CHILDHOOD CANCER SURVIVOR STUDY: ANALYSIS CONCEPT PROPOSAL

Study Title: Neurocognitive Impairment, Health Behaviors, and New Onset Chronic Health Conditions in Adult Survivors of the Childhood Cancer Survivor Study

Working Groups

Primary: Psychology
Secondary: Chronic Disease; Epidemiology & Biostatistics

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Background and Rationale

Survivors of childhood cancer experience disproportionately high rates of chronic health conditions (CHCs), which often emerge earlier in adulthood and progress more rapidly compared to the general population.[1] Neurocognitive impairment is a well-established late effect of childhood cancer and its treatment, affecting up to 60% of survivors [2–7] and occurring most commonly among survivors exposed to central nervous system (CNS)–directed therapies (e.g., cranial radiation, intrathecal methotrexate, and neurosurgical interventions).[8] Survivors exposed to CNS-directed therapies may face a dual burden: elevated treatment-related risk for chronic disease and neurocognitive impairment that can make long-term health management more difficult. Although neurocognitive impairment is not thought to directly cause new CHCs or worsen existing conditions, it may contribute to future CHC burden by interfering with daily self-management, healthcare engagement, and health behaviors.

Neurocognitive domains such as task efficiency, memory, or emotional regulation are critical for daily self-management, and challenges within these domains may lead to difficulty adhering to medical recommendations, organizing appointments, and navigating complex healthcare systems.[9] Indeed, prior research has documented cognitive impairment among adult survivors of childhood cancer was associated with greater nonadherence to healthcare utilization guidelines,[10,11] potentially allowing preventable or emerging health conditions to progress unnoticed. Additionally, neurocognitive deficits have been associated with engagement in risky or health-compromising behaviors, such as tobacco use and risky alcohol use [12,13], which further amplify the risk for long-term morbidity.[14–16] Though, nonadherent healthcare utilization and risky health behaviors have been associated with future CHCs among childhood cancer survivors, pathways between neurocognitive impairment and new onset chronic health conditions via healthcare utilization patterns and risky behaviors have not been fully delineated. Clarifying these mechanisms is critical to determine whether CHCs may, in-part, be explained by healthcare use and risky behaviors linked to neurocognitive impairment, enabling targeted interventions for this vulnerable group. Further, these pathways may vary by treatment exposure as CNS-exposed and non-CNS-exposed survivors may show different patterns of neurocognitive impairment, healthcare engagement, and health behaviors[13,17] Evaluating these differences is important for determining whether the same intervention targets are relevant across survivor subgroups.

Psychological distress, also a prevalent late effect among childhood cancer survivors,[18] increases vulnerability to poor health outcomes.[19] Survivors with neurocognitive difficulties often experience greater perceived distress due to the increased effort required to manage daily tasks, regulate emotions, and meet social and occupational demands.[20] Elevated distress, in turn, is associated with maladaptive coping and increased engagement in risky behaviors and healthcare use.[17,21] Psychological distress may be especially important because it can alter how neurocognitive impairment translates into everyday health management. For

example, difficulties with task efficiency, memory, organization, or emotional regulation may be more likely to contribute to risky health behaviors or disrupted healthcare engagement when survivors are also experiencing elevated distress.[13] Psychological distress may therefore amplify the degree to which neurocognitive impairment contributes to the adoption of risky health behaviors (both behavioral and healthcare use), potentially magnifying future CHC risk.

Although neurocognitive impairment is common among survivors of childhood cancer, the ways in which specific cognitive deficits (such as task efficiency, memory, executive functioning, and emotional regulation) shape long-term health trajectories remain insufficiently understood. Survivors exposed to CNS-directed therapies may be particularly vulnerable because they face both elevated treatment-related risk for CHCs and neurocognitive impairment that may complicate long-term health management. Psychological distress may further intensify behavioral risk and healthcare-engagement difficulties, yet it remains unclear whether distress amplifies the pathway linking neurocognitive impairment to health behaviors, health care use, and future CHCs. Determining whether neurocognitive impairments contribute to future CHC burden, and identifying the behavioral, healthcare-utilization, and stress-related mechanisms that explain these associations, will clarify which survivors are most vulnerable and generate the evidence needed to tailor lifestyle interventions for survivors who experience neurocognitive impairment. The proposed models shown in Figures 1–5 illustrate these hypothesized pathways and guide the aims below.

Specific Aims and Hypotheses

Aim 1: Evaluate domain-specific neurocognitive functioning and overall neurocognitive burden as a mediator between exposure to CNS-directed treatments (i.e., intrathecal methotrexate, cranial radiation therapy, neurosurgery) and subsequent global CHC burden**.**

Hypothesis 1: Survivors exposed to CNS-directed therapy will be more likely to have domain-specific as well as overall neurocognitive burden, and higher subsequent global CHC burden than survivors without CNS-directed therapy. Domain-specific and overall neurocognitive burden will partially mediate the association between CNS treatment exposure and subsequent CHC burden at follow-up after adjusting for relevant sociodemographic factors.

Aim 2: Identify the extent to which healthcare utilization, risky health behaviors, and psychological distress mediate the association between domains of neurocognitive functioning and neurocognitive burden and CHCs global burden score.

