1. **STUDY TITLE:** Social determinants of sleep health and their impact on quality-of-life and cardiovascular risk in the CCSS cohort.

2. WORKING GROUP AND INVESTIGATORS

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3. BACKGROUND AND RATIONALE

Adult survivors of childhood cancer are at increased risk for neurocognitive impairment[1] and chronic health conditions, including cardiovascular disease (CVD)[2]. Although cancer-directed therapies are common predictors of the development of chronic diseases and reduction of quality of life, other modifiable factors such as health habits and supportive systems in social environments also play an important role in risk[2,3]. Unhealthy behaviors such as poor sleep quality[4], poor quality diets[5], and lack of exercise[6] are associated with increased risk of treatment-related late effects[6]. Furthermore, socio-demographic and

neighborhood factors (e.g. rurality, socio-economic status, and access to exercise and healthy food options) influence the health outcomes of cancer survivors[3] as well as have important effects on sleep health[7,8].

Poor sleep health has serious long-term health consequences. Good sleep health implies adequate duration, satisfactory subjective quality, consistent sleep/wake times, and the absence of disturbances or fragmentation of sleep periods[9]. However, sleep health is a complex multidimensional construct, which integrates aspects of healthy habits and includes metabolic, sex-specific, and socio-environmental factors[10]. Poor sleep health can intensify the risk of severe chronic conditions[11,12] and adversely affect mental health[13,14]. Modifiable cardiovascular risk factors such as hypertension, obesity, diabetes, and dyslipidemia have been independently associated with poor sleep health, especially in cases of increased sleep fragmentation and intermittent sleep hypoxia[15,16]. Therefore, primary sleep disorders disturbing sleep health (e.g. sleep apnea, and insomnia) are predictors of cardiovascular, metabolic, and behavioral health over short- and long-term periods[8] that negatively impact overall quality-of-life[17].

Survivors living in the most disadvantaged US Census blocks have increased mortality and risk of chronic health conditions based on socio-demographic and neighborhood factors[18]. The most disadvantaged neighborhoods with top scores on an area deprivation index (ADI) are associated with a higher risk of heart failure[19], obesity[20], hypertension[21], and diabetes[22,23] in the general population. Likewise, higher ADI ratings are also associated with higher anxiety in patients with advanced cancer[24] and the general

population[25]. Sleep disorders can be affected by diverse social/community influences such as poor built and social environment, location, and socioeconomic conditions[11,17,26]. Equally, specific factors of neighborhood environment such as walkability, neighborhood noise, and air pollution have been associated with sleep quality and different sleep disorders in the general population[27–29]. Furthermore, sleep disorders have different etiologies depending on characteristics such as age, sex, race, and socioeconomic status[10]. In this sense, Billings et al.[29] established a model with the hypothetical associations between neighborhood-level environmental exposures, sleep outcomes, and behavioral characteristics in the general population (Annexed Figure 1). Following Billings' model, the associations between sleep, neighborhood factors, and cardiovascular and emotional outcomes can be specified as shown in Figure 1. In this case, the ADI acts as a proxy measure of ambient pollution, resident segregation, and build and social environment. Instead, the subjective sleep quality outcomes can be summarized by the Pittsburgh Sleep Quality Index (PSQI), with high scores indicating worse sleep levels. This model highlights the dual relationship between sleep outcomes and emotional distress, as well as relationships between sleep outcomes and cardiovascular risk factors[30–33].

