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Predictors of Fatigue and Poor Sleep in Adult Survivors of Childhood Hodgkin's Lymphoma: A Report from the Childhood Cancer Survivor Study

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Abstract

Purpose—Survivors of pediatric Hodgkin's Lymphoma (HL) are at risk for a number of debilitating late-effects. Excessive fatigue and poor sleep quality are primary complaints of HL survivors. Understanding the emotional and physical factors that influence fatigue and sleep quality may provide opportunities for intervention to improve health-related quality of life for HL survivors.

Methods—Data from 751 adult survivors of childhood HL who participated in the Childhood Cancer Survivor Study (CCSS) from 2000-2002 were analyzed. Multivariable logistic regression analyses investigated the demographic, psychological, and physical variables that predicted clinically significant levels of poor sleep quality, fatigue, and excessive daytime sleepiness.

Results—Survivors' self-reported level of emotional distress, pain, and physical functioning limitations did not differ from population norms. Clinically elevated levels of emotional distress (OR 8.38, 95% CI 4.28-16.42) and pain (OR 3.73, 95% CI 2.09-6.67) increased the risk for endorsing elevated levels of fatigue. Survivors with elevated levels of emotional distress (OR 6.83, 95% CI 2.71-15.90) and pain (OR 5.27, 95% CI 1.78-15.61) were more likely to report poor sleep quality. Pain (OR 2.11, 95% CI 1.39-3.34) was related to excessive daytime sleepiness.

Conclusions—Emotional and physical factors are associated with elevated levels of fatigue, excessive daytime sleepiness, and poor sleep quality in survivors of pediatric HL. This is consistent with findings from research conducted with non-cancer survivors.

Implications for cancer survivors—These results suggest that interventions designed to target sleep and fatigue difficulties in the general population may be well suited for pediatric HL survivors as well.

Keywords

Pediatric Cancer; Hodgkin's Lymphoma; Sleep; Fatigue; Psychological Distress

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Advancements in medical treatments have improved survival for children diagnosed with Hodgkin lymphoma (HL), with five-year survival rates now approaching 95% [1]. Unfortunately, pediatric HL survivors are at risk for developing physical and psychological late effects that can interfere with their ability to engage in daily tasks and lead fulfilling lives [2, 3]. Fatigue, excessive daytime sleepiness (EDS), and poor sleep quality are well established late effects of pediatric HL [4]. Fatigue is three times higher in both pediatric and adult survivors of HL than in the general population or siblings [5-9, 4], and EDS is endorsed by 14%-35% of pediatric cancer survivors [10, 11, 4]. Pediatric HL survivors report poorer sleep quality compared to their siblings [4]. Psychological, physical, and

environmental factors have been hypothesized to contribute to fatigue, EDS, and poor sleep quality in adult cancer patients [5], and it is important to consider whether these factors influence fatigue and sleep quality in adult survivors of childhood HL.

It is well established that long-term survivors of HL report higher levels of depression, anxiety, and somatization compared to sibling controls and normative values [13-15]. Less well understood; however, is the relationship between these disorders, fatigue, and sleep quality in the HL survivors. One report from the Childhood Cancer Survivor Study (CCSS) found survivors who met criteria for depression were nearly 8 times more likely to be classified as fatigued and 4 times more likely to report reduced sleep quality and EDS than their siblings [4]. To date, no study has investigated the associations between emotional distress and fatigue, EDS, and sleep quality in adult survivors of childhood HL.

Pain is a frequent complaint of long-term childhood cancer survivors [16, 17], with nearly 30% of survivors endorsing some type of bodily pain [18, 14]. Pediatric HL survivors endorse levels of bodily pain similar to that endorsed by both sibling controls and the US population, are unlikely to attribute their current pain to prior cancer treatments, and are unlikely to use pain medications [19, 18]. When pediatric HL survivors do endorse pain they appear to report greater amounts of head and chest pain than their siblings [18]. The increase in head and chest pain is believed to be related to the high dose chest radiation frequently used to treat childhood HL. High dose chest radiation has also been associated with a two-fold increase in self-reported physical limitations in pediatric HL survivors [20, 14]. One study investigating the influence of physical limitations on fatigue and poor sleep quality in a heterogeneous population of pediatric cancer survivors found a positive relation between physical limitations and fatigue, EDS, and poor sleep quality [4]. It is unknown whether pain sensations or physical functioning limitations contribute to fatigue and poor sleep quality in childhood cancer survivors, though this link has been identified in the general population [21-23].

