0.66; 95% CI, 0.51-0.85) but shorter sleep duration (PR = 1.14; 95% CI, 1.00-1.30), more snoring (PR = 2.05; 95% CI, 1.40-3.00), more pauses in breathing (PR = 2.37; 95% CI, 1.61-3.49), and later bedtimes (PR = 2.07; 95% CI, 1.32-

TABLE 2 Comparison of frequency of sleep behaviors and sleep/wake management strategies between survivors and siblings

Sleep Behaviors and Management Strategies	Siblings		Survivors		Unadjusted[a]	Adjusted[a,b]	
	n	%	n	%	PR (95% CI)	PR (95% CI)	*P*
Sleep onset latency (≥30 min)[c]	108	28.4	599	31.1	1.09 (0.92-1.30)	1.15 (0.97-1.36)	0.12
Sleep efficiency <85%[c]	**90**	**24.7**	**569**	**30.8**	**1.25 (1.03-1.51)**	**1.26 (1.04-1.53)**	**0.019**
Sleep time <7 h[c]	136	36.0	678	35.6	0.99 (0.85-1.15)	0.96 (0.83-1.12)	0.63
Night/early morning awakening[c]	92	24.2	520	27.3	1.13 (0.93-1.37)	1.08 (0.89-1.31)	0.45
Snoring[d]	**20**	**5.3**	**160**	**8.4**	**1.64 (1.02-2.65)**	1.60 (0.99-2.59)	0.054
Pauses in breathing[d]	24	10.0	161	13.8	1.45 (0.92-2.27)	1.36 (0.86-2.15)	0.18
Sleep onset after 1 AM[d]	25	6.7	115	6.1	0.90 (0.58-1.41)	1.01 (0.64-1.59)	0.96
Fatigue (FACIT ≤ 43)[c]	160	42.3	874	48.0	1.13 (1.00-1.29)	1.12 (0.99-1.27)	0.078
Daytime sleepiness (Epworth ≥ 10)[c]	**54**	**14.2**	**358**	**18.7**	**1.31 (1.01-1.71)**	**1.31 (1.00-1.71)**	**0.047**
Sleep medication use[c]	**25**	**6.6**	**195**	**10.1**	**1.54 (1.03-2.30)**	1.47 (0.99-2.21)	0.059
Sleep supplement use[c]	**31**	**8.3**	**259**	**13.5**	**1.62 (1.14-2.31)**	**1.56 (1.09-2.22)**	**0.014**
Strategies to manage sleep (relative to no strategies)							
Behavioral[e]	19	5.1	126	6.6	1.36 (0.83-2.24)	1.36 (0.82-2.23)	0.23
Nonbehavioral[e]	**12**	**3.2**	**122**	**6.4**	**2.09 (1.14-3.82)**	**1.96 (1.07-3.60)**	**0.030**

Bold emphasis denotes statistical significance.

[a]Siblings are the reference group.

[b]Adjusted for age.

[c]Modified Poisson model was used to directly estimate prevalence ratio (PR).

[d]Logistic regression model was used to estimate odds ratio as an approximation to PR.

[e]Multinomial logistic regression model was used to estimate odds ratio as an approximation to PR.

3.24; Data S1). Obesity was associated with shorter sleep duration (PR = 1.29; 95% CI, 1.10-1.52), more snoring, (PR = 4.73; 95% CI, 2.49-7.60), and more pauses in breathing (PR = 1.88; 95% CI, 1.17-3.04) but less likelihood of using supplements (PR = 0.69; 95% CI, 0.48-0.98). Older age (greater than 40) was associated with lower risk for prolonged sleep onset latency (PR = 0.74; 95% CI, 0.60-0.91) and delayed bedtime (PR = 0.40; 95% CI, 0.21-0.74) but higher risk of insufficient sleep (PR = 1.32; 95% CI, 1.08-1.62) and night awakenings (PR = 1.58; 95% CI, 1.23-2.04).