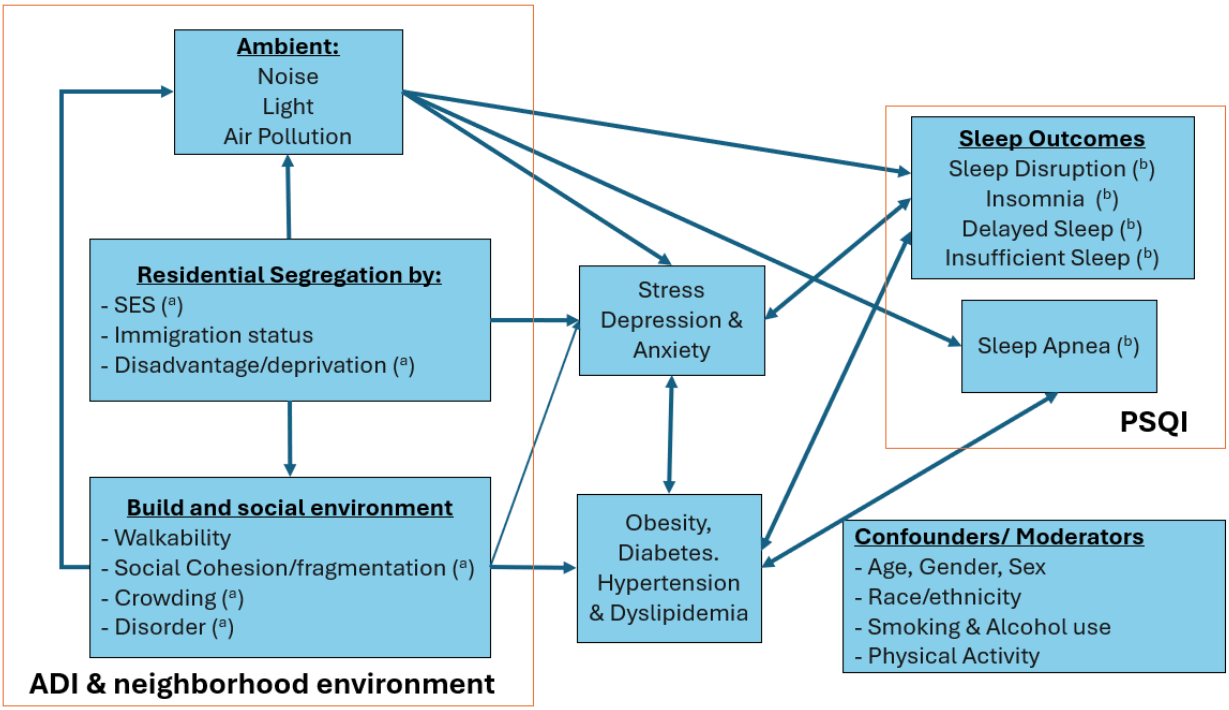


Figure 1. Summarized model indicating hypothetical associations between sleep outcomes (measured by PSQI) and neighborhood-level socioeconomic disadvantages (measured by ADI or neighborhood environment) in the general population. ([a]) indicates variables with components that are directly used for computing the ADI. Besides Immigration status, neighborhood environment can be further measured by walkability, neighborhood noise, air pollution, and greenery. ([b]) indicates variables with components that are directly or indirectly used for computing the PSQI.

Research on the socio-demographic and neighborhood factors affecting sleep health in cancer survivors is important in guiding the development of optimal interventions. A recent cross-sectional study on the CCSS cohort by Daniel et al. indicates that survivors are at higher risk of poor outcomes in different components of sleep health when compared to siblings[34]. Specifically, survivors were found to have 1.30 times the risk of short sleep duration (Total Sleep Time <6 hours), 1.20 times the risk of worse sleep quality (PSQI > 5), and 1.78 times the risk of Delayed Sleep Timing (Sleep onset after 1 am)[34]. Similarly, primary sleep disorders are common among adult survivors of pediatric cancer although

they are not the only cause of poor sleep. Considering cancer diagnosis within the CCSS cohort, sleep apnea is prevalent among Hodgkin Lymphoma survivors, and insomnia is commonly reported by survivors across all cancer continuum[35,36]. Evaluating symptoms of sleep apnea, Daniel et al. also reported that survivors have 1.11 times the risk of Sleep Disordered Breathing Symptoms (Snoring >3 times per week)[34]. Likewise, survivors also presented an increased risk for insomnia symptoms such as increased sleep onset latency (PR = 1.26), and reduced sleep efficiency (PR = 1.19)[34]. Furthermore, following Daniel et al. findings, race /ethnicity factors suggest survivors from the Black population have almost two times the prevalence of delayed bedtime and decreased total sleep time[34]. Instead, the white population has more prevalence of sleep medication use compared to Asian or Pacific Islander, Black, and Hispanic survivor populations[34]. These findings suggest ethnic and socio-demographic differences in independent components of sleep health and previously reported in the general population[37,38].

Despite survivors reporting more sleep concerns than siblings, it is difficult to properly address poor sleep related to cancer treatment because the factors affecting sleep health in survivors are not well understood[4]. Therefore, there is a need to develop translational research that can help understand the relationship between sleep health, socio-demographic factors, and clinical outcomes relevant to cancer survivors.

The goal of this study is to investigate the neighborhood factors that influence the sleep health of a diverse group of adult survivors of childhood cancer. Specifically, the study will analyze how neighborhood-level socioeconomic disadvantages, as measured by the

ADI and measures of neighborhood environment (walkability, neighborhood noise, air pollution) impact the relationships between sleep, quality of life, and cardiovascular risk. Hypothesized models (shown as directed acyclic graphs) of the effect of childhood cancer in the model of sleep and neighborhood-level socioeconomic disadvantages (Figure 2), and their relationships with emotional distress, and QoL[39] (Figure 3), and cardiovascular risk[39] (Figure 4) in this survivor population are shown within the Specific Aims described below.

4. SPECIFIC AIMS

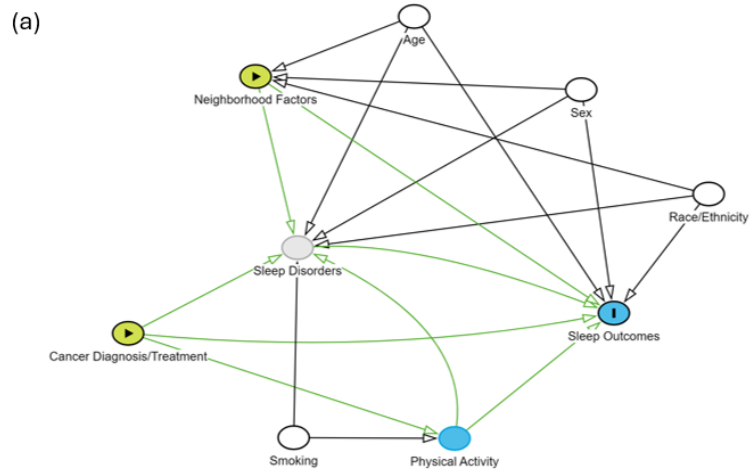
Aim 1: Describe the impact of personal and neighborhood-level socioeconomic disadvantages on self-reported sleep health outcomes in adult survivors of pediatric cancer compared to sibling controls.

