1. STUDY TITLE: The Impact of Sleep on Trajectories of Neurocognitive Functioning in Adult Survivors of Childhood Cancer

2. WORKING GROUPS AND INVESTIGATORS

2.1 Working groups: Psychology (primary), Chronic diseases (secondary)

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3. BACKGROUND AND RATIONALE

Improvements in treatment of childhood cancer have resulted in a growing population of survivors who, despite improving survival rates, experience adverse health outcomes and poor quality of life.[1] Long-term survivors of childhood cancer are at risk for neurocognitive impairment that can significantly limit their ability to attain expected social milestones.[2-4] While neurocognitive impairment in survivors is largely driven by exposure to CNS-directed therapies (including neurosurgery, cranial radiation, and intrathecal chemotherapy),[5] survivors treated without CNS-directed therapies also demonstrate increased risk of deficits,[4,6,7] suggesting that other factors contribute to long-term neurocognitive impairment.[5] Previous research has shown that chronic health conditions[8] and poor health behaviors (such as alcohol consumption)[9] increase risk of neurocognitive impairment in survivors. Elucidating the impact of such preventable and/or modifiable risk factors is vital to inform interventions that may ameliorate deficits or preserve neurocognition in long-term survivors.

Sleep disturbance is one such health behavior that may increase risk of neurocognitive impairment in survivors. Compared to sibling controls, adult survivors of childhood cancer report lower quality of sleep[10] and a higher prevalence of poor sleep efficiency[11] that negatively impact their quality of life and mental health. Importantly, sleep problems are associated with risk of neurocognitive impairment[12] and neurocognitive decline[13] in noncancer populations. To date, two studies have examined the impact of sleep on neurocognition in survivors of childhood cancer. One study within the Childhood Cancer Survivorship Study (CCSS) found higher risk of self-reported task efficiency and memory problems in survivors with poor sleep quality, however the sample included only a subgroup of the original cohort and was not representative of the whole cohort (i.e., over-sampling of Hodgkin lymphoma).[14] Another study from the St. Jude Lifetime Cohort Study (SJLIFE) demonstrated worse performance on verbal reasoning, memory, attention, executive function, and processing speed in survivors with insomnia symptoms, especially among females.[15] However, this sample was also not representative because it included a subgroup of survivors specifically recruited for an intervention study focused on sleep and cognition.[15] Importantly, the cross-sectional design of these studies has precluded investigation of how sleep may affect changes in neurocognitive function over time. A longitudinal approach would allow for

the identification of protective and/or risky sleep behaviors associated with changes in neurocognitive functioning, which could then serve as potential intervention targets. This is critical given the growing population of aging survivors, as data from CCSS indicate that around 9% and 13% show significant neurocognitive decline or persistent neurocognitive impairment over time, respectively. (Phillips et al., unpublished data).

In noncancer populations, individuals with chronic health conditions, such as diabetes[16] heart disease,[17] or with traumatic brain injury[18] demonstrate increased sensitivity to the detrimental effects of poor sleep quality and insomnia on neurocognition. As childhood cancer survivors who received neurotoxic treatments may have sustained diffuse cerebral injury, they may have increased sensitivity to the effects of sleep on neurocognitive processes, which could be further exacerbated by chronic health conditions.[8] In adolescence, female survivors of childhood cancer demonstrate greater susceptibility to neurocognitive deficits due in part to the detrimental impact of nighttime awakenings.[19] Better understanding how clinical and biological factors may influence associations between sleep disturbance and neurocognitive trajectories will be crucial to tailor interventions for the most vulnerable subgroups of survivors.

In the current study, we aim to assess the impact of sleep problems on changes in neurocognitive function in childhood cancer survivors and elucidate clinical and biological factors that may confer greater risk to the harmful effect of sleep disturbance on neurocognition. This analysis will use recent data on sleep (FU6) and neurocognitive functioning (FU5 and FU7) collected on all survivors enrolled in the CCSS (Original and Expansion cohorts). We acknowledge that the different administration timing of the sleep and neurocognitive questionnaires will preclude our ability to draw inferences regarding causal effects of sleep on neurocognitive changes. Nonetheless, this will be the first investigation of the associations between sleep and longitudinal changes in neurocognition in long-term survivors of childhood cancer. Results will inform interventions targeting sleep behaviors that may preserve or improve neurocognition, and in turn promote social attainment, especially in vulnerable survivors.