Maximum dose of cranial radiation conferred lower risk for short sleep duration (PR = 0.77; 95% CI, 0.63-0.94) and higher risk for delayed sleep onset (PR = 2.43; 95% CI, 1.49-3.96). Moderate neck radiation also conferred higher risk for delayed sleep onset (PR = 3.38; 95% CI, 1.15-9.93). Moderate abdominal radiation was associated with poor sleep efficiency (PR = 1.46; 95% CI, 1.07-1.99) and short sleep duration (PR = 1.45; 95% CI, 1.11-1.89), and high abdominal radiation was associated with high frequency of night time awakenings (PR = 1.32; 95% CI, 1.05-1.67). History of chemotherapy was related to a higher likelihood of taking supplements to manage sleep (PR = 1.37; 95% CI, 1.04-1.80).

There were no differences in sleep behaviors by diagnosis, with the exception that Hodgkin lymphoma survivors had higher risk for taking supplements to manage sleep relative to bone cancer survivors (PR = 1.83; 95% CI, 1.07-3.13; Data S1).

3.4 | Sleep and emotional distress

Compared with survivors who reported low emotional distress at both time points, survivors who developed high distress after baseline were more likely to have poor sleep efficiency (PR = 1.70; 95% CI, 1.40-2.07), restricted sleep time (PR = 1.35; 95% CI, 1.12-1.62), fatigue (PR = 2.11; 95% CI, 1.92-2.32), daytime sleepiness (PR = 2.19; 95% CI, 1.71-2.82), snoring (PR = 1.85; 95% CI, 1.08-3.16), and used sleep medications (PR = 2.86; 95% CI, 2.00-4.09) and supplements more frequently (PR = 1.89; 95% CI, 1.33-2.69). Similar patterns were evident for survivors who reported high distress at both time points (Table 3).

3.5 | Sleep and new-onset health conditions

Survivors with prolonged sleep onset latency (PR = 1.46; 95% CI, 1.02-2.08), frequent nighttime awakenings (PR = 1.63; 95% CI, 1.12-2.37), high daytime fatigue (PR = 1.31; 95% CI, 1.01-1.72), and sleep medication use (PR = 2.16; 95% CI, 1.13-4.12) were more likely to develop migraines (Table 4). Sleep behaviors were not related to the development of subsequent neoplasms or hypertension.

TABLE 3 Multivariable association of sleep behaviors with longitudinal patterns of psychological distress in survivors adjusted for age and body mass index (BMI)

	Increasing Distress	Resolving Distress	Persistent Distress
Variables	Low depression/anxiety at baseline, high depression/anxiety at follow-up N = 146 (10.0%) PR (95% CI)	High depression/anxiety at baseline, low depression/anxiety at follow-up N = 157 (10.7%) PR (95% CI)	High depression/anxiety at baseline and follow-up N = 82 (5.6%) PR (95% CI)
Sleep onset latency[a]	**1.94 (1.62-2.32)**	**1.53 (1.24-1.89)**	**1.97 (1.55-2.50)**
Sleep efficiency[a]	**1.70 (1.40-2.07)**	**1.48 (1.20-1.83)**	1.33 (0.98-1.80)
Sleep time[a]	**1.35 (1.12-1.62)**	1.07 (0.85-1.34)	**1.47 (1.18-1.84)**
Night awakening/early morning[a]	**2.04 (1.68-2.46)**	1.20 (0.91-1.58)	**1.99 (1.55-2.55)**
Snoring[b]	**1.85 (1.08-3.16)**	0.94 (0.49-1.81)	**2.21 (1.16-4.22)**
Pauses in breathing[a]	**2.30 (1.54-3.46)**	0.83 (0.41-1.69)	**2.75 (1.74-4.35)**
Bedtime after 1 AM[b]	1.39 (0.73-2.63)	1.30 (0.68-2.46)	**2.37 (1.22-4.58)**
Fatigue[a]	**2.11 (1.92-2.32)**	**1.32 (1.12-1.56)**	**2.29 (2.10-2.49)**
Daytime sleepiness[a]	**2.19 (1.71-2.82)**	1.05 (0.73-1.53)	**2.66 (2.02-3.51)**
Sleep management: medication use[a]	**2.86 (2.00-4.09)**	**2.28 (1.53-3.41)**	**3.06 (2.00-4.69)**
Sleep management: supplement use[a]	**1.89 (1.33-2.69)**	**1.78 (1.24-2.55)**	**2.41 (1.63-3.57)**