Hypothesis 1a: We hypothesize that there is a positive association between neighborhood-level disadvantages (measured by ADI) and sleep health outcomes (measured by PSQI) in which sleep quality would worsen with increased neighborhood deprivation.

Hypothesis 1b: We hypothesize that the impact of neighborhood-level socioeconomic disadvantages on sleep health outcomes will be greater for survivors than for siblings.

Hypothesis 1c: We hypothesize a significant positive association between sleep health

outcomes and individual factors of neighborhood environment (walkability, neighborhood noise, air pollution, and greenery) in survivors.



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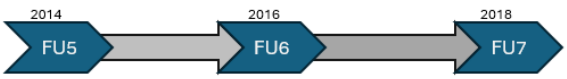


Sleep		PSQI	
CVD risk	Heart and circulatory system, BMI	BMI	Heart and circulatory system, BMI
ED & QoL	BSI-18, SF-36		BSI-18, SF-36
NF	ADI, Environment	ADI, Environment	ADI, Environment

Figure 2. (a) Hypothetical associations to evaluate in Aim 1 between sleep outcomes (measured by PSQI) and neighborhood-level socioeconomic disadvantages (Neighborhood Factors: measured by ADI or by neighborhood environment). (b) Timeline of questionnaires evaluating Sleep outcomes and neighborhood factors (NF) for Aim 1 in the CCSS cohort. Questionnaires to be used in this Aim are highlighted in color.

Aim 2: Examine the interaction effects of self-reported sleep health outcomes and neighborhood-level socioeconomic disadvantages on trajectories of quality of life and emotional distress in survivors.

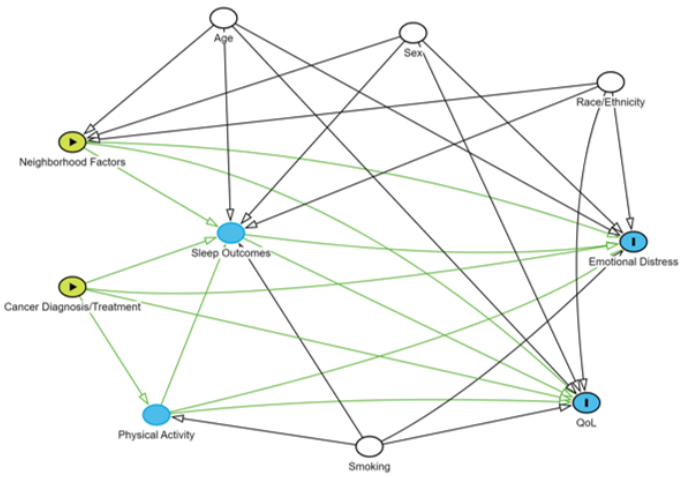
Hypothesis 2a: We hypothesize a significant interaction effect between neighborhood factors (measured by ADI at FU6) and sleep health outcomes (measured by PSQI at FU6)

on trajectories (from FU5 to FU7) of QoL (measured by SF36).

Hypothesis 2b: We hypothesize a significant interaction effect between neighborhood factors (measured by ADI at FU6) and sleep health outcomes (measured by PSQI at FU6) on trajectories of symptoms of depression, anxiety, and somatization (measured by BS18 from FU5 to FU7).

Hypothesis 2c: We hypothesize a significant interaction effect between sleep health outcomes (measured by PSQI at FU6) and individual factors of neighborhood environment (walkability, neighborhood noise, and air pollution at FU6) on trajectories (from FU5 to FU7) of symptoms of depression, anxiety, and somatization (measured by BS18) and on QoL (measured by SF36).

(a)



(b)

Sleep		PSQI	
CVD risk	Heart and circulatory system, BMI	BMI	Heart and circulatory system, BMI
ED & QoL	BSI-18, SF-36		BSI-18, SF-36
NF	ADI, Environment	ADI, Environment	ADI, Environment

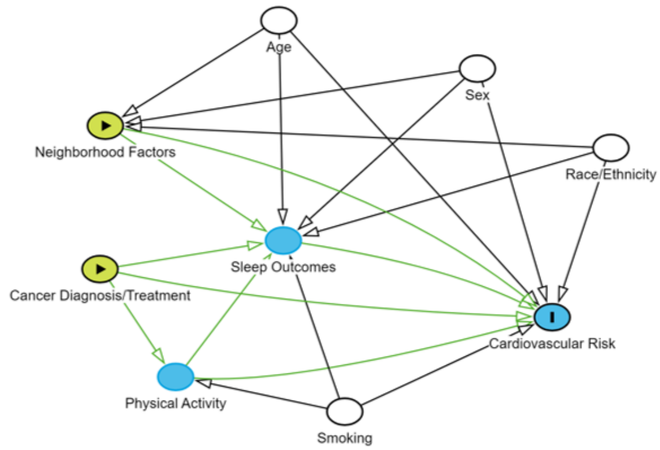
Figure 3. Hypothetical associations to evaluate in Aim 2 between sleep outcomes (measured by PSQI) and neighborhood-level socioeconomic disadvantages (Neighborhood Factors: measured by ADI or by neighborhood environment) on QoL and emotional distress (symptoms of depression, anxiety, and somatization). (b) Timeline of questionnaires evaluating Sleep outcomes, neighborhood factors (NF), and QoL and emotional distress (EM) for Aim 2 in the CCSS cohort. Questionnaires to be used in this Aim are highlighted in color.