Hypothesis 2: Healthcare utilization, risky behaviors, and psychological distress will mediate the association between domains of neurocognitive functioning and burden and CHC global burden score adjusting for relevant treatment exposures and sociodemographic factors.

Aim 3**:** Evaluate whether psychological distress moderates the pathway linking neurocognitive functioning to risky health behaviors.

Hypothesis 3**:** Higher psychological distress will exacerbate the association between domains of neurocognitive functioning and neurocognitive burden with risky health behaviors/healthcare use, resulting in a larger indirect effect between domains of functioning and global neurocognitive burden on global CHC burden through risky behaviors/healthcare use after adjusting for relevant treatment exposures and sociodemographic factors.

Proposed Conceptual Figures for Aims 2 and 3

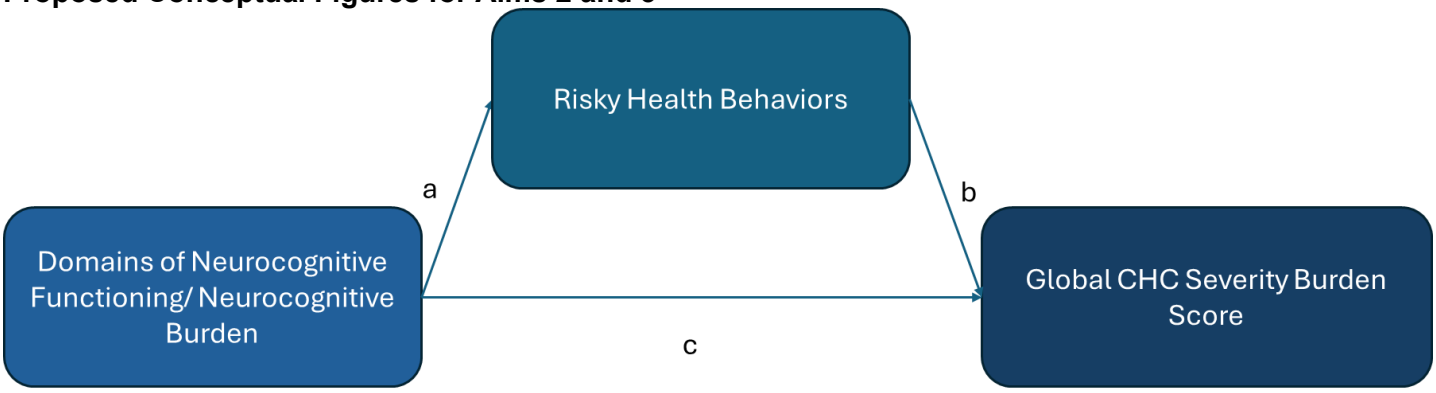


Figure 1. Proposed mediation model with risky health behavior as the mediator. Total effect = c + ab; c = direct effect; ab = indirect effect

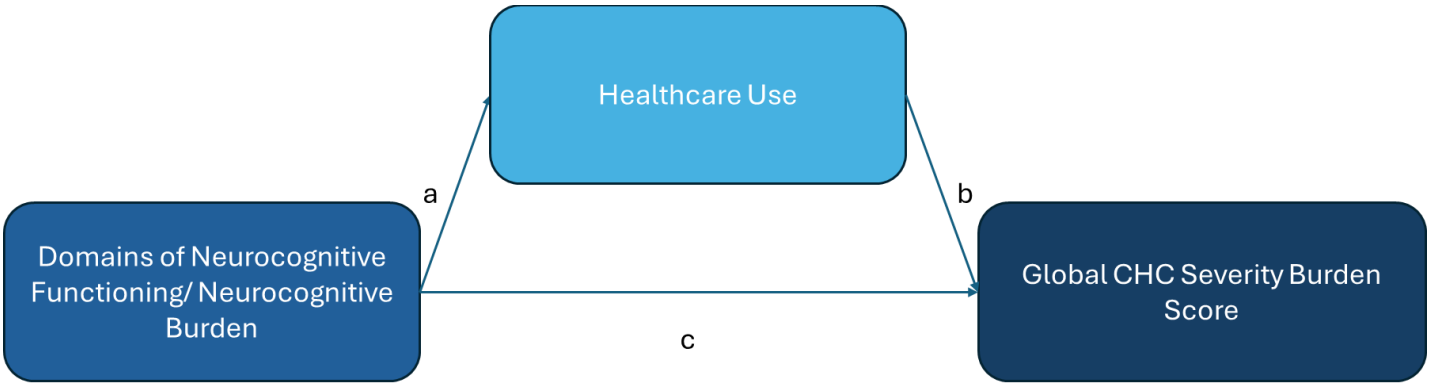


Figure 2. Proposed mediation model with healthcare use as the mediator. Total effect = c + ab; c = direct effect; ab = indirect effect

