The Impact of Sleep Disturbances on Trajectories of Neurocognitive Functioning in Adult Survivors of Childhood Cancer: A report from the Childhood Cancer Survivor Study (CCSS)

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Background: Adult survivors of childhood cancer are at risk for neurocognitive impairment and sleep problems related to early cancer treatment and late-onset morbidities. The contribution of sleep disturbances to neurocognitive trajectories over time remains unknown.

Methods: CCSS participants (N=7333, 55.2% female, median [min-max] 8 [0-20] years at diagnosis; 37 [18-65] years at baseline evaluation) completed the CCSS Neurocognitive Questionnaire at two timepoints (follow-up interval: 5 [2-7] years) and the Pittsburgh Sleep Quality Index (PSQI) at an interim timepoint. Trajectories of neurocognitive impairment (score > 90th %ile of sibling controls) were defined as: persistent impairment, impaired at both timepoints; new-onset impairment, unimpaired to impaired; resolved impairment, impaired to unimpaired; stable non-impairment, unimpaired at both timepoints. Multivariable logistic models examined associations between poor sleep quality (PSQI total score >5) and sleep components (separately) and trajectories of neurocognitive impairment. Stratified analyses examined differences by CNS-directed therapy exposure or grade 3-4 (severe to life-threatening) chronic conditions using the Common Terminology Criteria for Adverse Events v4.03. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported.

Results: Survivors with poor sleep quality had 3-fold increased risk of new-onset and persistent neurocognitive impairment in all domains including task efficiency (OR [95% CI] 2.55 [2.17-2.99] and 3.40 [2.91-3.96]) and memory (OR [95% CI] 3.05 [2.57-3.61] and 3.35 [2.88-3.91]). Sleep medication was associated with 76-94% and 106-129% increased risk of new-onset and persistent impairment in any domain, respectively. Sleep problems due to pain were also associated with new-onset and persistent impairment (eg, memory: OR [95% CI] 1.67 [1.23-2.27] and 2.23 [1.72-2.88]). Further associations were observed for all sleep components except

sleep efficiency (Table). Snoring was associated with new-onset and persistent impairment mostly in the CNS-directed therapy group (eg, memory: OR [95% CI] 1.54 [1.08-2.21] and 1.59 [1.15-2.21]), whereas sleep medication and sleep problems due to pain were associated with adverse neurocognitive trajectories in both CNS- and non-CNS-directed therapy groups. Among survivors with grade 3-4 chronic conditions, sleep medication and sleep problems due to pain were the only significant predictors of new-onset (OR [95% CI] 2.27 [1.49-3.46] and 1.68 [1.03-2.72]) and persistent (OR [95% CI] 1.58 [1.07-2.32] and 1.87 [1.25-2.79]) memory impairment.

Conclusions: Sleep disturbances confer an increased risk of new-onset and persistent neurocognitive impairment over time for childhood cancer survivors. Behavioral treatments for sleep, pain and sleep-disordered breathing are potential interventions to mitigate or prevent deterioration of neurocognitive functioning in long-term survivors of childhood cancer.

Table: Associations between sleep problems and trajectories of neurocognitive functioning, adjusted for demographic characteristics.

	Neurocognitive functioning trajectories							
	New-onset impairment (unimpaired to impaired)				**Persistent impairment (impaired at both timepoints)**			
	Task Efficiency	**Emotional Regulation**	**Organization**	**Memory**	**Task Efficiency**	**Emotional Regulation**	**Organization**	**Memory**
Sleep problems	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Model 1: overall sleep quality								
Poor sleep quality	**2.55 (2.17-2.99)**	**2.53 (2.15-2.99)**	**2.61 (2.17-3.13)**	**3.05 (2.57-3.61)**	**3.40 (2.91-3.96)**	**3.80 (3.18-4.54)**	**3.63 (3.02-4.36)**	**3.35 (2.88-3.91)**
Model 2: specific components								
Sleep duration	0.99 (0.68-1.42)	0.98 (0.68-1.41)	0.85 (0.57-1.28)	1.20 (0.83-1.73)	1.34 (0.97-1.87)	**1.44 (1.02-2.03)**	1.40 (0.97-2.02)	1.25 (0.91-1.71)
Long sleep onset latency	**1.34 (1.07-1.67)**	1.24 (0.99-1.56)	1.19 (0.92-1.54)	**1.73 (1.38-2.17)**	**1.44 (1.15-1.80)**	**1.59 (1.26-2.01)**	**1.30 (1.02-1.67)**	**1.36 (1.10-1.68)**
Poor sleep efficiency	1.13 (0.88-1.44)	1.27 (0.99-1.63)	1.26 (0.95-1.66)	0.91 (0.71-1.18)	1.03 (0.80-1.32)	0.96 (0.74-1.25)	0.89 (0.67-1.18)	1.11 (0.88-1.40)
Night/early morning awakening	**1.32 (1.05-1.64)**	**1.58 (1.26-1.98)**	1.25 (0.97-1.62)	1.13 (0.90-1.43)	1.10 (0.88-1.38)	1.27 (1.00-1.61)	1.26 (0.98-1.62)	**1.42 (1.15-1.75)**
Snoring	**1.36 (1.05-1.76)**	1.15 (0.88-1.50)	1.31 (0.99-1.75)	**1.31 (1.01-1.70)**	**1.38 (1.08-1.77)**	**1.47 (1.13-1.89)**	**1.32 (1.00-1.73)**	**1.41 (1.11-1.78)**
Pauses in breathing	1.24 (0.79-1.96)	1.03 (0.62-1.69)	**1.93 (1.23-3.03)**	1.14 (0.71-1.84)	0.79 (0.49-1.28)	0.79 (0.48-1.29)	1.42 (0.89-2.26)	1.07 (0.70-1.64)
Delayed sleep timing	1.52 (0.81-2.87)	1.39 (0.72-2.68)	**2.61 (1.44-4.72)**	1.08 (0.58-2.04)	**2.27 (1.34-3.85)**	1.35 (0.77-2.36)	**2.65 (1.51-4.66)**	1.61 (0.96-2.70)
Delayed wake timing	0.78 (0.39-1.57)	0.66 (0.31-1.42)	1.26 (0.67-2.38)	1.76 (0.93-3.33)	0.96 (0.53-1.74)	**2.18 (1.24-3.82)**	1.24 (0.66-2.31)	1.71 (1.00-2.92)
Sleep medication	**1.94 (1.48-2.54)**	**1.80 (1.36-2.39)**	**1.83 (1.35-2.48)**	**1.76 (1.33-2.34)**	**2.08 (1.60-2.69)**	**2.29 (1.75-3.01)**	**2.26 (1.71-3.00)**	**2.06 (1.61-2.64)**
Sleep problems due to pain	1.28 (0.94-1.76)	1.32 (0.97-1.81)	**1.96 (1.43-2.69)**	**1.67 (1.23-2.27)**	**2.49 (1.92-3.24)**	**1.71 (1.27-2.30)**	**1.76 (1.30-2.40)**	**2.23 (1.72-2.88)**

Separate models were used for each neurocognitive outcome, adjusted for sex, race/ethnicity, age and BMI at baseline. Neurocognitive impairment was assessed at two timepoints, and sleep problems were assessed at an interim timepoint. Resolved (impaired to unimpaired) and stable non-impaired (unimpaired at both timepoints) neurocognitive functioning trajectories were combined as reference group. Bold font indicates statistically significant results.
Abbreviations: CI, confidence interval; OR, odds ratio.