4. SPECIFIC AIMS AND RESEARCH HYPOTHESES

4.1 Aim 1: Examine associations between sleep problems (FU6) with changes in neurocognitive functioning (from FU5 to FU7) in adult survivors of childhood cancer.

4.1.1 *Hypothesis 1*: Survivors with poor sleep quality will be more likely to demonstrate adverse neurocognitive trajectories of task efficiency and memory (i.e., declined neurocognitive functioning, new on-set neurocognitive impairment) compared to survivors without sleep problems.

4.2 Aim 2: Examine how clinical factors influence the associations between sleep (FU6) and trajectories of neurocognitive functioning in long-term survivors of childhood cancer (from FU5 to FU7).

4.2.1 *Hypothesis 2a*: Survivors who received CNS-directed therapies (i.e., neurosurgery, cranial irradiation, intrathecal chemotherapy) will be more vulnerable to the effect of sleep problems on neurocognitive function compared to survivors who received non-CNS-directed therapies.

4.2.2 *Hypothesis 2b:* Survivors with high burden of treatment-related chronic health conditions will be more vulnerable to the effects of sleep problems on neurocognitive function compared to survivors with low burden of such conditions.

5. ANALYSIS FRAMEWORK

5.1 Population: This study will include all eligible survivors in CCSS. Inclusion criteria will be ≥18 years of age at FU5, completion of the *Neurocognitive Questionnaire (NCQ)*[20,21] at FU5 and FU7 by either self or proxy, and completion of the *Pittsburgh Sleep Quality Index (PSQI)* at FU6 by self (i.e., no proxy). Participants with history of unrelated brain injury or genetic syndromes associated with neurocognitive impairment will be excluded.

5.2 Outcomes: Neurocognitive functioning will be assessed using the *Neurocognitive Questionnaire (NCQ)* administered at FU5 [Q1-QN33] and FU7 [P1-P33] for both the original and expansion cohorts. The NCQ, which was developed to identify neurocognitive problems in childhood cancer survivors,[20,21] assesses four neurocognitive domains: task efficiency, emotional regulation, organization, and memory. Age-adjusted T-scores will be calculated using sibling norms, and impairment will be defined as a score ≥90th percentile based on sibling distribution.

Neurocognitive change in each domain will be defined based on impaired or unimpaired scores at the two time points and will be classified into four categories:

a) persistent neurocognitive impairment: impaired at both FU5 and FU7;
b) resolved neurocognitive impairment: impaired at FU5 and not impaired at FU7;
c) new-onset neurocognitive impairment: not impaired at FU5 and impaired at FU7;
d) stable unimpaired neurocognitive functioning: not impaired at both FU5 and FU7.

This approach is consistent with other CCSS publications for emotional distress,[11] loneliness,[22] and pain.[23] An alternative approach will be considered that defines neurocognitive change as a change of ≥ ±1 standard deviation between FU5 and FU7 and categorized as either "declined", "similar" or "improved" neurocognitive function.[24]

5.3 Predictors: Sleep problems will be assessed using the *Pittsburgh Sleep Quality Index (PSQI)*[25] administered at FU6 [B1-B10]. This 19-item questionnaire assesses sleep habits over the past month on a 4-point scale, with higher scores indicating worse sleep. Sleep outcomes will be dichotomized using a priori defined clinical cut offs, consistent with previous definitions used in the CCSS cohort.[11] The following items will be used and dichotomized to indicate clinically significant cut-points:

<u>Sleep Quality</u>

- PSQI Total Score: dichotomized as total scores of ≥5 (clinically poor sleep quality)[25] vs <5 (good sleep quality).