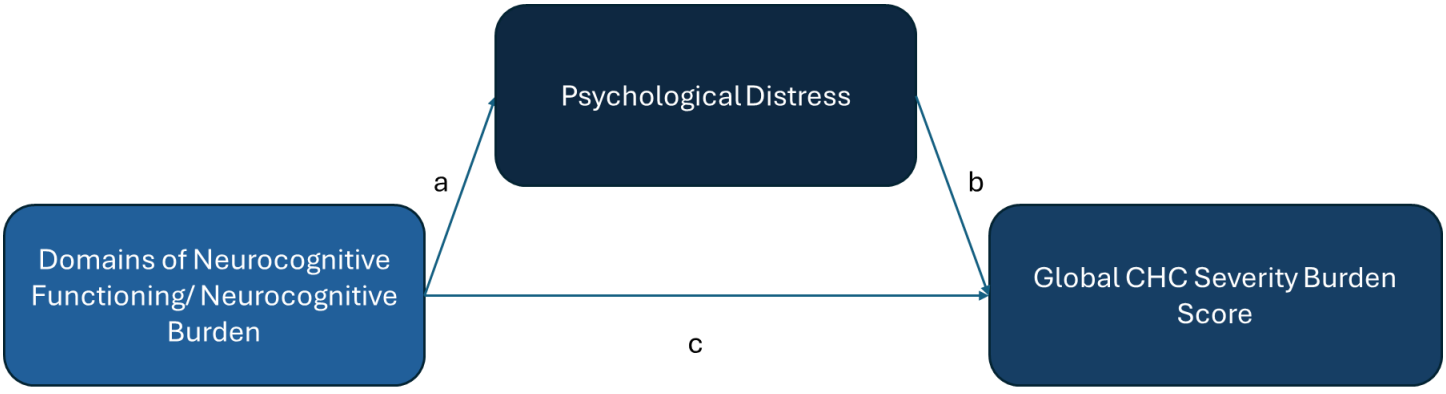


Figure 3. Proposed mediation model with psychological distress as the mediator. Total effect = c + ab; c = direct effect; ab = indirect effect

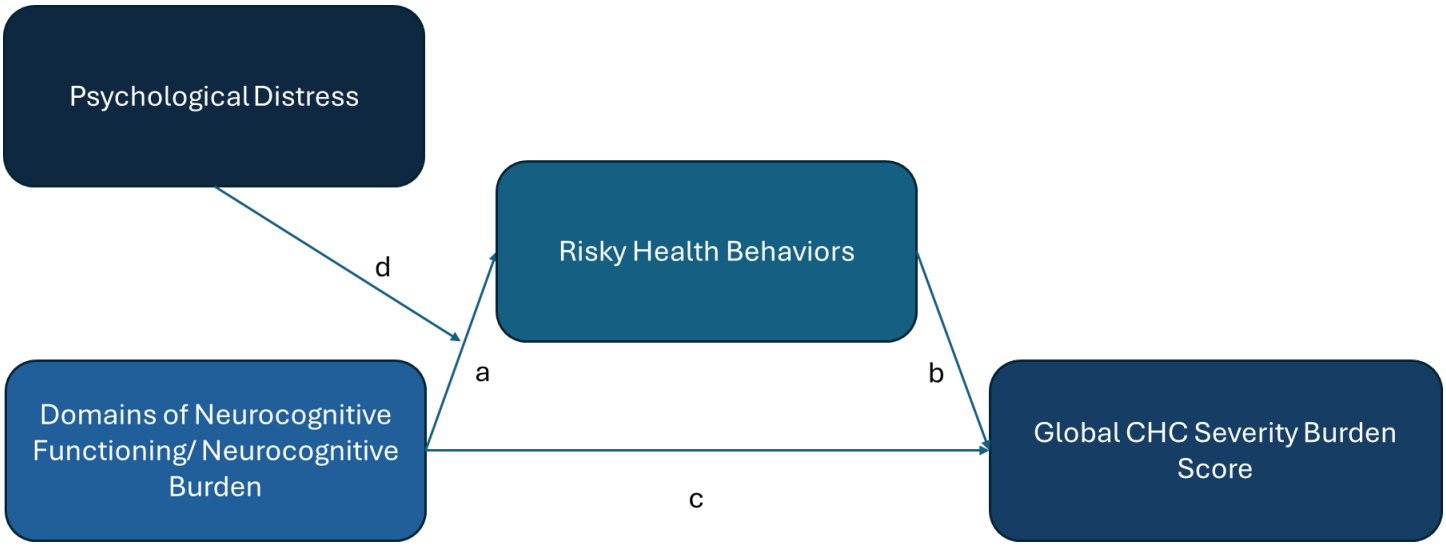


Figure 4. Proposed moderated mediation model with risky health behavior as the mediator. Total effect = c + ab; c = direct effect; ab = indirect effect; d = moderation effect

