1. STUDY TITLE: Associations between Frailty and Sleep in Adult Survivors of Childhood Cancer

2. WORKING GROUP AND INVESTIGATORS

2.1. Working Group: Psychology (primary), Epidemiology/Biostatistics (secondary), Chronic Disease (secondary)

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3. BACKGROUND AND RATIONALE

Despite advances in cancer therapy, childhood cancer survivors experience a lifelong risk of treatment-related late-effects.[1] Survivors experience a high and variable burden of chronic health conditions[2] and these conditions occur at younger ages, compared to siblings[3] and the general population.[4] Moreover, evidence suggests that young adult survivors of childhood cancer may have reduced physiologic reserve,[5] increasing their vulnerability to frailty. Adult survivors of childhood cancer have a 3-fold increased prevalence of physiologic frailty compared to siblings[6] and overall, young adult survivors have rates of physiologic frailty similar to older adult populations.[5] Frailty is associated with increased morbidity and mortality,[7] and research is needed to identify modifiable health behaviors especially among young adult survivors who may be able to strengthen their depleted physiologic reserve.

Sleep is a physiological process associated with lifespan development. Among older adult populations, various dimensions of sleep (e.g. sleep quality, wake after sleep onset, sleep duration, sleep-disordered breathing) have been identified as both an antecedent[8] and consequent of frailty, though most associations have been described based on cross-sectional models.[9] While the directionality of the association between sleep and frailty has not been fully elucidated, there is support for a bidirectional relationship. Sleep-wake disturbances may serve as a modifiable factor that contribute to frailty. In a prospective study of older adults, the transition from prefrail

to frail over a two-year time period was accelerated by short sleep duration.[10] Alternatively, a reduced physiological reserve could contribute to sleep disturbances. In a sample of breast cancer survivors, baseline frailty was associated with sleep disturbances assessed approximately 4 years later.[11]

Research on sleep and frailty is especially needed among childhood cancer survivors who experience a high prevalence of sleep disturbances,[12,13] the understanding of which is complicated by complex etiologies that may be unique to survivors. For example, an increased prevalence of excessive sleepiness and narcolepsy observed in craniopharyngioma survivors is related to degree of hypothalamic involvement of the tumor.[14] The increased prevalence of sleep apnea among Hodgkin Lymphoma survivors may be related to upper airway changes due to chest radiation (current NCI funded R01, PIs Krull and Mandrell). Insomnia may present differently in cancer survivors due to several perpetuating factors that can be associated with survivorship, psychological distress, fatigue, pain, hormonal disruptions, and chronic health conditions associated with treatment exposures.[13,15] Despite established associations between sleep and frailty in non-cancer samples, a better understanding of this relationship is needed among childhood cancer survivors.

Purpose of the Study

The purpose of this study is to examine associations between physiologic frailty and sleep disturbances in a large cohort of long-term survivors of childhood cancer. Additionally, we will examine the proportion and severity of sleep disturbance among frail/pre-frail survivors with and without chronic health conditions, emotional distress and pain.

Proposal Team:

The project team includes researchers with expertise in long-term survivorship, frailty, and sleep health. Drs. Brinkman, Krull, and Mulrooney have expertise in long-term survivorship and have conducted several sleep research projects within the CCSS cohort, including an active sleep intervention project that is funded as an ancillary study. Drs. Lubas, Szklo-Coxe, and Daniels have extensive training in sleep research, and Dr. Ness has expertise and conducted previous research in frailty among long-term survivors. Together, these research team members are well positioned to collaborate on study examining sleep and frailty among long-term survivors.

4. SPECIFIC AIMS

<u>Aim 1:</u> To examine associations between "the frailty phenotype" and self-reported sleep disturbances.

<u>Hypothesis 1:</u> Frail and pre-frail survivors will have a greater prevalence of a self-reported sleep disturbance (poor sleep quality, short/long sleep duration, prolonged sleep onset latency, increased wake after sleep onset, poor sleep efficiency) compared to non-frail survivors. We hypothesize these associations (exposure=frailty; outcomes=sleep) will remain statistically significant, even after adjustments for known treatment exposures associated with frailty, sociodemographic variables and risky health behaviors.

<u>Aim 2:</u> To examine associations between "the frailty phenotype" and self-reported sleep

disturbances after adjustment for chronic health conditions.

Hypothesis 2: The association between the frailty phenotype and self-reported sleep disturbances will be attenuated but remains an independent risk factor after adjustment for chronic health conditions. We plan to examine chronic health conditions across organ systems and by an aggregate/burden score in separate models.