<u>Sleep Parameters</u>

- Bedtime (PSQI Item 1)
- Wake time (PSQI Item 3)
- Sleep duration (PSQI Item 4): dichotomize into <6 hours vs. ≥6[26]

<u>Insomnia Symptoms</u>

- Sleep onset latency (PSQI Item 2): dichotomized as <30 vs. ≥30 minutes (diagnostic criterion for insomnia)[27]
- Sleep efficiency: percent of time in bed spent asleep ([PSQI Item 3 - PSQI Item 1] / PSQI Item 4), dichotomized as <85% vs. ≥85% (diagnostic criterion for insomnia)[27]
- Night/early morning awakenings (PSQI Item 5b): dichotomized as "not at all"/"< once per week"/"1-2 times per week" vs. "3 or more times"

<u>Sleep Management</u>

- Sleep medication use (PSQI Item 7a): dichotomized as no use vs. any use.

<u>Delayed Sleep/Wake Timing</u>

- Sleep onset after 1 am (PSQI Item 1): dichotomized as "before 1 am" vs. "after 1 am"[28]
- Wake time after 10 am (PSQI Item 3): dichotomized as "before 10 am" vs. "after 10 am"

<u>Symptoms of Sleep Disordered Breathing (i.e., Snoring)</u>

- Self-report of snoring (PSQI Item 5e) and bed partner report of long pauses in breathing (PSQI Item 10b): dichotomized as “not at all”/“< once per week”/“1-2 times per week” vs. “3 or more times” (snoring/long pauses in breathing more than 3 nights per week is suggestive of obstructive sleep apnea).[29]

5.4 Covariates

Clinical variables

- Diagnosis
  - CNS tumors
  - Leukemia
  - Hodgkin lymphoma
  - non-Hodgkin lymphoma
  - Wilms’ tumor
  - Neuroblastoma
  - Soft tissue sarcoma
  - Bone tumor
- Age at diagnosis, in years
- Time since diagnosis, in years

Treatment exposures

All treatment exposures refer to the first 5 years after the primary cancer diagnosis.

- Radiation, maximum target dose (maxTD; dose categories, or as a continuous variable if warranted)
  - Cranial (none, <30Gy, ≥30Gy)*
  - Neck (none, <30Gy, ≥30Gy)
  - Chest (none, <30Gy, ≥30Gy)
- Chemotherapy (yes/no, or as a continuous variable if warranted)
  - High-dose IV methotrexate (HD MTX)
  - Standard dose IV methotrexate
  - Intrathecal methotrexate (IT MTX)*
  - High dose IV cytarabine
  - Vincristine
  - Anthracycline equivalent dose
  - Alkylating agent equivalent dose
  - Corticosteroids (prednisone equivalent dose)
  - Platinum agents
- Neurosurgery (yes/no)*
- Shunt (yes/no)

* For aim 2, exposures to cranial radiation, neurosurgery, and/or IT MTX (yes/no) will be used to define the CNS-directed therapy group.

Health-related factors (at FU5)

- Physical activity (yes/no met CDC guidelines) [N15-N21]
- Alcohol use (yes/no for heavy/risky drinking) [N1-N6]
- Smoking status (current/ever, never) [N7-N11]
- Emotional distress (yes/no; yes if any one of the following is met)
  - Anxiety: BSI Anxiety subscale T-score ≥63 [L1-L18]
  - Depression: BSI Depression subscale T-score ≥63 [L1-L18]
  - Current use of antidepressant and/or anxiolytic medications [C2], as previously defined in CCSS.[30,31]

- Pain (yes/no; yes if any one of the following is met):
    - Headaches (migraines, severe headaches) still present [K3-K4]
    - Moderate to very severe bodily pain [O7-O8]
    - Current use of opioid and/or non-opioid analgesics [C2], as previously defined in CCSS.[30,31]
- SF-36 Vitality scale (T-score <40) [O1-P3]
- BMI [A1-A2]
    - Underweight (BMI < 18.5)
    - Normal (BMI ≥ 18.5 and < 25)
    - Overweight (BMI ≥ 25 and <30)
    - Obese (BMI ≥30)
- Chronic Health Conditions (CHCs; CTCAE grade 0-4) [D1-I9]
    - Endocrine, cardiac, pulmonary, neurologic, hearing, vision