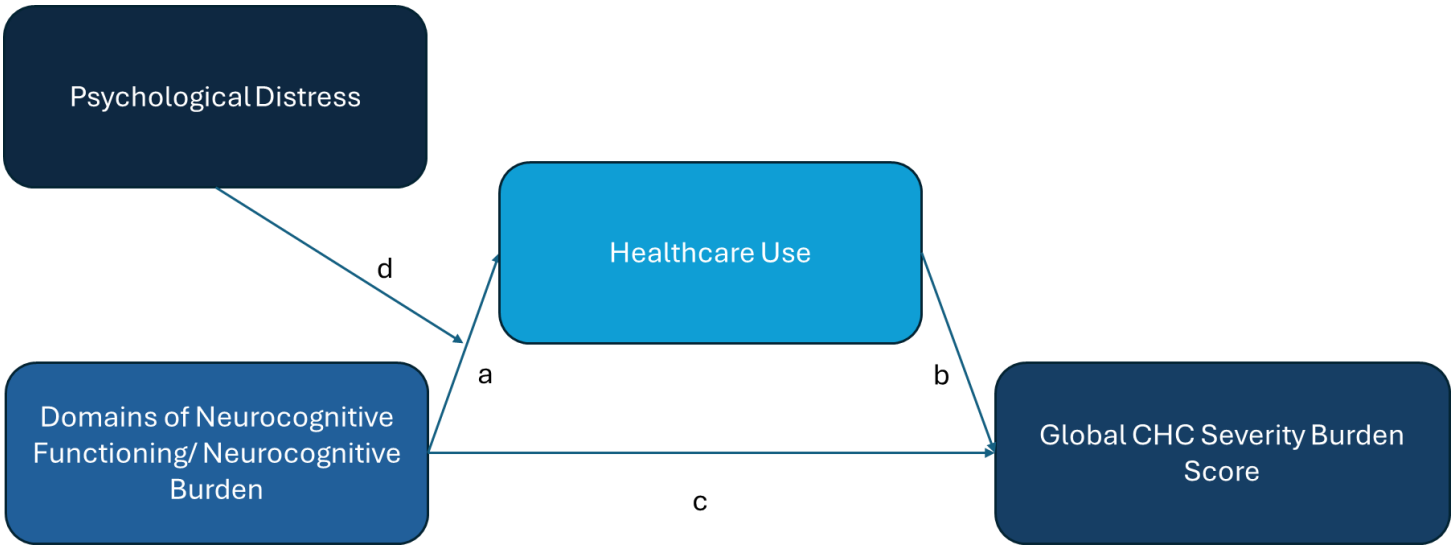


Figure 5. Proposed moderated mediation model wit healthcare use as the mediator. Total effect = c + ab; c = direct effect; ab = indirect effect; d = moderation effect

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Analysis Framework

Overview
This study will use longitudinal data from survivors in the Childhood Cancer Survivor Study (CCSS) cohort.

Study Population
Survivors who are at least 18 years old at the date of survey will be included in this study. CCSS participants who have completed at least 2 qualifying survey evaluations (completed a neurocognitive questionnaire [NCQ] at FU2/5/6 and a follow-up health questionnaire subsequent to NCQ completion) will be considered in longitudinal analysis. Participants will be excluded if they have a history of brain injury unrelated to cancer (e.g., traumatic brain injury), genetic syndromes associated with neurocognitive impairment, or other neurocognitive impairment unrelated to cancer diagnosis.

Primary Outcome
CHC Global Burden: Global CHC burden will be operationalized prospectively as incident or worsening CHC burden occurring after the NCQ assessment. CHCs will be derived from self-reported follow-up (FU) data at FU5, FU6, FU7, or FU8 (whichever follows the NCQ assessment assessment) for the original cohort and FU6, FU7, or FU8 (whichever follows the NCQ assessment) expansion cohort. Because CHCs may be reported at a follow-up survey but have onset years earlier, we will use the CCSS-derived age of onset for each condition and grade to determine whether each condition first occurred, or increased in severity, *after* the participant's NCQ assessment. To count as having progressed, a higher CHC grade must be noted after the NCQ assessment. Incident CHCs will be defined as newly reported conditions with onset after the NCQ assessment. Among participants with CHCs present before or at the NCQ assessment, worsening CHC burden will be defined as an increase in grade/severity after the NCQ assessment. The primary outcome will reflect the highest post-NCQ global burden category based on incident conditions and/or post-NCQ worsening of existing conditions. The severity of each condition was graded using CCSS' adaptation of the Common Terminology Criteria for Adverse Events (CTCAE) system developed by the National Cancer Institute. Conditions were coded as absent (0), mild (grade 1), moderate (grade 2), severe/disabling (grade 3), or life-threatening (grade 4).[22] Consistent with previous studies,[8,23] global burden scores will be categorized as followed: none/low (grade 1 conditions only), medium (≥1 grade 2 and/or 1 grade 3 condition[s]), high (≥2 grade 3, or 1 grade 4 and 1 grade 3 conditions), and very high severity/burden (≥2 grade 4 or ≥2 grade 3 and 1 grade 4 condition[s]).

Predictors:
CNS-directed treatment exposure: CNS-directed treatment exposure will serve as the primary predictor. Exposure will be defined based on treatment history indicating receipt of intrathecal methotrexate, cranial radiation therapy, and/or neurosurgery. Each CNS-directed treatment exposure will be examined as a separate predictor to estimate its association with domain-specific neurocognitive functioning and overall neurocognitive burden, as well as its indirect association with subsequent global CHC burden through neurocognitive outcomes. Survivors without the specified CNS-directed treatment exposure will serve as the reference group for each model.