Bold emphasis denotes statistical significance. Reference group: low epression /anxiety BL—low depression/anxiety FU2 (N = 1457).

[a]Modified Poisson model was used to directly estimate prevalence ratio (PR).

[b]Logistic regression model was used to estimate odds ratio as an approximation to PR.

TABLE 4 Multivariable associations between sleep behaviors and health outcomes among survivors, adjusted for age and body mass index (BMI)

		Hypertension		Migraines		Subsequent Neoplasms[d]	
		Before sleep survey	Longitudinal follow-up	Before sleep survey	Longitudinal follow-up	Before sleep survey	Longitudinal follow-up
	N (%)	173 (8.9%)	84 (4.3%)	549 (28.4%)	49 (2.5%)	253 (13.1%)	87 (4.5%)
	Total in group	1933	1933	1933	1933	1920	1920
Variable	Category	PR (95%CI)	PR (95%CI)	PR (95%CI)	PR (95%CI)	PR (95%CI)	PR (95%CI)
Sleep onset latency[b]	<30 min	1.00	1.00	1.00	1.00	1.00	1.00
	≥30 min	**1.67 (1.38-2.01)**	1.11 (0.79-1.56)	**1.32 (1.15-1.52)**	**1.46 (1.02-2.08)**	1.20(0.97-1.49)	0.74 (0.48-1.13)
Sleep efficiency[b]	≥85%	1.00	1.00	1.00	1.00	1.00	1.00
	<85%	**1.31 (1.07-1.62)**	1.01 (0.72-1.41)	**1.33 (1.15-1.53)**	1.30 (0.88-1.92)	1.23 (1.00-1.51)	0.96 (0.67-1.38)
Sleep time[b]	≥7 h	1.00	1.00	1.00	1.00	1.00	1.00
	<7 h	1.17 (0.97-1.40)	0.96 (0.72-1.29)	**1.18 (1.04-1.34)**	0.87 (0.56-1.35)	1.06 (0.87-1.28)	1.11 (0.83-1.48)
Night Awakening[b]	<3 times a week	1.00	1.00	1.00	1.00	1.00	1.00
	≥3 times a week	**1.34 (1.08-1.66)**	0.91 (0.62-1.33)	**1.22 (1.04-1.43)**	**1.63 (1.12-2.37)**	1.04 (0.83-1.29)	1.09 (0.78-1.53)
Snoring[c]	<3 times a week	1.00	1.00	1.00	1.00	1.00	1.00
	≥3 times a week	**1.80 (1.12-2.88)**	0.69 (0.29-1.65)	1.39 (0.97-1.99)	1.65 (0.67-4.09)	0.78 (0.44-1.39)	0.38 (0.12-1.26)
Pauses in breathing[b]	None	1.00	1.00	1.00	1.00	1.00	1.00
	>0 times per week	1.34 (0.89-2.02)	0.79 (0.36-1.71)	1.10 (0.81-1.49)	0.28 (0.04-1.95)	1.05 (0.69-1.60)	0.97 (0.49-1.92)
Bedtime after 1 AM[c]	Before 1 AM	1.00	1.00	1.00	1.00	1.00	1.00
	After 1 AM	1.29 (0.64-2.59)	0.96 (0.34-2.73)	0.96 (0.62-1.47)	0.65 (0.15-2.75)	**0.30 (0.11-0.84)**	0.38 (0.09-1.61)
Fatigue[b]	>43[a]	1.00	1.00	1.00	1.00	1.00	1.00
	≤43	**1.37 (1.20-1.56)**	0.96 (0.74-1.23)	**1.27 (1.15-1.40)**	**1.31 (1.01-1.72)**	1.13 (0.98-1.31)	1.02 (0.81-1.30)
Daytime sleepiness[b]	<10	1.00	1.00	1.00	1.00	1.00	1.00
	≥10	**1.60 (1.24-2.07)**	0.97 (0.60-1.55)	1.18 (0.96-1.43)	1.31 (0.77-2.24)	0.98 (0.71-1.35)	1.18 (0.76-1.82)
Sleep medication use[b]	<1 time per week	1.00	1.00	1.00	1.00	1.00	1.00
	≥1 times per week	**1.55 (1.04-2.31)**	1.52 (0.88-2.62)	**1.73 (1.31-2.28)**	**2.16 (1.13-4.12)**	1.13 (0.77-1.67)	1.45 (0.83-2.52)
Sleep supplement use[b]	No	1.00	1.00	1.00	1.00	1.00	1.00
	Yes	1.39 (0.99-1.95)	1.04 (0.59-1.81)	**1.61 (1.27-2.03)**	1.62 (0.86-3.05)	**1.46 (1.07-2.00)**	1.16 (0.68-1.97)