  We will analyze CHCs with onset before FU6. We will examine grade 2+ conditions in each organ system, as well as any grade 3+ condition across all organ systems. Additionally, we will utilize a method developed by Geenen et al,[32] to aggregate chronic health conditions across organ systems taking into account the frequency and grade of conditions. This method will be adapted for CCSS, where chronic conditions are based on self-report and grade 1 conditions are mostly asymptomatic. For survivors who have multiple chronic health conditions within the same organ system, we will use the highest grade within that organ system. This severity/burden score will be classified via the following ordinal categories: none/low (< grade 2 conditions), medium [having (≥1 grade 2) and/or (1 grade 3 condition)], high [having (≥ 2 grade 3 conditions) or (1 grade 4 and 1 grade 3 conditions)], and severe score [(≥ 1 grade 4 events) or (≥ 2 grade 3 conditions and a grade 4 condition)]. This information is also summarized in the table below. Further groupings (e.g., ≤medium vs. high/severe) will be evaluated based on frequency distribution.

Burden Category	**Definition**
Severe	more than one grade 4 event, or one grade 4 event and two or more grade 3 events
High	two or more grade 3 events, or one grade 4 event and at most one grade 3 event
Medium	one or more grade 2 event(s) and/or one grade 3 event
None/low	any condition < grade 2[#]

[#] adapted from the original method by Geenen, where “low” indicated one or more grade 1 event(s).

<u>Sociodemographic factors (at FU5)</u>

- Age at evaluation
- Sex
- Race/ethnicity
    - White, non-Hispanic
    - Black, non-Hispanic
    - Other
- Employment [A5]
    - Full-time
    - Part-time
    - Retired/disabled/unemployed

- Educational attainment [A4]
    - < High school, completed high school
    - Training after high school/some college, college graduate/post-graduate

6. ANALYTIC APPROACH

Frequency distributions will be generated to categorize relevant outcome variables, predictors, and covariates according to a prior and/or reasonable groupings. Descriptive statistics including means, standard deviation, medians, ranges, frequencies, and percentages will be calculated for all outcomes, predictors, and covariates. Given the longitudinal component, participation at FU's will be examined for need of inverse probability weighting.

Aim 1: Examine the impact of sleep problems on changes in neurocognitive functioning in adult survivors of childhood cancer. Multivariable multinomial regression models will be used to investigate associations between sleep parameters (predictors) and trajectories of neurocognitive functioning (outcomes).

As previously mentioned, sleep parameters will be dichotomized using a priori defined clinical cut offs, but some sleep parameters (e.g., sleep duration, sleep onset latency, sleep efficiency) may also be examined as continuous variables. For sleep duration, we will examine how many survivors report ≥10 hours of sleep per night (which is also considered problematic[33,34]) and we will consider whether to exclude them from subsequent analyses or consider them as a separate category. Only self-completed questionnaires will be used. One set of models will include the overall PSQI sleep quality score. Another set of models will include the specific components of sleep available in the PSQI; if necessary due to frequency distribution, we will collapse specific subcomponents of sleep as sleep parameters, insomnia symptoms, sleep medications, delayed sleep/wake timing, and symptoms of sleep-disordered breathing (see predictor definitions).

Trajectories of neurocognitive functioning will be defined as changes in NCQ impairment between FU5 and FU7 as previously described (i.e., persistent, resolved or new-onset neurocognitive impairment vs. stable unimpaired neurocognitive functioning in the primary approach; "declined" or "improved" vs. "similar" in the alternative approach), using separate models for each NCQ domain score. Alternatively, generalized linear models will be used to determine the relative risk of new-onset impairment at follow-up in each domain among survivors who did not report impairment in that domain at baseline. Both self- and proxy- completed NCQ measures will be used. We will compare survivors with self-completed versus proxy-completed questionnaires to examine potential bias in the analysis.