Neurocognitive Questionnaire (NCQ): Neurocognitive outcomes in CCSS participants will be assessed with the NCQ. The NCQ outcomes are available at follow-up (FU) 2 (J1-25), FU5 (Q1-Q33), and FU6 (G1-G33) for the original cohort and FU5, and FU6 for the expansion cohort. For participants with more than one NCQ assessment, the first available NCQ assessment will serve as the index neurocognitive assessment and analytic baseline. The NCQ was developed to measure neurocognitive outcomes in childhood cancer survivors.[37] Since inception, the NCQ has been optimized and validated against in-person direct neurocognitive assessment.[38] Neurocognitive domains assessed in the NCQ include attention and processing speed (task efficiency), emotional reactivity and frustration tolerance, organization and memory. Both overall T-scores for each domain (Task Efficiency, Emotional Regulation, Working Memory, and Organization) will be used. In addition, an overall neurocognitive burden score will be calculated. Across each domain survivors will be classified as impaired vs non-impaired, with impairment defined as a T-score above the 90th percentile (T ≥

63). Neurocognitive burden will be grouped into the following categories: no impairment, 1 domain impaired, 2 domains impaired, 3 domains impaired, 4 domains impaired.

Mediators:

Healthcare Use: Participants reported healthcare utilization over the past two years. Data from FU2, FU5, or FU6 (**whichever occurred at the same timepoint as the NCQ assessment**). Responses will be categorized using the framework published previously.[24] into no healthcare, general health care (doctor's office), survivor-focused care (oncology cancer center), long-term survivorship care (long-term follow-up clinic), and emergency room care.

Health behaviors: Data from FU2, FU5, or FU6 (**whichever occurred at the same timepoint as the NCQ assessment**) expansion cohort will be used in this study. *Note data for alcohol use was not collected at FU6.

- **Physical Activity:** The frequency and intensity of *physical activity* were captured using a dichotomized variable (i.e., not active vs. active), in which ≥150 minutes of moderate activity or 75 minutes of vigorous activity per week was used as the threshold.[25]
    - Metabolic equivalents; [#days per week vigorous activity x minutes per day vigorous x 6] + [#days per week moderate activity x minutes per day moderate X 3])
    - MET hours/week: 0; 3-6; 9-12; 15-21
- **Alcohol use**
    - Heavy drinking (operationalized as ≥5 drinks/day for women and ≥6 drinks/day for men at least once/month for the past year)
    - Risky drinking (>3 drinks/day or 7 drinks/week for women, and >4 drinks/day or 14 drinks/week for men)
    - No alcohol use (<2 drinks in lifetime)
- **Smoking behavior**
    - Ever smoked ("yes" 100 cigarettes, "no" smoke now)
    - Currently smoke ("yes" 100 cigarettes, "yes" smoke now)
    - Never smoke ("no" 100 cigarettes, "no" smoke now)

Moderators

Psychological Distress: Psychological distress will be assessed using the Brief Symptom Inventory- 18 (BSI-18). The BSI-18 is a self-report questionnaire specifically designed to screen for psychological distress symptoms experienced in the previous seven days.[26,26,27] The Global Severity Index (GSI) provides an overall measure overall psychological distress. T-score ≥ 63 is considered clinically elevated and indicative of emotional distress. Since this is a moderator variable, **we will use participants' GSI from the same timepoint as the NCQ assessment.**

Other relevant variables

- **Demographic variables**
    - age at evaluation
    - age at diagnosis
    - sex
    - race/ethnicity
    - time since treatment
    - education (at time of NCQ)
    - employment status (at time of NCQ)
    - marital status (at time of NCQ)
    - household income (at time of NCQ)
- **Treatment exposures**
    - Radiation (yes/no, or as a continuous variable if warranted)
        - Pelvic
        - Abdominal
        - Cranial
        - Chest

- Chemotherapy (yes/no, or as a continuous variable if warranted)
  - IV methotrexate (cumulative dose)
  - Intrathecal methotrexate (IT MTX)
  - IV cytarabine (cumulative dose)
  - Vincristine
  - Anthracycline in terms of doxorubicin equivalent dose
  - Alkylating agent in terms of cyclophosphamide equivalent dose
  - Corticosteroids (yes/no)
  - Platinum agents
  - Epipodophyllotoxins
- Surgery (where available)
  - Neurosurgery
- Hematopoietic stem cell transplant

Statistical Analysis
Frequency distributions will be generated to categorize relevant outcome variables, predictors and covariates according to reasonable groupings. Descriptive statistics including means, standard deviation, medians, ranges, frequencies, and percentages will be calculated for outcomes of interest, as well as predictors and covariates.

Aim 1: Identify the extent to which domain-specific neurocognitive functioning and neurocognitive burden mediate the association between CNS-directed treatment exposure and post-NCQ incident or worsening CHC global burden score. Structural equation modeling will be used to examine the direct and indirect effects of CNS-directed treatment exposure on CHCs global burden after NCQ assessment via domains of neurocognitive functioning and neurocognitive burden. CNS-directed treatment exposure will serve as the exogenous predictor; neurocognitive domains (task efficiency, memory, organization, emotional regulation) and neurocognitive burden, modeled separately, as the mediators; and global burden CHCs as the distal outcome. CNS-directed treatment exposure will be defined as exposure to intrathecal methotrexate, cranial radiation therapy, and/or neurosurgery. Models will be adjusted for theoretically and empirically relevant sociodemographic factors. If needed to support model parsimony, data-driven variable selection approaches such as LASSO or elastic net may be considered as exploratory or sensitivity procedures rather than primary determinants of covariate inclusion. Variables may include age at assessment, sex, race/ethnicity, age at diagnosis, time since NCQ assessment, and time from diagnosis. Other treatment exposures not included in the CNS-directed treatment exposure definition may be considered as covariates. Model Fit Estimation: The Comparative Fit Index (CFI), chi-square goodness of fit (X^2), and the Root Mean Square Error of Approximation (RMSEA) will evaluate overall model fit. CFI values greater than 0.95 are considered to reflect good model fit, whereas X^2 tests should be non-significant. RMSEA values of 0.08 or less indicate acceptable fit to the data. We will use the bootstrap method, with 200, 500, or 1000 iterations depending on model complexity to determine the significance of the indirect mediation effect, where 95% CI that do not include zero are considered significant at the $p < .05$ level.