Aim 3: In a subset of survivors, evaluate potential cross-sectional associations between self-reported sleep health outcomes, and neighborhood-level socioeconomic disadvantages on the prevalence of self-reported risk factors for cardiovascular disease (obesity, hypertension, diabetes, and dyslipidemia) in survivors.

Hypothesis 3a: Sleep health outcomes (FU6) will be associated with risk factors for prevalent cardiovascular disease, and there will be an interaction between sleep and ADI (FU6) such that survivors with sleep problems and higher ADI will be at greatest risk for cardiovascular risk factors.

Hypothesis 3b: We hypothesize a significant interaction effect between sleep health outcomes (FU6) and individual factors of neighborhood environment (walkability, neighborhood noise, and air pollution at FU6) on prevalent risk factors for cardiovascular disease.

(a)



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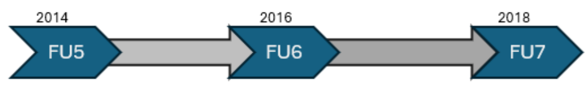

Sleep		PSQI	
CVD risk	Heart and circulatory system, BMI	BMI	Heart and circulatory system, BMI
ED & QoL	BSI-18, SF-36		BSI-18, SF-36
NF	ADI, Environment	ADI, Environment	ADI, Environment

Figure 4. Hypothetical associations (links in color) to evaluate in Aim 3 between sleep outcomes (measured by PSQI) and neighborhood-level socioeconomic disadvantages (measured by ADI or by neighborhood environment) on CVD risk factors. (b) Timeline of questionnaires evaluating Sleep outcomes, neighborhood factors (NF), and CVD risk factors for Aim 3 in the CCSS cohort. Modifiable cardiovascular risk factors will be defined based on modified CTCAE definitions, which are assessed at baseline, FU1, FU2, FU4, FU5, and FU7.

5. ANALYSIS FRAMEWORK

5.1 Overview: We will examine cross-sectional associations between socio-demographic and neighborhood factors and sleep disturbance in the CCSS cohort. Furthermore, we will analyze associations between neighborhood deprivation and sleep problems on the trajectories of the risk of poor quality of life and emotional distress. Finally, we will examine possible cross-sectional associations between sleep outcomes and neighborhood factors in prevalent risk factors for cardiovascular

disease (obesity, hypertension, dyslipidemia, and diabetes).

5.2 Population:

(Aim 1) Survivors and siblings in the CCSS cohort who are ≥ 18 years attained age, who completed sleep (PSQI) at FU6. Criteria for exclusion include diagnosis of genetic disorders that would predispose the survivor to sleep disorders not related to disease or treatment.

(Aim 2) Survivors in the CCSS cohort who are ≥ 18 years attained age (at FU6), who completed sleep assessment (PSQI) at FU6, and who completed quality of life (SF-36), and emotional distress (BSI-18) assessments on the long questionnaires at FU5 and FU7. Criteria for exclusion include diagnosis of genetic disorders that would predispose the survivor to sleep disorders not related to disease or treatment.

(Aim 3) Survivors in the CCSS cohort who are ≥ 18 years attained age (at FU6), who completed sleep assessment (PSQI) at FU6, and who have chronic condition information available for the selected cardiovascular disease risk factors. Criteria for exclusion include diagnosis of genetic disorders that would predispose the survivor to sleep disorders not related to disease or treatment.

5.3 Outcomes of Interest

i. *Self-reported sleep health outcomes* evaluated by the Pittsburg Sleep Quality Index (PSQI) at FU6. The PSQI measures different self-report factors of sleep quality and quantity over the previous month. Overall sleep health outcomes 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 global score > 5 identifies the clinical cut-off for poor sleepers[40]. We will evaluate the individual components of the PSQI as in a previous report by Daniel et al from the CCSS[34]: sleep onset latency, sleep duration, wake after sleep onset, sleep efficiency, and snoring. The PSQI global score only or the individual components will be used in separate statistical models to prevent collinearity.

Sleep Quality. Global PSQI Score.

- Continuous measure
- For evaluating OR, dichotomize into a total score of > 5 indicating clinically significant poor sleep quality[40].

Sleep Components (used to calculate the global PSQI)

Insomnia Symptoms

- Sleep duration (PSQI Item 4)

    - Continuous measure.
        - Categorize into “<6 hours,” “6 – 9 hours,” “> 9 hours”
- Sleep onset latency (PSQI Item 2)
    - Dichotomize into <30 minutes vs. ≥30.
    - 30 minutes is a diagnostic criterion for insomnia.
- Sleep efficiency—percent of the time spent asleep.
    - Dichotomize result into <85% and ≥85%
    - < 85% sleep efficiency is a diagnostic criterion for insomnia.