One set of models will be adjusted a priori for sex, race/ethnicity, age at FU5, and BMI at FU5 (Table 2). Another set of models will adjust also for FU5 covariates of health behaviors (physical activity, smoking, alcohol consumption) and psychological problems (emotional distress, pain, and vitality) (Table 3).

Aim 2: Examine how clinical factors influence the effect of sleep problems (FU6) on trajectories of neurocognitive functioning in long-term survivors of childhood cancer (FU5 and FU7). The clinical factors of interest are treatment exposure and physical morbidities, which will always be examined separately. For treatment exposure, we will examine CNS-directed therapies (neurosurgery, cranial radiation, and intrathecal methotrexate) versus non-CNS-directed therapies. For physical morbidities, we will examine chronic health conditions with onset before FU6, and we will compare any grade 3-4 versus grade 2-0 condition. An alternative approach using the severity/burden score will also be explored (e.g., ≤medium vs. high/severe).

First, we will use crosstabulations to examine the frequency of sleep quality (PSQI total score: poor vs. good sleep quality) by treatment exposures (CNS-directed vs. non-CNS-directed

therapies), and by physical morbidities (any grade 3-4 vs. grade 2-0 chronic conditions, or ≤medium vs. high/severe burden), separately. If there is a sufficient number of survivors in each cell, we will examine the interactions between sleep quality and treatment exposures, and between sleep quality and physical morbidities, in relation to the neurocognitive trajectories.

If an interaction between sleep and treatment exposure is not present, multivariable multinomial regression models will be used to investigate associations between sleep parameters (predictors) and trajectories of neurocognitive functioning (outcomes) adjusting for CNS-directed therapies (neurosurgery, cranial radiation, and intrathecal methotrexate) as covariates (Table 4a). If an interaction is present, the same models will be repeated using stratification based on history of CNS-directed therapies (Table 4b). Additional covariates will be sex, race/ethnicity, age at FU5, BMI at FU5, age at diagnosis and other non-CNS directed therapies (high-dose IV cytarabine and IV methotrexate) that impact neurocognitive functioning.

If an interaction between sleep and physical morbidities is not present, multivariable multinomial regression models will be used to investigate associations between sleep parameters (predictors) and trajectories of neurocognitive functioning (outcomes) adjusting for any grade 3-4 vs. 2-0 conditions (or ≤ medium vs. high/severe) as covariate (Table 5a). If an interaction is present, the same models will be repeated using stratification based on the presence of any grade 3-4 conditions (or high to severe burden) (Table 5b). Additional covariates will include sex, race/ethnicity, age at FU5, BMI at FU5, and psychological problems at FU5.

Table 1. Sociodemographic and clinical characteristics at FU5 of childhood cancer survivors.

	Total sample (N =)	**CNS-directed therapies * (n =)**	**Non-CNS-directed therapies * (n =)**
	No (%)	**No (%)**	**No (%)**
Sex			
Male			
Female			
Race/Ethnicity			
White, non-Hispanic			
Black, non-Hispanic			
Other			
Age at assessment, years			
18-29			
30-39			
40-49			
50+			
Age at diagnosis, years			
0-4			
5-9			
10-14			
15-21			
Diagnosis			
Leukemia			
CNS tumors			
Hodgkin lymphoma			
Non-Hodgkin lymphoma			
Neuroblastoma			
Wilms' tumor			
Soft tissue sarcoma			
Bone tumor			
Cranial radiation, Gy			
None		/	
>0 to < 30		/	
≥ 30		/	
Neck radiation, Gy			
None			
>0 to < 30			
≥ 30			
Chest radiation, Gy			
None			
>0 to <30			
≥ 30			
IT Methotrexate			
IV Methotrexate, g/m^2			

Median (IQR) dose		/	
None		/	
>0 to <40		/	
≥ 40		/	
High-dose IV cytarabine			
Yes			
No			
Anthracycline, mg/m^2			
Median (IQR) dose			
None			
1-249			
≥250			
Neurosurgery		/	
BMI			
Underweight			
Normal			
Overweight			
Obese			
Physical activity			
Smoking			
Alcohol drinking			
Emotional distress			
Pain			
Vitality			
Chronic conditions			
Any (grade 3-4)			
Endocrine (grade 2-4)			
Cardiac (grade 2-4)			
Pulmonary (grade 2-4)			
Neurologic (grade 2-4)			
Vision (grade 2-4)			
Hearing (grade 2-4)			

Note. CNS-directed therapies include neurosurgery, cranial radiation, and intrathecal methotrexate.