Despite research identifying the negative impact of fatigue and sleep disturbance on quality of life [24, 25], as well as elevated levels of emotional distress, pain, and physical limitations in pediatric HL survivors, the relation between these factors is largely unknown. The purpose of this study was to investigate the associations between clinically elevated levels of pain, emotional distress, and physical functioning limitations and clinically elevated sleep outcomes.

Methods

Participants

The Childhood Cancer Survivor Study (CCSS) is an ongoing epidemiologic study of health outcomes in long-term survivors of childhood cancer [26]. Survivors were diagnosed with childhood cancer at one of 26 participating institutes across the United States and Canada between 1970 and 1986. A total of 20,720 survivors of pediatric cancers were eligible to participate, 17,703 were located, and 14,372 completed a baseline survey beginning in 1994. Survivors of Hodgkin lymphoma (n=955) were randomly selected from the larger cohort to complete a sleep survey completed from 2000-2002; these survivors also completed a

comprehensive psychosocial follow-up survey completed from 2003-2007. Participants were eligible for the current study if they were treated for Hodgkin's lymphoma, younger than 21 years of age at diagnosis, and survived for >5 years. Complete data from 751 adult survivors of pediatric HL who completed the sleep and psychosocial surveys were analyzed.

The human subjects committee at each collaborating institution approved the study protocol and documents prior to participant enrolment. Participants provided informed consent to participate and completed a separate consent for medical record abstraction.

Demographic and medical characteristics

Data on chemotherapy (Anthracycline, Alkylating Agents, Bleomycin, and Vinca Alkaloids & Heavy Metals) and chest radiation dose were abstracted from medical records. Chest radiation was treated as a dichotomous variable (<30 Gy; ≥30 Gy). Demographic variables included gender, age at diagnosis (0-10, 11-15, 16-20), age at sleep survey (18-24, 25-29, 30-34, ≥35), current work status (employed or unemployed), cancer related pain (none/a small amount of cancer related pain or medium/a lot cancer related pain), and body mass index (BMI normal weight 18.5-24.99, overweight 25.00-29.99, obese ≥30.00).

Psychosocial Variables

Emotional distress was measured by the Brief Symptom Inventory-18 (BSI-18). The BSI-18 is a self-report inventory measuring symptoms of depression, anxiety, and somatization over the previous seven days [27]. Symptoms are combined to create the Global Severity Index (GSI), where a T-score ≥63 indicates clinically elevated levels of emotional distress [28].

The Medical Outcomes Short Form-36 (SF-36) was used to measure bodily pain and physical functioning. The bodily pain subscale measures pain frequency and the extent that pain interferes with normal activities [29]. The physical functioning subscale measures the presence and extent of physical limitations. A T-score ≤40 indicates elevated levels of bodily pain or impaired levels of physical functioning.

Outcome Variables

The Functional Assessment of Chronic Illness Therapy- Fatigue (FACIT-F) scale was used to measure fatigue[30]. The 13-items of the FACIT-F measure subjective levels of fatigue while completing daily activities over the past week. Scores range from 0 to 52, with lower scores indicating more fatigue. Based on the results of previous literature with cancer patients, survivors with a FACIT-F total score ≤ 30 were classified as having clinically significant fatigue [31].

Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI)[32]. The 19-item scale assesses subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep promoting medications, and daytime dysfunction. Items are combined to make a total score ranging from 0 to 21, where higher scores indicate poorer sleep quality. Consistent with test publisher recommendations, survivors with a PSQI total score ≥ 5 were classified as having a sleep problem.