Aim 2: Identify the extent to which healthcare utilization, risky health behaviors, and psychological distress mediate the association between domains of neurocognitive functioning and neurocognitive burden and post-NCQ assessment or worsening CHC global burden score. Structural equation modeling will be used to examine the direct and indirect effects of domains of neurocognitive functioning and neurocognitive burden on CHCs global burden after NCQ assessment via risky health behaviors (Figure 1) healthcare use (Figure 2), and psychological stress (Figure 3). Neurocognitive domains (task efficiency, memory, organization, emotional regulation) and neurocognitive burden will serve as exogenous predictors; risky health behaviors, healthcare use, and psychological distress (modeled separately) as the mediators; and global burden CHCs as the distal outcome. Healthcare use and risky health behaviors will be modeled separately, though pending sample size, previously established index scores may be used. Model Fit Estimation: CFI, chi-square goodness of fit (X^2), and RMSEA will evaluate overall model fit. We will use the bootstrap method to determine the significance of the indirect mediation effect, where 95% CI that do not include zero are considered significant at the $p < .05$ level.

Aim 3: Evaluate whether psychological distress moderates the pathway linking neurocognitive functioning and burden to risky health behaviors/healthcare use. To test this aim, we will use moderated mediation modeling within a SEM framework to determine whether psychological stress modifies the association between domains of neurocognitive impairment and risky health behaviors, and whether this results in differential indirect effects on global CHC burden. Specifically, we will test first-stage moderation, in which psychological distress interacts with neurocognitive functioning domains and overall burden to predict risky health behaviors (Figure 4) and healthcare use (Figure 5; modeled separately). This approach allows us to evaluate whether the strength or direction of the neurocognition-risky behavior/healthcare utilization path varies across levels of distress. Consistent with Aim 2, SEM will be used to estimate the direct, indirect, and moderated indirect effects. Neurocognitive domains (task efficiency, memory, organization, emotional regulation) and overall neurocognitive burden will serve as exogenous predictors; risky health behaviors/healthcare use as the mediator; psychological distress as the moderator; and global CHC burden as the distal outcome. Interaction terms (neurocognitive functioning domain/burden × distress) will be computed and included in the structural model to evaluate moderation of the first-stage pathway. Model Fit and Estimation: Model fit will be evaluated using the same indicators as Aim 2. To test the significance of moderated indirect effects, we will use bias-corrected bootstrapping (5,000 resamples) to generate 95% confidence intervals for conditional indirect effects at different levels of stress (e.g., mean, +1 SD, −1 SD). Moderated mediation will be considered present when conditional indirect effects differ significantly across stress levels and confidence intervals do not include zero.

Missingness and Multiplicity Adjustments

Missing data will be summarized for each analysis variable and survey wave, reported as counts and percentages. Missing covariate and mediator data will be addressed using multiple imputation when appropriate, assuming the data are missing-at-random. The imputation model will include the exposure, mediator, outcome, adjustment covariates, survey wave, and other variables associated with missingness. Complete-case analyses will be performed as sensitivity analyses.

To address multiplicity in the models of this study, the Benjamini-Hochberg false discovery rate (FDR) procedure will be applied separately within prespecified families of indirect-effect tests. For instance, in Aim 1, the family will include indirect effects through the four NCQ domains and overall neurocognitive burden. For Aim 2, separate families will include indirect effects through health behaviors and healthcare-utilization measures. Both unadjusted and FDR-adjusted p-values will be reported.

Study Tables
Table 1. Sample Characteristics

Variable	Levels		
Sex	Males N (%)		
	Females N (%)		
Age at assessment	Median (Range)		
	Mean (SD)		
Age at diagnosis	Median (Range		
	Mean (SD)		
Time since treatment	Median (Range		
	Mean (SD)		
Race/Ethnicity	White, non-Hispanic N (%)		
	Black, non-Hispanic N (%)		