* If interaction between sleep and CNS-directed therapies, sleep and physical morbidities, are found and stratification will be used, the sample characteristics in each stratum will be reported.

Abbreviations: CI, confidence interval; CNS, central nervous system; Gy, grey; IQR, interquartile range; IT, intrathecal; IV intravenous.

Table 2 (aim 1). Associations between sleep problems at FU6 and trajectories of neurocognitive outcomes between FU5 and FU7, adjusted for demographic characteristics.

Sleep problems, yes vs. no (FU6)	**Neurocognitive functioning trajectories (FU5 to FU7)***											
	Persistent impairment				**New-onset impairment**				**Resolved impairment**			
	TE	**ER**	**Org**	**Mem**	**TE**	**ER**	**Org**	**Mem**	**TE**	**ER**	**Org**	**Mem**
	RR (95%CI)	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**
Model 1: overall sleep quality												
Poor sleep quality												
Model 2: specific sleep components												
Sleep duration												
Long sleep onset latency												
Poor sleep efficiency												
Night/early morning awakening												
Snoring												
Pauses in breathing												
Delayed sleep timing												
Delayed wake timing												
Sleep medication												

* Persistent impairment = impaired to impaired; new-onset impairment = non-impaired to impaired; resolved impairment; impaired to non-impaired; stable non-impairment as reference group.

Separate models for each neurocognitive outcome, adjusted for sex, race/ethnicity, age at FU5, and BMI at FU5. Poor sleep quality in a separate model because it is an overall score that combines the other sleep subcomponents.

Abbreviations: CI, confidence interval; CNS, central nervous system; ER, Emotional regulation; Mem, Memory; Org, Organization; RR, relative risk; TE, Task efficiency.

Table 3 (aim 1). Associations between sleep problems at FU6 and trajectories of neurocognitive outcomes between FU5 and FU7, adjusted for demographic characteristics as well as health behaviors and psychological problems at FU5.

Sleep problems yes/no (FU6)	**Neurocognitive functioning trajectories (FU5 to FU7)***											
	Persistent impairment				**New-onset impairment**				**Resolved impairment**			
	TE	**ER**	**Org**	**Mem**	**TE**	**ER**	**Org**	**Mem**	**TE**	**ER**	**Org**	**Mem**
	RR (95%CI)	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**
Model 1: overall sleep quality												
Poor sleep quality												
FU5 physical activity												
FU5 smoking												
FU5 alcohol consumption												
FU5 emotional distress												
FU5 pain												
FU5 vitality												
Model 2: specific sleep components												
Sleep duration												
Long sleep onset latency												
Poor sleep efficiency												
Night/early morning awakening												
Snoring												
Pauses in breathing												
Delayed sleep timing												
Delayed wake timing												
Sleep medication												
FU5 physical activity												
FU5 smoking												
FU5 alcohol consumption												
FU5 emotional distress												
FU5 pain												
FU5 vitality												

* Persistent impairment = impaired to impaired; new-onset impairment = non-impaired to impaired; resolved impairment; impaired to non-impaired; stable non-impairment as reference group.

Separate models for each neurocognitive outcome, adjusted for sex, race/ethnicity, age at FU, and BMI at FU5. Poor sleep quality in a separate model because it is an overall score that combines the other sleep subcomponents.

Abbreviations: CI, confidence interval; CNS, central nervous system; ER, Emotional regulation; Mem, Memory; Org, Organization; RR, relative risk; TE, Task efficiency.