Sleep Management

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

Delayed Sleep Timing

- Sleep onset after 1 am (PSQI Item 1)
    - Dichotomize into before 1 am AND after 1 am

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.
    - Categorize into “not at all,” “< once per week,” “1-2 times per week”, and “3 or more times.”

ii. *Quality-of-life* evaluated by the SF-36 score. (FU5 and FU7). This 36-item Short Form Health Survey developed by the Rand Corporation quantifies eight different health-related components of quality of life[41]. These components include physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH)[42]. Reduced HRQOL will be defined as a t-score <40 on individual components. Trajectories will be evaluated as consistently good QoL (ie, those who never reported Reduced HRQOL on both questionnaires), consistently bad QoL (ie, those who reported Reduced HRQOL on both questionnaires), or inconsistently QoL.

iii. *Emotional distress* assessed by the Brief Symptom Inventory (BSI-18). (FU5 and FU7). The BSI-18 provides scores for subscales of anxiety, depression, and somatization. Elevated emotional distress will be defined as a t-score >63 on individual subscales. Trajectories will be evaluated as consistently not distressed (ie, those who never reported elevated emotional distress on both questionnaires), consistently bad QoL (ie, those who reported elevated emotional distress on both questionnaires), or inconsistently Distressed.

iv. *Risk factors of cardiovascular disease* based on CCSS' adaptation of the Common Terminology Criteria for Adverse Events. The age of the first occurrence will be used to control the prevalence at years of PSQI assessment (FU6).

Modifiable risk factors of interest based on CTCAE (Table A) plus BMI status as defined by self-reported height and weight.

Table A. Risk factor grading of modifiable cardiovascular risk factors based on modified CTCAE definitions, which are assessed at baseline, FU1, FU2, FU4, FU5, and FU7.

Grade	Hypertension	Dyslipidemia	Diabetes	Obesity
1	No requiring medication	No requiring medication	No requiring medication	Not applicable
2	Requiring medication	Requiring medication	Controlled with pills or tablets	BMI 25 - 29.9 kg/m2
3	Requiring medication but not taking medication currently	Requiring medication but not taking medication currently	Controlled with insulin shots	BMI 30 - 39.9 kg/m2
4	Not applicable	Not applicable	Requiring medication but not taking medication currently	BMI >=40 kg/m2

These Risk factors for cardiovascular disease can also be aggregated into chronic health conditions across the cardiac system considering the frequency and grade of conditions[43]. Therefore, we will also examine grade 3+ conditions at the organ system level (CTCAE grade 0-2 versus grade 3-4). We will use the highest grade within the cardiac system for survivors with multiple chronic health conditions within the same organ system. This severity/burden score will be classified via the ordinal categories described in Table B:

Table B. Cumulative burden of cardiovascular risk factors CTCAE graded.

Burden Category	Definition
Severe	More than one grade 4 event or one grade 4 event and two 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 2 event(s)

5.4 Primary Predictors

i. Socio-demographic and neighborhood factors

a. *Grouped Neighborhood factors* will be assessed by using the Area Deprivation Index (ADI). The ADI is a metric of socioeconomic disadvantage created by the Health Resources & Services Administration (HRSA) and based on census group neighborhood information summarizing 17 measures of education, employment, housing quality, and poverty. This tool uses data from the American Community Survey (ACS) and ADI can be linked to Census Block Groups and 9-digit zip codes[44]. ADI is a standardized index provided in national percentile rankings at the block group level from 1 to 100 where lower scores indicate the least deprived US census blocks and high scores indicate the most disadvantaged area neighborhoods with higher neighborhood and racial disparities[44]. Geolocation will be based on the reported address at the year of the follow-up of interest (FU6 (2016) for sleep questionnaires in *Aim 1*, *Aim 2*, and *Aim 3*).

- Continuous variable (*Aim 1*)
- Categorize into Tertiles[19,45]. (*Aim 2, Aim 3*)

- Least neighborhood disparities [0 to 33],
- Middle neighborhood disparities [34 to 66],
- Most deprived neighborhood disparities [67 to 100]

b. *Individual Neighborhood factors* will be assessed for Air and Noise pollution, Walkability, and Greenery. Geolocation will be based on the reported address at year of the follow-up of interest (FU6 (2016) for sleep questionnaires in *Aim 1* and *Aim 2*, same timepoints for FU5 (2014) or FH7 (2017) with CVD questionnaires in *Aim 3*).

- Air pollution will be evaluated from historic estimated levels of $PM_{2.5}$ and NO2 obtained from the Socioeconomic Data and Applications Center (SEDAC) which is part of Data Center in NASA's Earth Observing System Data and Information System (EOSDIS). Six main categories of air pollution are the SEDAC, but this could be collapsed based on frequency count after evaluating the samples size of included participants. Considering $PM_{2.5}$ (24h) concentrations in $\mu g/m^3$, and NO2 (1h) concentrations in ppm, air pollution will be categorized as:
  - Good: $PM_{2.5}$, 0 – 12.0; NO2, 0 – 0.053.
  - Moderate: $PM_{2.5}$, 12.1 – 35.4; NO2, 0.054 – 0.100
  - Unhealthy for sensitive groups: $PM_{2.5}$, 35.5 – 55.4; NO2, 0.101 – 0.360.
  - Unhealthy: $PM_{2.5}$, 55.5 – 150.4; NO2, 0.361 – 0.649.