Aim 3: To examine associations between "the frailty phenotype" and self-reported sleep disturbances after adjustment for depression/anxiety.

Hypothesis 3: The association between the frailty phenotype and self-reported sleep disturbances will be attenuated but remains an independent risk factor after adjustment for symptoms of depression, and anxiety.

Aim 4: To examine associations between "the frailty phenotype" and self-reported sleep disturbances after adjustment for bodily pain.

Hypothesis 4: The association between the frailty phenotype and self-reported sleep disturbances will be attenuated but remains an independent risk factor after adjustment for bodily pain.

5. ANALYSIS FRAMEWORK

5.1 Overview: We plan to examine associations between the physiologic frailty phenotype and sleep disturbances in the CCSS cohort. Additionally, we will compare the severity of sleep disturbances among frail/pre-frail survivors with and without chronic health conditions, depression, anxiety and pain.

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5.2 Population: **(Aim 1)** Survivors who completed surveys at FU5 (frailty assessment) and FU6 (sleep assessment); we estimate this to be approximately 10,000 survivors. Although examining the associations between frailty and sleep disturbances involves two time points in Aim 1, this proposed association cannot be examined causally, because there is no assessment of sleep at FU5. Therefore, we will also explore alternate models, wherein sleep disturbances are the exposures and frailty is the outcome. For example, we could do this by analyzing the sub-sample of survivors from the cohort who completed the 2002-2004 sleep survey and FU5. We estimate this to be approximately 2,000 survivors.

(Aims 2-4) Survivors who completed surveys at FU5 and FU6. We estimate this to be approximately 10,000 survivors. Models for aims 2-4 represent separate models to examine physical and emotional health variables distinctly. We plan to examine chronic health conditions in separate models at the organ system level, but may include an incremental model including all organ systems. Additionally, we may examine emotional health variables (anxiety, depression, and bodily pain) in an incremental model.

5.3 Outcome of interest:

i. *Self-reported sleep disturbances* will be assessed by the Pittsburg Sleep Quality Index (PSQI).[16] The PSQI measures sleep quality and quantity over the previous month and is comprised of self-report items and roommate/bed-partner report items (if applicable). Overall sleep quality scores on the PSQI range from 0 to 21 and are based on the scoring of seven components: subjective sleep quality, sleep onset latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. A score > 5 identifies the clinical cut-off for poor sleepers. In addition to the overall sleep quality score, we plan to examine individual components of the PSQI such as: sleep onset latency, sleep duration, wake after sleep onset, sleep efficiency and snoring. **(Aim 1).**

Sleep Parameters (used to describe sample's sleep and calculate other variables)

- Bedtime (PSQI Item 1)
- Wake time (PSQI Item 3)
- Sleep duration (PSQI Item 4)
    - Dichotomize into <6 hours or ≥6 hours based on evidence of poor health outcomes related to short sleep duration[21]

Insomnia Symptoms

- Sleep onset latency (PSQI Item 2)
    - Dichotomize into <30 minutes vs. ≥30
    - 30 minutes is a diagnostic criterion for insomnia
- Sleep efficiency—percent of time in bed spent asleep.
    - Difference between item 3 and 1 divided by item 4
    - Dichotomize result into <85% and ≥85%
    - < 85% sleep efficiency is a diagnostic criterion for insomnia
- Night awakening/early morning awakenings
    - Dichotomize into "not at all;" "< once per week," "1-2 times per week;" vs. "3 or more times per week"

Sleep Management

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

Delayed Sleep/Wake Timing

- Sleep onset after 1 am (PSQI Item 1)
    - Dichotomize into before 1 am AND after 1 am
- Wake time after 10 am (PSQI Item 3)
    - Dichotomize into before 10 am AND after 10 am

Sleep Quality. PSQI Total Score. A total score of >5 indicating clinically significant poor sleep quality

Symptoms of Sleep Disordered Breathing (i.e., Snoring.)