Table 4a (Aim 2a). Associations between sleep problems at FU6 and trajectories of neurocognitive outcomes between FU5 and FU7, adjusted for CNS-directed therapies.

	Persistent neurocognitive impairment (FU5 to FU7)*			
	TE (RR [95%CI])	**ER (RR [95%CI])**	**Org (RR [95%CI])**	**Mem (RR [95%CI])**
Model 1: overall sleep quality (FU6)				
Poor sleep quality				
Neurosurgery				
Cranial radiation dose				
IT MTX dose				
Model 2: specific sleep components (FU6)				
Sleep duration				
Long sleep onset latency				
Poor sleep efficiency				
Night/early morning awakening				
Snoring				
Pauses in breathing				
Delayed sleep timing				
Delayed wake timing				
Sleep medication				
Neurosurgery				
Cranial radiation dose				
IT MTX dose				
	New-onset neurocognitive impairment (FU5 to FU7)*			
	TE (RR [95%CI])	**ER (RR [95%CI])**	**Org (RR [95%CI])**	**Mem (RR [95%CI])**
Model 1: overall sleep quality (FU6)				
Poor sleep quality				
Neurosurgery				
Cranial radiation dose				
IT MTX dose				
Model 2: specific sleep components (FU6)				
Sleep duration				
Long sleep onset latency				
Poor sleep efficiency				
Night/early morning awakening				
Snoring				
Pauses in breathing				
Delayed sleep timing				
Delayed wake timing				
Sleep medication				
Neurosurgery				

Cranial radiation dose				
IT MTX dose				

* Persistent impairment = impaired to impaired; new-onset impairment = non-impaired to impaired; resolved impairment; impaired to non-impaired; stable non-impairment as reference group.

Separate models for each neurocognitive outcome, adjusted for sex, race/ethnicity, age at FU5, BMI at FU5, age at diagnosis, high-dose IV cytarabine, and IV methotrexate. Poor sleep quality in a separate model because it is an overall score that combines the other sleep subcomponents.

Abbreviations: CI, confidence interval; CNS, central nervous system; ER, Emotional regulation; Mem, Memory; Org, Organization; RR, relative risk; TE, Task efficiency.

Table 4b (Aim 2a). Associations between sleep problems at FU6 and trajectories of neurocognitive outcomes between FU5 and FU7, stratified by CNS-directed therapy group.

Sleep problems yes/no (FU6)	**CNS-directed therapies**				**Non-CNS-directed therapies**			
	TE	**ER**	**Org**	**Mem**	**TE**	**ER**	**Org**	**Mem**
	RR (95%CI)	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**
	Persistent neurocognitive impairment (FU5 to FU7)*							
Model 1: overall sleep quality								
Poor sleep quality								
Model 2: specific sleep components								
Sleep duration								
Long sleep onset latency								
Poor sleep efficiency								
Night/early morning awakening								
Snoring								
Pauses in breathing								
Delayed sleep timing								
Delayed wake timing								
Sleep medication								
	New-onset neurocognitive impairment (FU5 to FU7)*							
Model 1: overall sleep quality								
Poor sleep quality								
Model 2: specific sleep components								
Sleep duration								
Long sleep onset latency								
Poor sleep efficiency								
Night/early morning awakening								
Snoring								
Pauses in breathing								
Delayed sleep timing								
Delayed wake timing								
Sleep medication								

* Persistent impairment = impaired to impaired; new-onset impairment = non-impaired to impaired; resolved impairment; impaired to non-impaired; stable non-impairment as reference group.

Separate models for each neurocognitive outcome, adjusted for sex, race/ethnicity, age at FU5, age at diagnosis, high-dose IV cytarabine, and IV methotrexate. Poor sleep quality in a separate model because it is an overall score that combines the other sleep subcomponents.

Abbreviations: CI, confidence interval; CNS, central nervous system; ER, Emotional regulation; Mem, Memory; Org, Organization; RR, relative risk; TE, Task efficiency.