    - Very Unhealthy: $PM_{2.5}$, 150.5 – 250.4; NO2, 0.650 – 1.249.
    - Hazardous: $PM_{2.5}$, 250.5 – 500.4; NO2, 1.250 – 2.049.

- Noise pollution will be evaluated considering the National Transportation Noise Exposure Map. Considering exposure in dB recommended by the WHO, sound pollution will be categorized as:
    - Low: 0 – 50dB.
    - Moderate: 50 – 70dB.
    - High: > 70dB.

- Walkability will be evaluated as the geocoded average distance in a 10 minute walk. Categories could be collapsed based on frequency count after evaluating the samples size of included participants.
    - Very Slow: < 0.33 mile.
    - Slow: 0.34 – 0.42 mile.
    - Normal Slow: 0.43 – 0.5 mile.
    - Normal Fast: 0.51 – 0.58 mile.
    - Fast: 0.59 – 0.74 mile.
    - Very Fast: > 0.75 mile.

- and greenery will be considered depending on the National Land Cover Database (NLCD) Legends. Categories could be further collapsed based on frequency count after evaluating the samples size of included

participants:

- Urban developed (NLCD types: 22,23,24)
- Developed open space (NLCD types: 21)
- All forest (NLCD types: 41,42,43)
- Other vegetation (NLCD types: 51,52,71,72,73,74)
- Planned Cultivation (crops) (NLCD types:81,82)

c. Personal factors will be assessed from sociodemographic information reported in the questionnaires:

- Sex
  - Male
  - Female
- Race
  - White
  - Black
  - Others
- Ethnicity
  - Hispanic

ii. Covariates will include cancer-related variables (diagnosis group, age at diagnosis, time since diagnosis), treatment exposures (chemotherapy, radiation, surgery), medications, sociodemographic variables (age, health insurance), health behaviors (smoking, alcohol use, and physical activity). For cancer diagnosis,

categories could be collapsed based on frequency count after evaluating the sample size of included participants.

Cancer-Related Variables

- Age at diagnosis, Years
- Age during follow-up (FU6), Years.
- Cancer diagnosis
    - Leukemia
    - CNS malignancy
    - Hodgkin disease
    - Other
- Chemotherapy variables (Yes/No)
    - Anthracyclines
    - Alkylating agents
    - Corticosteroids
    - Other
- Surgery (any) (Yes/No)
    - Lung
    - Cranial
    - Other
- Radiation variables, maximum target dose (maxTD) to the following body regions
    - Cranial

        - None
        - < 30 Gy
        - ≥ 30 Gy
    - Chest/ Neck
        - None
        - < 30 Gy
        - ≥ 30 Gy
    - Other
        - None
        - < 30 Gy
        - ≥ 30 Gy

Health Related Factors

- Smoking (FU5)
    - Current, ever, never
- Alcohol use (FU5)
    - Heavy/Risky drinking
- Physical inactivity (FU5)
    - Calculate time spent in moderate/vigorous physical activities per week according to CDC guidelines: doing 150 minutes of vigorous-intensity aerobic activity a week.

Medication (FU5, FU6)

- Anxiolytics (Yes/No)
- Antidepressants (Yes/No)

Subsequent malignant neoplasm (FU5, FU6) (Yes/No)

6. ANALYSIS APPROACH

Analytic Approach

We will create frequency distributions to classify relevant outcome variables, predictors, and covariates based on predetermined groupings. We will then compute descriptive statistics, such as means, standard deviations, medians, ranges, frequencies, and percentages for all outcomes, predictors, and covariates. Using separated models for diagnosis and treatment exposures, all models will be adjusted for age at diagnosis, age at the time of the survey, sex, race, ethnicity, smoking, risky/heavy alcohol use, physical inactivity, and cancer diagnosis or treatment exposures. We will examine unadjusted and adjusted associations for all models.

Aim 1: Multivariable multinomial regression models will be used to evaluate the cross-sectional associations between sleep factors and neighborhood disadvantage. The Pittsburgh Sleep Quality Index will be evaluated in separate models from its other sleep components (e.g., sleep duration, sleep onset latency, sleep efficiency, etc.). Associations will be analyzed in both ways, separate multivariable linear regression models using ADI or “neighborhood environment”, and PSQI as continuous measures as well as logistic regression models with categorized versions of sleep measures according to clinical cut-offs (as defined in section 5.1 Outcome of interest). Hierarchical multiple regressions will be computed using stage models to evaluate the associations of neighborhood-level socioeconomic disadvantages on sleep outcomes. Hence, sleep

outcomes will be evaluated adjusted for age, sex, race/ethnicity, BMI (model 1), age at diagnosis, diagnosis/treatment exposure (model 2; includes model 1 covariates), and neighborhood-level socioeconomic disadvantages (ADI or “neighborhood environment”) (model 3 includes models 1+2 covariates). Models including covariates of medication, subsequent neoplasm, physical activity, tobacco use, and alcohol intake conditions will be assessed considering the responses of subjects that responded to questionnaires in FU5. For Hypothesis 1b, sleep measures will be grouped into Tertile of ADI for siblings and survivors and the association between population (survivor vs. siblings) and sleep within each of these subgroups will be evaluated including covariates.