Sleepiness was evaluated using the Epworth Sleepiness Scale (ESS)[33]. The 8-item questionnaire measures daytime sleepiness on a 4-point Likert Scale. The scale results in a total score ranging from 0 to 24, where higher scores reflect greater daytime sleepiness. Survivors with an ESS total score ≥ 10 were classified as having excessive daytime sleepiness (EDS).

Statistical Analysis

Descriptive statistics were obtained for demographic, treatment, and sleep variables. Multivariable logistic regression analysis was used to calculate odds ratios (OR) and 95% confidence intervals (CI) to identify demographic and treatment variables that predicted poor sleep quality, fatigue, and EDS. Based on previous literature [4], gender and BMI were included in model as covariates, the remaining variables were selected using Bayesian Model Averaging and implemented using "GMULTI" package in R. The model with the smallest Bayesian Information Criterion value was chosen [34]. Potential variables included age at diagnosis, current work status, cancer treatment, cancer related pain, emotional distress, bodily pain, and physical functioning. P-values equal to or less than 0.05 were considered significant.

Results

Demographic and sleep characteristics are shown in Table 1. The majority of survivors were diagnosed between ages 11-15 years and were ≥ 35 years of age at time of follow-up survey. Over 90% of survivors reported being employed and gender was evenly divided. Most reported experiencing either a small amount or no cancer related pain (90%). Almost half of the sample was normal weight (47%), 32% were overweight, and 17% were obese. Treatment exposures are listed in Table 1.

The HL survivors reported levels of emotional distress ($M = 50.3$, $SD = 9.6$), pain ($M = 48.9$, $SD = 10.2$), and physical functioning ($M = 50.2$, $SD = 9.8$) consistent with population norms. The proportion of survivors endorsing elevated fatigue, excessive daytime sleepiness, and poor sleep quality were 17%, 22%, and 46% respectively. The proportions of males and females endorsing poor sleep quality and excessive daytime sleepiness were similar (Table 1).

Fatigue

Emotional distress, pain, and physical functioning limitations were all associated with fatigue. Emotional distress increased risk for fatigue eight fold (OR 8.38, 95% CI 4.28-16.42) compared to survivors without distress. Survivors with elevated bodily pain were four times more likely to endorse fatigue (OR 3.73, 95% CI 2.09-6.67) compared to those with subclinical pain, and survivors with physical functioning limitations were three times more likely to endorse fatigue (OR 3.28, 95% CI 1.75-6.15; Table 3) than those without limitations. Female survivors (OR 4.75, 95% CI 2.47-9.15), and survivors not currently employed (OR 2.90, 95% CI 1.27-6.62), had higher risk of fatigue (Table 3).

Sleep Quality

Cancer-related pain, bodily pain, and emotional distress were related to sleep quality (Table 3). Survivors who reported a “medium”, “a lot”, or “very bad” amounts of cancer-related pain were over five times more likely to endorse poor sleep quality (OR 5.27, 95% CI 1.78-15.61) compared to survivors with a small amount or no cancer-related pain (Table 3). Survivors with emotional distress were over six times more likely to report poor sleep quality (OR 6.83, 95% CI 2.71-15.90) compared to those without distress, and those reporting significant bodily pain were nearly three times as likely to report poor sleep quality (OR 2.94, 95% CI 1.72-4.52).

Excessive Daytime Sleepiness

Survivors reporting significant bodily pain were two times more likely to meet criteria for excessive daytime sleepiness than survivors without elevated pain (OR 2.11, 95% CI 1.39-3.34). BMI was the only demographic variable related to excessive daytime sleepiness (Table 2). Survivors classified as overweight or obese were more likely than survivors classified as normal weight to report excessive daytime sleepiness (overweight: OR 2.14, 95% CI 1.38-3.34; obese: OR 2.70, 95% CI 1.63-4.48).