Table 5a (Aim 2b). Associations between sleep problems at FU6 and trajectories of neurocognitive outcomes between FU5 and FU7, adjusted for physical morbidities.

	Persistent neurocognitive impairment (FU5 to FU7)*			
	TE (RR [95%CI])	**ER (RR [95%CI])**	**Org (RR [95%CI])**	**Mem (RR [95%CI])**
Model 1: overall sleep quality (FU6)				
Poor sleep quality				
Any grade 3-4 CHCs				
Model 2: specific sleep components (FU6)				
Sleep duration				
Long sleep onset latency				
Poor sleep efficiency				
Night/early morning awakening				
Snoring				
Pauses in breathing				
Delayed sleep timing				
Delayed wake timing				
Sleep medication				
Any grade 3-4 CHCs				
	New-onset neurocognitive impairment (FU5 to FU7)*			
	TE (RR [95%CI])	**ER (RR [95%CI])**	**Org (RR [95%CI])**	**Mem (RR [95%CI])**
Model 1: overall sleep quality (FU6)				
Poor sleep quality				
Any grade 3-4 CHCs				
Model 2: specific sleep components (FU6)				
Sleep duration				
Long sleep onset latency				
Poor sleep efficiency				
Night/early morning awakening				
Snoring				
Pauses in breathing				
Delayed sleep timing				
Delayed wake timing				
Sleep medication				
Any grade 3-4 CHCs				

* Persistent impairment = impaired to impaired; new-onset impairment = non-impaired to impaired; resolved impairment; impaired to non-impaired; stable non-impairment as reference group.

§ Chronic conditions with onset before FU6 will be included in this analysis. An alternative approach will consider the burden score and grouped categories (e.g., ≤medium vs. high/severe) based on observed frequencies.

Poor sleep quality in a separate model because it is an overall score that combines the other sleep subcomponents. Separate models for each neurocognitive outcome, adjusted for sex, race/ethnicity, age at FU5, BMI at FU5, and psychological problems at FU5.

Abbreviations: CI, confidence interval; ER, Emotional regulation; Mem, Memory; Org, Organization; RR, relative risk; TE, Task efficiency.

Table 5b (Aim 2b). Associations between sleep problems at FU6 and trajectories of neurocognitive outcomes between FU5 and FU7, stratified by physical morbidities.

Sleep problems yes/no (FU6)	**Chronic conditions§**							
	Grade 3-4				**Grade 0-2**			
	TE	**ER**	**Org**	**Mem**	**TE**	**ER**	**Org**	**Mem**
	RR (95%CI)	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**
	Persistent neurocognitive impairment (FU5 to FU7)*							
Model 1: overall sleep quality								
Poor sleep quality								
Model 2: specific sleep components								
Sleep duration								
Long sleep onset latency								
Poor sleep efficiency								
Night/early morning awakening								
Snoring								
Pauses in breathing								
Delayed sleep timing								
Delayed wake timing								
Sleep medication								
	New-onset neurocognitive impairment (FU5 to FU7)*							
Model 1: overall sleep quality								
Poor sleep quality								
Model 2: specific sleep components								
Sleep duration								
Long sleep onset latency								
Poor sleep efficiency								
Night/early morning awakening								
Snoring								
Pauses in breathing								
Delayed sleep timing								
Delayed wake timing								
Sleep medication								

* Persistent impairment = impaired to impaired; new-onset impairment = non-impaired to impaired; resolved impairment; impaired to non-impaired; stable non-impairment as reference group.

§ Chronic conditions with onset before FU6 will be included in this analysis. An alternative approach will consider the burden score and grouped categories (e.g., ≤medium vs. high/severe) based on observed frequencies.

Poor sleep quality in a separate model because it is an overall score that combines the other sleep subcomponents. Separate models for each neurocognitive outcome, adjusted for sex, race/ethnicity, age at FU5, BMI at FU5, and psychological problems at FU5.

Abbreviations: CI, confidence interval; ER, Emotional regulation; Mem, Memory; Org, Organization; RR, relative risk; TE, Task efficiency.

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