Aim 2: Associations and interactions between neighborhood factors (ADI), and sleep quality (PSQI) on trajectories of QoL (SF-36) and symptoms (BS-18) measures will be evaluated using multivariable multinomial regression models. Each of the individual QoL and symptom factors will be considered as outcomes in separate regression models. Sleep measures might be evaluated as continuous or categorized variables following clinical cut-offs (as defined in section 5.1). We will evaluate independent sleep measures in hierarchical regressions to determine what sleep measure may constitute a risk factor for QoL or symptom change. We will include interactions between sleep quality and ADI in the regression models. Then, QoL/“Emotional Distress” will be evaluated adjusted for age, sex, race/ethnicity, BMI (model 1), age at diagnosis, diagnosis/treatment exposure (model 2; includes model 1 covariates), Sleep and neighborhood-level socioeconomic disadvantages (ADI or “neighborhood environment”)(model 3 includes models 1+2 covariates), and interaction between Sleep Outcomes and neighborhood-level

socioeconomic disadvantages (ADI or “neighborhood environment”)(model 4 includes models 1+2+3 covariates). Models including covariates of medication, subsequent neoplasm, physical activity, tobacco use, and alcohol intake conditions will be assessed considering the responses of subjects that responded to questionnaires in FU5.

Aim 3. We will use multivariable logistic regression models to evaluate associations between sleep outcomes and risk factors of cardiovascular disease. Associations will be evaluated as separate models for each cardiovascular factor (hypertension, diabetes, and obesity). Sleep measures might be evaluated as continuous or categorized variables following cut-offs (as defined in section 5.1). Hierarchical multiple regressions will be computed using stage models to evaluate the associations of neighborhood-level socioeconomic disadvantages and sleep outcomes on individual risk factors of CVD. Individual models for each CVD risk factor will be evaluated adjusted for age, sex, race/ethnicity, BMI (model 1), age at diagnosis, diagnosis/treatment exposure (model 2; includes model 1 covariates), Sleep Outcomes and neighborhood-level socioeconomic disadvantages (ADI or “neighborhood environment”)(model 3 includes models 1+2 covariates), and interaction between Sleep Outcomes and neighborhood-level socioeconomic disadvantages (ADI or “neighborhood environment”)(model 4 includes models 1+2+3 covariates). Models including covariates of medication, subsequent neoplasm, physical activity, tobacco use, and alcohol intake conditions will be assessed considering the responses of subjects that responded to questionnaires in FU5.

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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		
Leukemia		
Hodgkin lymphoma		
Others		
Chemotherapy variables (Yes)		
Anthracyclines		
Alkylating agents		
Corticosteroids		
Others		
Surgery		
Any		
Yes		
No		
Cranial		
Yes		
No		
Lung		
Yes		
No		
Radiation variables		
Cranial		
None		
< 30 Gy		
≥ 30 Gy		
Chest		
None		
< 30 Gy		
≥ 30 Gy		
Neck		
None		
< 30 Gy		
≥ 30 Gy		
Other		
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 /postgraduate		
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		
Emotional Distress		
Depression		
Anxiety		

Cardiovascular Risk Factors		
Hypertension		
Obesity		
Diabetes		
Dyslipidemia		

Table 2. Adjusted Associations between Sleep Outcomes[a] and ADI (Aim 1: Hypothesis 1a and 1b)

	ADI in survivors		ADI in siblings	
	β	*P*	*β*	*P*
Sleep Quality				
Sleep Duration				
Sleep Onset Latency				
Sleep Efficiency				
Sleep Medication				
Sleep Timing				
Snoring/pauses in breathing				

[a] some sleep disturbances (outcome) will be dichotomized using pre-determined cut-offs and others will be operationalized continuously.

Table 3. Adjusted Associations between Neighborhood Environment and Sleep Outcomes[a] (Aim 1: Hypothesis 1c)

	Air pollution	Noise pollution	Walkability	Greenery
Sleep Quality *RR (95% CI)*				
Sleep Duration *RR (95% CI)*				
Sleep Onset Latency *RR (95% CI)*				
Sleep Efficiency *RR (95% CI)*				
Sleep Medication *RR (95% CI)*				
Sleep Timing *RR (95% CI)*				
Snoring/pauses in breathing *RR (95% CI)*				

[a] some sleep disturbances (outcome) will be dichotomized using pre-determined cut-offs and others will be operationalized continuously.

[b] snoring and pauses in breathing require a report from a bed partner, will examine if the sample permits.

Table 4. Adjusted Interactions between Sleep Outcomes[a] and ADI associated with QoL and emotional distress (Aim 2: Hypothesis 2a and 2b)

	QoL trajectories in survivors		Emotional distress trajectories in survivors	
	β	*P*	*β*	*P*
Sleep Quality ADI Sleep Quality * ADI				
Sleep Duration ADI Sleep Duration * ADI				
Sleep Onset Latency ADI Sleep Latency * ADI				
Sleep Efficiency ADI Sleep Efficiency * ADI				
Sleep Timing ADI Sleep Timing * ADI				
Sleep Medication ADI Sleep Timing * ADI				
Snoring/pauses in breathing. ADI Snoring/breathing * ADI				

[a] some sleep disturbances (predictor) will be dichotomized using pre-determined cut-offs and others will be operationalized continuously.