Discussion

Survivors of childhood HL are at-risk for a number of health complications decades after completion of cancer-directed therapies. Fatigue, poor sleep, and excessive daytime sleepiness are common symptoms endorsed by HL survivors, and our results suggest that symptoms of emotional distress and pain were associated with clinically significant levels of fatigue, excessive daytime sleepiness, and poor sleep quality in long-term survivors Understanding these associations may facilitate the development of interventions to improve quality of life for the ever-growing population of childhood HL survivors.

Poor emotional health, bodily pain, and physical functioning limitations all contributed to elevated levels of fatigue. Poor emotional health showed the strongest relationship, which is consistent with the extensive body of literature linking depression and fatigue in the general population and cancer survivors [35-37]. Since bodily pain and physical functioning limitations also contributed to fatigue, treatments targeting fatigue in pediatric HL survivors may be implemented to alleviate emotional distress without aggravating pain or requiring significant physical functioning abilities. One intervention that has shown promise is an at home aerobic exercise program. After 20 weeks of 40-60 minutes of continuous movement, fatigued HL survivors reported less fatigue and improved physical functioning limitations [38]. Of note, the emotional health variable used in this study was a combination of symptoms of depression, anxiety, and somatic distress. Anxiety in cancer survivors may be manifest as a combination of somatic distress related to their current state of health and fears of cancer recurrence or severe late effects [15]. This is an important and necessary consideration as it has implications for prescribed treatments.

Pain and emotional distress increased risk for poor sleep quality. The link between bodily pain and sleep quality is well established in the literature; however, the relation is not well

understood in pediatric cancer survivors. Given that presence of cancer-related pain, as well as pain severity were related to poor sleep quality, providing pediatric HL survivors with appropriate pain management would appear prudent. This may be difficult given the previous CCSS study finding that HL survivors are less likely to use pain medications than survivors of other types of pediatric cancers [18]. Nonpharmacologic pain management may be an acceptable and appropriate intervention for HL survivors with chronic pain. Further, the lack of association between physical functioning limitations and poor sleep quality suggests that both pharmacological and physical interventions (e.g., yoga) may have particular utility when attempting to improve sleep quality.

Overweight or obese survivors and those with excessive bodily pain were more likely to report excessive daytime sleepiness. Such sleepiness is routinely associated with obesity in otherwise healthy individuals [39-41], and weight management strategies are a common treatment approach in the general population [42]. Our results suggest that weight reduction in HL survivors may not only improve physical functioning but also excessive daytime sleepiness. Although depression has been identified as the strongest risk factor for excessive daytime sleepiness [39, 43], emotional distress was not a significant predictor in HL survivors. In HL survivors, BMI and bodily pain may be more important than emotional functioning in driving sleepiness. Body pain increased the risk for excessive daytime sleepiness two-fold. This is an unexpected finding and has not been identified in the literature. Given that body pain was also related to poor sleep quality, addressing pain in pediatric HL survivors is an area of significant importance. Previous literature has established that women are more likely to endorse excessive daytime sleepiness [44-46]; however, gender was not a significant risk factor in our study.

Consistent with previous literature [13-15], the pediatric HL survivors in our study endorsed levels of emotional distress, pain, and physical functioning that were congruent with the normative population. Overall, poor sleep quality was the chief complaint, endorsed by nearly 50% of survivors, though fatigue and daytime sleepiness was reported by only 17% and 22% of survivors, respectively. This mirrors the findings of a 2005 study which also found little to no relation between poor sleep quality and either excessive daytime sleepiness or fatigue [39]. Sleep, fatigue, and sleepiness are distinct late effects experienced by HL survivors, and interventions must be tailored to address specific presenting symptoms.