Bold font denotes statistical significance.

[a]Lower Fatigue scores indicate higher fatigue reported.

[b]Modified Poisson model was used to directly estimate PR.

[c]Logistic regression model was used to estimate odds ratio as an approximation to PR.

[d]Adjusted for radiation in the first 5 years, anthracycline, and alkylating agents.

4 | CONCLUSIONS

Survivors of childhood cancer report more sleep behaviors consistent with insomnia, sleep disordered breathing, and daytime sleepiness, as well as more frequent use of sleep medications, supplements, and nonbehavioral sleep management strategies than siblings. The higher use of strategies to manage sleep in survivors suggests that sleep is a greater concern in this group relative to siblings. These sleep behaviors are closely tied to late onset and persistent emotional distress in survivors and the late onset of migraines/headaches. A hypertension diagnosis at the study baseline was associated with prolonged sleep onset, poor sleep efficiency, frequent night awakening, snoring, fatigue, and daytime sleepiness.

The current study extends the prior CCSS report by Mulrooney and colleagues,[14] which first described higher fatigue, poorer sleep quality, and more daytime sleepiness in survivors relative to siblings. However, the previous report concluded that the relatively small differences were not clinically significant. Additional analyses from this cohort demonstrated that survivor's sleep quality significantly predicted multiple domains of neurocognitive functioning,[34] and the current results demonstrate associations with emotional and physical health problems, indicating that these differences are indeed of clinical significance.

Diagnosis and treatment factors were inconsistently related to sleep behaviors. Mulrooney and colleagues' analyses[14] indicated an almost twofold higher risk for poor global sleep quality for soft-tissue sarcoma survivors; however, the current analyses did not find differences in sleep behaviors by diagnosis. Individuals who underwent high doses of cranial radiation were less likely to report short sleep but more likely to report a delayed sleep phase, suggesting a shifted or delayed circadian rhythm. Longer sleep duration with a lower tolerance for changes to sleep patterns have been reported previously in childhood cancer survivors who have undergone cranial radiation.[35] Similarly, the twofold and threefold higher risk for delayed sleep phase in those who had high doses of cranial radiation and moderate doses of neck radiation, respectively, may indicate an impact of radiation on the hypothalamus, which is largely responsible for regulating sleep-wake cycles.[36] Grouping brain tumors together may have obscured understanding how tumor location and treatment variability impact sleep differentially.