	Hispanic N (%)	
	Other N (%)	
	Unknown N (%)	
Education	<High School N (%)	
	High school N (%)	
	Some College N (%)	
	College/Post Grad N (%)	
Marital status	Single N (%)	
	Married/Common law N (%)	
	Divorced/Widowed N (%)	
Employment status	Employed N (%)	
	Unemployed N (%)	
	Unable to work N (%)	
	Student N (%)	
	Homemaker N (%)	
Household income	<$20,000 N (%)	
	$20,000-39,999 N (%)	
	$40,000-59,999 N (%)	
	≥$60,000 N (%)	
Global Chronic Health Condition Severity Burden Score	None/Low: N (%)	
	Medium: N (%)	
	High: N (%)	
	Very High: N (%)	
Neurocognitive Functioning	Task Efficiency: M (SD)	
	Task Efficiency: Impaired %	
	Emotion Regulation: M (SD)	
	Emotion Regulation: Impaired %	
	Organization: M (SD)	
	Organization: Impaired %	
	Working Memory: N (%)	
	Working Memory: Impaired %	
Neurocognitive Burden	0 Impaired Domains: N (%)	
	1 Impaired Domain: N (%)	
	2 Impaired Domains: N (%)	
	3 Impaired Domains: N (%)	
	4 Impaired Domains: N (%)	
Currently smoking	Yes N (%)	
≤9 MET hours/week	Yes N (%)	
Risky/Heavy alcohol use	Yes N (%)	
Healthcare use	No Healthcare: N (%)	
	General Healthcare: N (%)	
	Oncology Care: N (%)	
	Long-term Survivorship Care: N (%)	
	Emergent Care: N (%)	
Clinically Elevated Psychological Distress	Yes: N (%)	

Table 2 Cancer and treatment characteristics

Variable	Levels	N (%)
Diagnosis	Leukemia	
	CNS Tumor	
	Hodgkin's Lymphoma	
	Non-Hodgkin's Lymphoma	
	Neuroblastoma	
	Wilms tumor	
	Soft tissue sarcoma	
	Bone Tumor	
Radiation Treatment	Yes	
	No	
Head/neck	Yes	
	No	
Chest	Yes	
	No	
Abdomen	Yes	
	No	
Pelvis	Yes	
	No	
Chemotherapy	Yes	
	No	
Alkylating agents	Yes	
	No	
Anthracycline	Yes	
	No	
Platinum agents	Yes	
	No	
Vinca alkaloids	Yes	
	No	
Retinoic acid	Yes	
	No	
High-Dose IV Methotrexate	Yes	
	No	
Standard dose IV methotrexate	Yes	
	No	
Intrathecal methotrexate	Yes	
	No	
Corticosteroids	Yes	
	No	
Neurosurgery	Yes	
	No	

Table 3. Proposed table for Aim 1: Identify the extent to which domain-specific neurocognitive functioning and neurocognitive burden mediate the association between CNS-directed treatment exposure and CHCs global burden score

	Mediator	Effect of Domain of CNS-Directed Tx Exposure on Neurocognitive Domain (a)	Effect of Mediator on Number of Global Chronic Health Conditions (b)	Indirect Effect (c+ab)	95% Bootstrapped Confidence Interval	
					Lower	Upper
Intrathecal Methotrexate						
Domains of Neurocognitive Functioning	Task Efficiency					
	Emotion Regulation					
	Working Memory					
	Organization					
	Global Neurocognitive Burden					
Cranial Radiation						
Domains of Neurocognitive Functioning	Task Efficiency					
	Emotion Regulation					
	Working Memory					
	Organization					
	Global Neurocognitive Burden					
Neurosurgery						
Domains of Neurocognitive Functioning	Task Efficiency					
	Emotion Regulation					
	Working Memory					
	Organization					
	Global Neurocognitive Burden					

Each neurocognitive domain represents a unique model. Models will be adjusted for treatment exposures and sociodemographic identified by elastic net.

Table 4 Proposed table for Aim 2: Identify the extent to which healthcare utilization and risky health behaviors mediate the association between neurocognitive functioning/neurocognitive burden and global CHC burden score.

	Mediator	Effect of Domain of Impairment on Mediator (a)	Effect of Mediator on Number of Global Chronic Health Conditions (b)	Indirect Effect (c+ab)	95% Bootstrapped Confidence Interval	
					Lower	Upper
Task Efficiency						
Health behaviors	Smoking status (current/ never or former)					
	≤9 MET Hours (yes/no)					
	Heavy/Risky Alcohol Use (yes/no)					
Healthcare use	No Healthcare (yes/no)					
	General Healthcare (yes/no)					
	Long-term Survivorship Care (yes/no)					
	Emergent Care (yes/no)					
Psychological Distress	GSI clinically elevated (yes/no)					
Emotion Regulation						
Health behaviors	Smoking status (current/ never or former)					
	≤9 MET Hours (yes/no)					
	Heavy/Risky Alcohol Use (yes/no)					
Healthcare use	No Healthcare (yes/no)					
	General Healthcare (yes/no)					
	Long-term Survivorship Care (yes/no)					
	Emergent Care (yes/no)					
Psychological Distress	GSI clinically elevated (yes/no)					
Working Memory						
Health behaviors	Smoking status (current/ never or former)					
	≤9 MET Hours (yes/no)					
	Heavy/Risky Alcohol Use (yes/no)					
Healthcare use	No Healthcare (yes/no)					
	General Healthcare (yes/no)					
	Long-term Survivorship Care (yes/no)					
	Emergent Care (yes/no)					
Psychological Distress	GSI clinically elevated (yes/no)					
Organization						
Health behaviors	Smoking status (current/ never or former)					
	≤9 MET Hours (yes/no)					
	Heavy/Risky Alcohol Use (yes/no)					
Healthcare use	No Healthcare (yes/no)					
	General Healthcare (yes/no)					
	Long-term Survivorship Care (yes/no)					
	Emergent Care (yes/no)					
Psychological Distress	GSI clinically elevated (yes/no)					
Global Neuropsychological Functioning Score						
Health behaviors	Smoking status (current/ never or former)					
	≤9 MET Hours (yes/no)					
	Heavy/Risky Alcohol Use (yes/no)					