With fatigue a common complaint within the general population [49, 50], survivors of childhood cancers frequently endorse levels of fatigue similar to peers without childhood cancer [7]. We categorized our sample using empirically derived cut offs to compare survivors that met clinical criteria for fatigue or a sleep problem to those who did not. Female survivors were more likely to report elevated levels of fatigue [6,9,52]. Although the association between female gender and fatigue is not unique to pediatric cancer survivors, this is an important finding for practitioners working with female HL survivors. Additionally, unemployed survivors were more likely to endorse fatigue [7]. A meta-analysis that included 10 studies related to childhood survivors of blood cancers found that survivors were nearly 1.5 times more likely to become unemployed than controls; however, the difference was not significant [51]. Our results may suggest that significant fatigue could be a possible cause for the greater rates of unemployment for pediatric HL survivors, and thus

interventions and work place adaptations, such as more frequent breaks, reduced work hours, and the possibility to work from home may be beneficial for HL survivors. Alternatively, the limited daytime activity associated with being unemployed may serve to further exacerbate fatigue and contribute to decreased energy levels.

As has been noted in previous CCSS studies, one limitation of studies with large sample sizes is that although statistically significant differences are detected between survivors and the comparison group, the clinical relevance of such findings is unclear. An advantage of the current study was the comparison between survivors with clinical elevations of fatigue and sleep problems to HL survivors without these elevations to circumvent this drawback and provides a clearer understanding of the emotional and physical disorders that contribute to elevated fatigue and sleep problems. A second limitation is the use of self-report measures to assess outcome variables. Although this study employed clinically validated measures with cut points derived from the general population, which allowed us to determine the degree of clinically significant impairment in childhood cancer survivors, we nevertheless recommend that future studies consider correlating self-report with objective sleep quality measures (e.g., polysomnography, actigraphy). Finally, the cross-sectional nature of this research prevents us from determining the temporal associations between emotional and physical disorders and fatigue, excessive daytime sleepiness, and poor sleep quality. Our findings highlight a number of areas where interventions may positively impact the quality of life for childhood HL survivors in adulthood; however, only a prospective longitudinal study can offer evidence fully supporting our suggestions.

In summary, fatigue and sleep difficulties are frequently experienced late-effects of pediatric HL survivors. The domains that influence these problems in survivors are variable but are highly consistent with what has been found in the general population. This is encouraging and suggests that interventions that have been developed for individuals who did not experience childhood cancer may be as effective in this population. However, additional research is necessary.

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Table 1

Survivor Demographic Statistics

	Survivors		FACIT		PSQI		ESS	
	N=751		≤30	>30	>5	≤5	≥10	10
	N	%	N (row %)	N (row %)	N (row %)	N (row %)	N (row %)	N (row %)
Sex								
Male	372	49.5	37 (9.9)	335 (90.1)	188 (50.5)	184 (49.5)	82 (22.0)	290 (78.0)
Female	379	50.5	91 (24.0)	288 (76.0)	218 (57.5)	161 (42.5)	83 (21.9)	296 (78.1)
CCSS 2003 survey age								
18-29	53	7.1	12 (22.6)	41 (77.4)	33 (62.3)	20 (37.7)	9 (17.0)	44 (83.0)
30-34	154	20.5	16 (10.4)	138 (89.6)	81 (52.6)	73 (47.4)	37 (24.0)	117 (76.0)
≥ 35	544	72.4	100 (18.4)	444 (81.6)	292 (53.7)	252 (46.3)	119 (21.9)	425 (78.1)
Age at diagnosis								
0-10	150	20	25 (16.7)	125 (83.3)	77 (51.3)	73 (48.7)	29 (19.3)	121 (80.7)
11-15	319	42.5	47 (14.7)	272 (85.3)	171 (53.6)	148 (46.4)	74 (23.2)	245 (76.8)
16-20	282	37.5	56 (19.9)	226 (80.1)	158 (56.0)	124 (44.0)	62 (22.0)	220 (78.0)
Current work status								
Employed	680	90.6	96 (14.1)	584 (85.9)	350 (51.5)	330 (48.5)	145 (21.3)	535 (78.7)
Unemployed	66	8.8	31 (47.0)	35 (53.0)	54 (81.8)	12 (18.2)	19 (28.8)	47 (71.2)
Unknown	5	0.7	1 (20.0)	4 (80.0)	2 (40.0)	3 (60.0)	1 (20.0)	4 (80.0)