- Self-report of snoring (PSQI Item 5e) and bed partner report of long pauses in breathing (PSQI Item 10b). Snoring/long pauses in breathing more than 3 nights per week is suggestive of obstructive sleep apnea[23].
- Dichotomize into "not at all," "< once per week," "1-2 times per week" VERSUS "3 or more times"

5.4 Primary Predictors

i. *Frailty* will be assessed by using a modified Fried frailty criteria[17] previously defined and applied by Hayek et al.[6] in the CCSS cohort. These measures include: 1) low lean muscle mass (defined by BMI or unintentional weight loss); 2) exhaustion (SF-36 vitality subscale); 3) low energy expenditure (convert frequency and duration of low, moderate and vigorous physical activity levels into kilocalories); 4) slowness (limitations in walking uphill/upstairs, or limitation in walking one block); 5) weakness ("have you ever been told that you have, or have had weakness or inability to move arms"). The frailty phenotype will be defined accordingly (consistent with previous analyses in CCSS): 1) non-frail (less two components of frailty); 2) pre-frail (two components of frailty); 3) frail (three components of frailty).

ii. *Covariates* will include cancer-related variables (diagnosis group, age at diagnosis, time since diagnosis), treatment exposures (chemotherapy, radiation, surgery), medications, sociodemographic variables (age, sex, race/ethnicity, education, employment, household income, health insurance), health behaviors (smoking, alcohol use, and physical activity), bodily pain, emotional distress, and chronic health conditions. These variables will primarily be obtained from FU5, but some variables (e.g. age at survey will be obtained at FU6).

Cancer-Related Variables

- Age at diagnosis, Years
- Age during follow up, Years (FU6)
- Cancer diagnosis
    - CNS Tumors
        - Astrocytoma
        - Medulloblastoma
        - Ependymoma
    - Leukemia
        - ALL
        - AML
    - Hodgkin lymphoma
    - Non-Hodgkin lymphoma
    - Wilms
    - Neuroblastoma

    - Soft tissue sarcoma
    - Bone tumors
- Chemotherapy variables (Yes/No)
    - Anthracyclines
    - Alkylating agents
    - Antimetabolites
        - Methotrexate
        - Cytarabine
    - Corticosteroids
    - Vina Alkaloids & Heavy Metals
    - Platinum based agents
- Surgery (any)
    - Yes
    - No
- Amputation
    - Yes
    - No
- Lung Surgery
    - Yes
    - No
- Radiation variables, maximum target dose (maxTD) to the following body regions
    - Cranial
        - None
        - < 30 Gy
        - ≥ 30 Gy
    - Chest
        - None
        - < 30 Gy
        - ≥ 30 Gy
    - Abdominal
        - None
        - < 30 Gy
        - ≥ 30 Gy
    - Pelvic
        - None
        - < 30 Gy
        - ≥ 30Gy
    - Neck
        - None

- < 30 Gy
- ≥ 30Gy

Sociodemographic Factors

- Sex
  - Male
  - Female
- Race/Ethnicity
  - White
  - Black
  - Hispanic
  - Others
- Employment (full-time, part-time, retired, disabled, unemployed) (FU5, A5)
- Educational attainment (< high school, completed high school, training after high school/some college, college graduate/post graduate) (FU5, A4)
- House Income (less than $19,999; $20,00 – 39,000; $40,000-$60,000; over $60,000) (FU5, A5)

Health Related Factors

- Smoking (FU5 N8, N9, N10, N11)
  - Current, ever, never
- Alcohol use (FU5 N6)
  - Risky drinking
- Physical inactivity (FU5 N15-N21)
  - Calculate time spent in moderate/vigorous physical activities per week
- Chronic health conditions will be assessed for the following CTCAE conditions: cardiovascular, pulmonary, endocrine, neurologic, gastrointestinal, musculoskeletal, and renal. We will examine grade 2 conditions at organ system level, but we will also review the prevalence of grade 3-4 conditions at the organ system level to consider a more stringent cut-off. Additionally, we will utilize a method developed by Geenen et al[18]., to aggregate chronic health conditions across organ systems taking into account the frequency and grade of conditions. 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 (only grade 1 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. **(Aim 2)**

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
Low	one or more grade 1 event(s)
None	*will be collapsed with low category

- Depression **(Aim 3)** dichotomize T-score ≥ 63 (FU5, BSI 18 Subscale from L1-L18)
- Anxiety **(Aim 3)** dichotomize T-score ≥ 63 (FU5, BSI Subscale from L1-L18)
- Bodily pain (dichotomize not at all, a little bit and ≥ moderate) **(Aim 4)** (FU5 O8)

6. ANALYSIS APPROACH

Analytic Approach

Aim 1: Multivariable logistic or linear regression models may be employed to examine associations between the frailty phenotype and sleep disturbances. For binary logistic regression models, sleep outcomes will be dichotomized using a priori defined clinical cut offs, largely following previous definitions used in the CCSS cohort.[12] However, for some sleep outcomes (e.g. sleep duration, sleep onset latency, sleep efficiency), we may define these outcomes continuously. We hypothesize that frailty and pre-frailty (FU5, 2014-2016) will be associated with statistically significant increased prevalence of sleep disturbances (FU6 2017-2019). As mentioned previously, as our plan is to examine the association between frailty and sleep cross-sectionally (because there is no assessment of sleep at FU5), we will also explore alternate models, namely we will employ multinomial logistic regression models to examine the association between sleep and the frailty phenotype (frail, pre-frail, non-frail) by utilizing the sub-sample of survivors from the cohort who completed the 2002-2004 sleep survey and FU5. In all models, we will examine unadjusted and adjusted associations.