The finding that clinically significant sleep behaviors consistent with insomnia, sleep disordered breathing, and daytime symptoms (sleepiness and fatigue) were related to patterns of late onset or persistent psychological distress is consistent with prior research in cancer survivors[15] and the general population.[11] Mental health suffers when sleep is disrupted, highlighting the need for prospective screening and treatment as part of comprehensive survivorship follow-up care. The cross-sectional nature of the sleep survey without indication of the onset of problematic sleep behaviors limits our ability to determine whether poor sleep is an antecedent or consequence of late effects. Late effects were reported in 8% to 28% of our sample at baseline, before the sleep survey, limiting our ability to detect new onset conditions.

Sleep disordered breathing symptoms (snoring, fatigue, daytime sleepiness, night awakenings, and poor sleep efficiency) were associated with preexisting hypertension. However, since sleep was evaluated only once and not prospectively, we do not know if these sleep behaviors were present for many years prior to the survey. In the general population, sleep disordered breathing alters vascular functioning over time resulting in increased risk for hypertension and cardiovascular disease.[37] This increased risk in cancer survivors, many of whom are already at high risk for cardiovascular disease, is concerning. Interventions treating sleep apnea with positive airway pressure (PAP) have demonstrated clinically meaningful improvements in blood pressure in the general population.[37] Early identification and treatment of obstructive sleep apnea may be especially important for survivors at high risk for cardiovascular disease.

4.1 | Study limitations

Self-report of sleep and health conditions may have resulted in an underrepresentation of late effects, specifically with regard to hypertension, which may be underdiagnosed, and sleep disordered breathing, which is typically underrepresented by self-report of snoring.[38] Biomarkers of cardiovascular functioning may be more sensitive to changes in hypertension due to inadequate sleep and snoring. We included bed partner report of pauses in breathing to support self-report of snoring, but it is notable that survivors were less likely to have a bed partner than siblings. We included both self-report of snoring and bed partner report of pauses in breathing to limit the effects of missing data of the bed partner reports on our outcomes. Self-report of sleep efficiency also has limitations as it can be difficult to accurately assess time in bed asleep.

Rates of sleep medication and supplement use were higher in survivors than siblings, and their use was associated with a 1.89 to 3.06 higher risk of psychological distress and development of migraines. If the sleep medications and supplements are effective in improving sleep, the true prevalence of sleep disturbance in survivors may be higher than presented here. Sleep medications (prescribed or over the counter) were reported categorically as over the last month; further study examining specific medications and their duration of use is necessary to understand how these medications and supplements impact health and psychosocial functioning.

4.2 | Clinical implications

A small but significant portion of childhood cancer survivors are actively trying to manage sleep, some through efficacious means (eg, exercise and relaxation) and others through less effective (eg, warm milk) and even potentially harmful means (eg, alcohol). Given the modest improvement in sleep onset latency and sleep duration with sleep medications,[39] balanced with potential concerns for tolerance, dependence, and poor health outcomes, sleep medication is not a sustainable long-term solution. Medications and supplements do not treat the underlying cause of sleep disturbances. Survivors reported lower

sleep efficiency but similar time in bed to siblings, suggesting poor sleep hygiene, which may perpetuate insomnia. Behaviorally based treatments for insomnia, such as cognitive behavioral therapy for insomnia (CBTI), are well supported in the general population.[40] CBTI is similarly effective as hypnotic medications, and improvements in sleep are maintained after treatment is concluded, a benefit not seen with medications.[41]

Assessing sleep and medication/supplement use for sleep is important to understand psychological functioning in cancer survivors. The close relationship between sleep and psychological functioning underscores the importance of clinical screening for sleep problems. Survivors are rarely asked about sleep during survivorship visits,[8] yet given the widely available treatments, this screening target may yield meaningful results.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY

The Childhood Cancer Survivor Study is an NCI-funded resource (U24 CA55727) to promote and facilitate research among long-term survivors of cancer diagnosed during childhood and adolescence. Investigators interested in potential uses of this resource are encouraged to visit http://ccss.stjude.org.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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