Table 2

Survivor Treatment and Health Demographic Statistics

	Survivors		FACIT		PSQI		ESS	
	N=751		≤30	>30	>5	≤5	≥10	10
	N	%	N (row %)	N (row %)	N (row %)	N (row %)	N (row %)	N (row %)
Radiation Therapy								
Chest RT<30Gy	230	30.6	36 (15.7)	194 (84.3)	116 (50.4)	114 (49.6)	45 (19.6)	185 (80.4)
Chest RT≥30Gy	445	59.3	80 (18.0)	365 (82.0)	249 (56.0)	196 (44.0)	98 (22.0)	347 (78.0)
Chemotherapy *								
Anthracycline	158	21.0	27 (17.1)	131 (82.9)	86 (54.4)	72 (45.6)	32 (20.3)	126 (79.7)
Alkylating Agents	419	55.8	70 (16.7)	349 (83.3)	228 (54.4)	191 (45.6)	93 (22.2)	326 (77.8)
Bleomycin	147	19.6	24 (16.3)	123 (83.7)	83 (56.5)	64 (43.5)	34 (23.1)	113 (76.9)
Vinca Alkaloids & Heavy Metals	418	55.7	71 (17.0)	347 (83.0)	230 (55.0)	188 (45.0)	94 (22.5)	324 (77.5)
None	326	43.4	57 (17.5)	269 (82.5)	174 (53.4)	152 (46.6)	71 (21.8)	255 (78.2)
Cancer related pain								
None/Small amount	682	90.8	88 (12.9)	594 (87.1)	344 (50.4)	338 (49.6)	143 (21.0)	539 (79.0)
Medium/A lot/Very bad	69	9.2	40 (58.0)	29 (42.0)	62 (89.9)	7 (10.1)	22 (31.9)	47 (68.1)
Body Mass Index								
Normal	355	47.3	55 (15.5)	300 (84.5)	194 (54.6)	161 (45.4)	54 (15.2)	301 (84.8)
Overweight	246	32.8	41 (16.7)	205 (83.3)	128 (52.0)	118 (48.0)	64 (26.0)	182 (74.0)
Obese	131	17.4	27 (20.6)	104 (79.4)	76 (58.0)	55 (42.0)	46 (35.1)	85 (64.9)

* Patients may receive multi chemotherapy so the percentage exceeds 100

Table 3

Multivariable Logistic Regression Analysis of Pain, Emotional Distress, Physical Functioning and Treatment Characteristics on Fatigue, Sleep Quality, and Excessive Daytime Sleepiness.

	Fatigue (≤30)		PSQI		ESS	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Sex						
Male	1.00		1.00		1.00	
Female	4.75	2.47-9.15***	1.18	0.86-1.69	1.07	0.73-1.58
Emotional Distress						
Not impaired	1.00		1.00		NA	
Impaired	8.38	4.28-16.42***	6.57	2.83-16.50***	NA	
Current work						
Employed	1.00		NA		NA	
Unemployed	2.90	1.27-6.62**	NA		NA	
Body Pain						
Not impaired	1.00		1.00		1.00	
Impaired	3.73	2.09-6.67***	2.79	1.82-4.74***	2.11	1.39-3.20***
Cancer related						
None/ Small	NA		1.00		NA	
Medium/A	NA		5.27	1.78-15.61***	NA	
Physical Function						
Not impaired	1.00		NA		NA	
Impaired	3.28	1.75-6.15***	NA		NA	
Body Mass Index						
Normal	1.00		1.00		1.00	
Overweight	0.95	0.50-1.79	0.80	0.54-1.17	2.14	1.38-3.34***
Obese	1.06	0.52-2.15	0.96	0.60-1.54	2.70	1.63-4.48***

Note: OR: Odds ratio;

*statistically significant p <0.5;

**statistically significant $p < 0.01$;

***statistically significant $p < 0.001$.

NA= variables not accepted into models by BIC criteria.