Models will be adjusted for: age at diagnosis, age at time of survey, cancer diagnosis*, treatment exposures*, sex, race/ethnicity, smoking, risky/heavy alcohol use, and physical inactivity.
*We will utilize separate models for diagnosis and treatment exposures.
Only treatment exposures associated with frailty and/or sleep disturbances will be included: cranial radiation, pelvic radiation abdominal radiation, surgery, cisplatin, carboplatin, alkylating agents and corticosteroids.

Aims 2-4: Using similar methods as for Aim 1, separate additional multivariable logistic or linear regression models will be employed to examine associations between the frailty phenotype and sleep disturbances, while adjusting for 1) chronic health conditions, 2a) anxiety, 2b) depression and 3) pain. Assessing chronic health conditions in models will constitute a series of models, initially examining grades from each organ system separately, potentially building a full model with all chronic conditions included (organ system level) that are associated with sleep disturbance, and finally, a separate model with the composite burden measure described above from Geenan[18]. Chronic health conditions will be limited to those present up to the time of the frailty assessment (FU5). This will be determined using age at onset for each of the chronic health conditions. Models for aims 2-4 will also be adjusted for age, sex, race/ethnicity.

In all models, in addition to evaluating confounding, we may also explore additive interactions. The focus of these individual models is to determine whether frailty constitutes an independent risk factor for sleep disturbances distinct from each set of additional variables.

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Examples of Tables

Table 1: Characteristics of Study Participants (Survivors)

Study Variable	**No. of Participants**	**%**
Age at diagnosis, Years (M ,SD)		
Age during follow up, Years (M, SD)		
Cancer diagnosis		
CNS Tumors		
Astrocytoma		
Medulloblastoma		
Ependymoma		
Leukemia		
ALL		
AML		
Hodgkin lymphoma		
Non-Hodgkin lymphoma		
Wilm's		
Neuroblastoma		
Soft tissue sarcoma		
Bone tumors		
Chemotherapy variables (Yes)		
Anthracyclines		
Alkylating agents		
Antimetabolites		
Methotrexate		
Cytarabine		
Corticosteroids		
Vina Alkaloids & Heavy Metals		
Platinum based agents		
Surgery		
Any		
Yes		
No		
Amputation		
Yes		
No		
Lung		
Yes		
No		
Radiation variables		
Cranial		
None		
< 20 Gy		
≥ 20 Gy		
Chest		
None		
< 30 Gy		
≥ 30 Gy		

Abdominal		
None		
< 30 Gy		
≥ 30 Gy		
Pelvic		
None		
< 30 Gy		
≥ 30Gy		
Neck		
None		
< 30 Gy		
≥ 30Gy		
Sociodemographic Factors		
Sex		
Male		
Female		
Race/Ethnicity		
White NH		
Black NH		
Hispanic		
Others		
Employment		
Full time		
Part time		
Retired/disabled/unemployed		
Educational attainment		
< High school		
Completed high school		
Training after hs / some college		
College graduate /post graduate		
House Income		
Less than $19,999		
$20,000 – $39,000		
$40,000 – $60,000		
> $60,0000		
Health Related Factors		
Smoking		
Current		
Ever		
Never		
Risky/heavy alcohol use (yes)		
Physical inactivity (yes)		
Medications		
Psychiatric medications		
Stimulants		
Sedatives/hypnotics		
Insulin		
High blood pressure medication		
Triglycerides		

Medications for heart conditions		
Thyroid medication		
Chronic Health Conditions		
Cardiovascular		
Grades 0-1		
Grades 2		
Grades 3-4		
Pulmonary		
Grades 0-2		
Grade 2		
Grades 3-4		
Endocrine		
Grades 0-1		
Grade2		
Grades 3-4		
Musculoskeletal		
Grades 0-1		
Grade2		
Grades 3-4		
Neurologic		
Grades 0-1		
Grade2		
Grades 3-4		
Gastrointestinal		
Grades 0-1		
Grade2		
Grades 3-4		
Emotional Distress		
Depression		
Anxiety		
Bodily Pain		
≥ moderate		