Table 5. Adjusted Interactions between Sleep Outcomes[a] and neighborhood environment associated with QoL and emotional distress (Aim 2: Hypothesis 2c)

	QoL trajectories in survivors		Emotional distress trajectories in survivors	
	β	*P*	*β*	*P*
Sleep Quality Air Pollution Sleep Quality * Air Pollution				
Sleep Quality Neighborhood Noise Sleep Quality * Neighborhood Noise				
Sleep Quality Walkability Sleep Quality * Walkability				
Sleep Quality Greenery Sleep Quality * Greenery				

[a] some sleep disturbances (outcome) will be dichotomized using pre-determined cut-offs and others will be operationalized continuously.

Table 6. Adjusted Interactions between Sleep Outcomes[a] and ADI associated with CVD risk factors (Aim 3: Hypothesis 3a and 3b)

	Hypertension		Diabetes		Obesity	
	β	*P*	*β*	*P*	*β*	*P*
Sleep Quality ADI Sleep Quality * ADI						
Sleep Duration ADI Sleep Duration * ADI						
Sleep Onset Latency ADI Sleep Latency * ADI						
Sleep Efficiency ADI Sleep Efficiency * ADI						
Sleep Timing ADI Sleep Timing * ADI						
Sleep Medication ADI Sleep Timing * ADI						
Snoring/pauses in breathing. ADI Snoring/breathing * ADI						

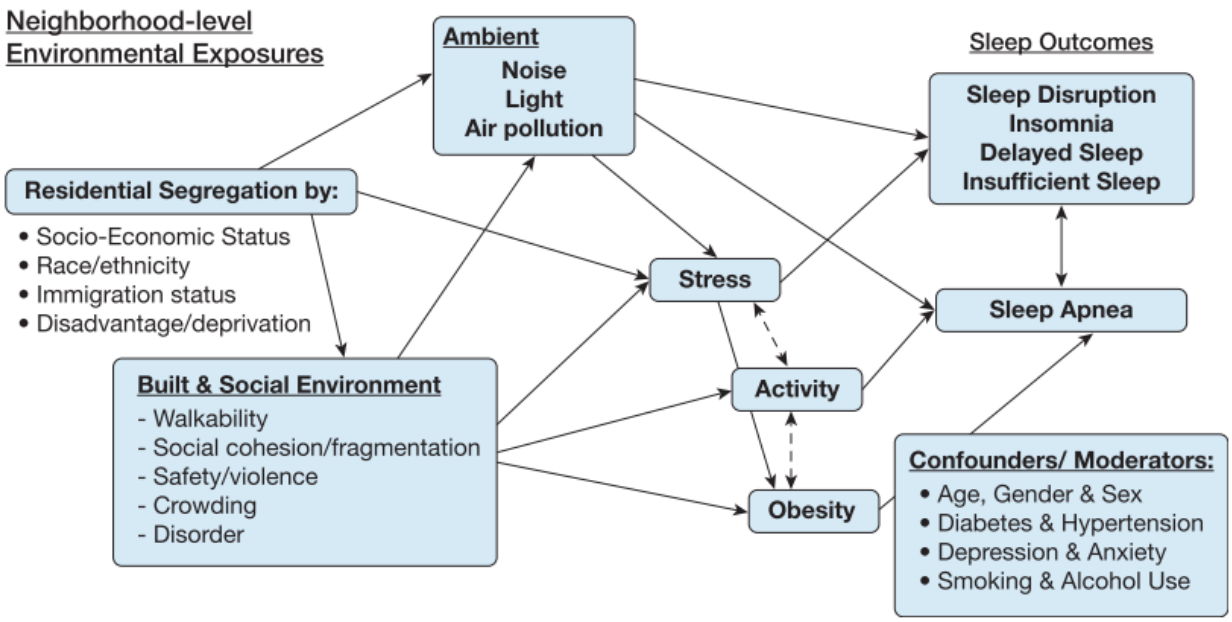
[a] some sleep disturbances (predictor) will be dichotomized using pre-determined cut-offs and others will be operationalized continuously.

Table 7. Adjusted Interactions between Sleep Outcomes[a] and neighborhood environment associated with QoL and emotional distress (Aim 3: Hypothesis 3c)

	Hypertension		Diabetes		Obesity	
	β	*P*	*β*	*P*	*β*	*P*
Sleep Quality Air Pollution Sleep Quality * Air Pollution						
Sleep Quality Neighborhood Noise Sleep Quality * Neighborhood Noise						
Sleep Quality Walkability Sleep Quality * Walkability						
Sleep Quality Greenery Sleep Quality * Greenery						

[a] some sleep disturbances (outcome) will be dichotomized using pre-determined cut-offs and others will be operationalized continuously.

Annexes



Annexed Figure 1. Proposed model for the associations between sleep outcomes and neighborhood-level socioeconomic disadvantages proposed by Billings et al.[29]