Table 2a. Adjusted Associations between Frailty and Sleep Disturbances[a] (Primary Model, Aim 1)

	Poor Sleep Quality	Sleep duration	Sleep Onset Latency	Sleep Timing	Sleep Efficiency	Snoring[c] Pauses in breathing
	OR (95% CI)	*RR (95% CI)*	*RR (95% CI)*	*OR (95% CI)*	*RR (95% CI)*	*RR (95% CI)*
Frail[b]						
Pre-frail[b]						

[a]some sleep disturbances (outcome) will be dichotomized using pre-determined cut-offs and others will be operationalized continuously
[b]frailty/pre-frail may be collapsed; reference group = non-frail survivors
[c]snoring and pauses in breathing require report from a bed partner, will examine if sample permits

Table 2b. Adjusted Associations between Sleep Disturbances[a] and Frailty (Alternate Model, Aim 1)

	Frail[b]	Prefail[b]
	OR (95% CI)	OR (95% CI)
Poor Sleep Quality		
Short Sleep Duration (≤ 6 hours)		
Long Sleep Duration (≥ 10 hours)		
Sleep Onset Latency (≥ 30 minutes)		
Sleep Efficiency (< 85%)		
Sleep Timing (onset after 1 AM)		
Snoring/pauses in breathing		

[a]all sleep disturbances (predictors) will be dichotomized using pre-determined cut-offs in Daniels et al. 2019
[b]frailty/pre-frail may be collapsed; reference group = non-frail survivors

Table 3. Adjusted Associations between Frailty and Sleep Disturbances[a] (Aim 2, adjustment chronic health conditions[b])

	Poor Sleep Quality	Sleep duration	Sleep Onset Latency	Sleep Timing	Sleep Efficiency	Snoring Pauses in breathing
	OR (95% CI)	*RR (95% CI)*	*RR (95% CI)*	*OR (95% CI)*	*RR (95% CI)*	*RR (95% CI)*
Frail[c]						
Pre-frail[c]						

[a]some sleep disturbances (outcome) will be dichotomized using pre-determined cut-offs and others will be operationalized continuously
[b]each organ system will be assessed separately in models and then one model will utilize the Geenen burden score
[c]frailty/pre-frail may be collapsed; reference group = non-frail survivors

Table 4a. Adjusted Associations between Frailty and Sleep Disturbances[a] (Aim 3, adjustment for depression)

	Poor Sleep Quality	Sleep duration	Sleep Onset Latency	Sleep Timing	Sleep Efficiency	Snoring Pauses in breathing
	OR (95% CI)	*RR (95% CI)*	*RR (95% CI)*	*OR (95% CI)*	*RR (95% CI)*	*RR (95% CI)*
Frail[b]						
Pre-frail[b]						

[a]some sleep disturbances (outcome) will be dichotomized using pre-determined cut-offs and others will be operationalized continuously
[b]frailty/pre-frail may be collapsed; reference group = non-frail survivors

Table 4b. Adjusted Associations between Frailty and Sleep Disturbances[a] (Aim 3, adjustment for anxiety)

	Poor Sleep Quality	Sleep duration	Sleep Onset Latency	Sleep Timing	Sleep Efficiency	Snoring Pauses in breathing
	OR (95% CI)	*RR (95% CI)*	*RR (95% CI)*	*OR (95% CI)*	*RR (95% CI)*	*RR (95% CI)*
Frail[b]						
Pre-frail[b]						

[a]some sleep disturbances (outcome) will be dichotomized using pre-determined cut-offs and others will be operationalized continuously
[b]frailty/pre-frail may be collapsed; reference group = non-frail survivors

Table 5. Adjusted Associations between Frailty and Sleep Disturbances[a] (Aim 3, adjustment for bodily pain)

	Poor Sleep Quality	Sleep duration	Sleep Onset Latency	Sleep Timing	Sleep Efficiency	Snoring Pauses in breathing
	OR (95% CI)	*RR (95% CI)*	*RR (95% CI)*	*OR (95% CI)*	*RR (95% CI)*	*RR (95% CI)*
Frail[b]						
Pre-frail[b]						

[a]some sleep disturbances (outcome) will be dichotomized using pre-determined cut-offs and others will be operationalized continuously
[b]frailty/pre-frail may be collapsed; reference group = non-frail survivors