Healthcare use	No Healthcare (yes/no)	
	General Healthcare (yes/no)	
	Long-term Survivorship Care (yes/no)	
	Emergent Care (yes/no)	
Psychological Distress	GSI clinically elevated (yes/no)	

Each health behavior, healthcare use domain, and Psychological distress represents a unique model. Models will be adjusted for treatment exposures and sociodemographic identified by elastic net.

Table 5. Proposed table for Aim 3: Identify the extent to which healthcare utilization and risky health behaviors mediate the association between neurocognitive functioning and burden and global CHC Burden.

	Mediator	Effect of Domain of Impairment on Mediator Moderated by Psychological Distress (a*d)	Effect of Mediator on Number of Global Chronic Health Conditions (b)	Indirect Effect (c+[a*d]b)	95% Bootstrapped Confidence Interval	
					Lower	**Upper**
Task Efficiency*Clinically Elevated Distress						
Health behaviors	Smoking status (current/ never or former)					
	≤9 MET Hours (yes/no)					
	Heavy/Risky Alcohol Use (yes/no)					
Healthcare use	No Healthcare (yes/no)					
	General Healthcare (yes/no)					
	Long-term Survivorship Care (yes/no)					
	Emergent Care (yes/no)					
Task Efficiency* Non-Clinically Elevated Distress						
Health behaviors	Smoking status (current/ never or former)					
	≤9 MET Hours (yes/no)					
	Heavy/Risky Alcohol Use (yes/no)					
Healthcare use	No Healthcare (yes/no)					
	General Healthcare (yes/no)					
	Long-term Survivorship Care (yes/no)					
	Emergent Care (yes/no)					
Emotion Regulation*Clinically Elevated Distress						
Health behaviors	Smoking status (current/ never or former)					
	≤9 MET Hours (yes/no)					
	Heavy/Risky Alcohol Use (yes/no)					
Healthcare use	No Healthcare (yes/no)					
	General Healthcare (yes/no)					
	Long-term Survivorship Care (yes/no)					
	Emergent Care (yes/no)					
Emotion Regulation*Non-Clinically Elevated Distress						
Health behaviors	Smoking status (current/ never or former)					
	≤9 MET Hours (yes/no)					
	Heavy/Risky Alcohol Use (yes/no)					
Healthcare use	No Healthcare (yes/no)					
	General Healthcare (yes/no)					
	Long-term Survivorship Care (yes/no)					
	Emergent Care (yes/no)					

Each health behavior and healthcare use domain represents a unique model. Models will be adjusted for treatment exposures and sociodemographic identified by elastic net.

Table 5 (continued). Proposed table for Aim 3: Identify the extent to which healthcare utilization and risky health behaviors mediate the association between neurocognitive functioning and burden and global CHC Burden.

	Mediator	Effect of Domain of Impairment on Mediator Moderated by Psychological Distress (a*d)	Effect of Mediator on Number of Global Chronic Health Conditions (b)	Indirect Effect (c+[a*d]b)	95% Bootstrapped Confidence Interval	
					Lower	**Upper**
Working Memory*Clinically Elevated Distress						
Health behaviors	Smoking status (current/ never or former)					
	≤9 MET Hours (yes/no)					
	Heavy/Risky Alcohol Use (yes/no)					
Healthcare use	No Healthcare (yes/no)					
	General Healthcare (yes/no)					
	Long-term Survivorship Care (yes/no)					
	Emergent Care (yes/no)					
Working Memory* Non-Clinically Elevated Distress						
Health behaviors	Smoking status (current/ never or former)					
	≤9 MET Hours (yes/no)					
	Heavy/Risky Alcohol Use (yes/no)					
Healthcare use	No Healthcare (yes/no)					
	General Healthcare (yes/no)					
	Long-term Survivorship Care (yes/no)					
	Emergent Care (yes/no)					
Organization*Clinically Elevated Distress						
Health behaviors	Smoking status (current/ never or former)					
	≤9 MET Hours (yes/no)					
	Heavy/Risky Alcohol Use (yes/no)					
Healthcare use	No Healthcare (yes/no)					
	General Healthcare (yes/no)					
	Long-term Survivorship Care (yes/no)					
	Emergent Care (yes/no)					
Organization*Non-Clinically Elevated Distress						
Health behaviors	Smoking status (current/ never or former)					
	≤9 MET Hours (yes/no)					
	Heavy/Risky Alcohol Use (yes/no)					
Healthcare use	No Healthcare (yes/no)					
	General Healthcare (yes/no)					
	Long-term Survivorship Care (yes/no)					
	Emergent Care (yes/no)					
Neurocognitive Burden*Clinically Elevated Distress						
Health behaviors	Smoking status (current/ never or former)					
	≤9 MET Hours (yes/no)					
	Heavy/Risky Alcohol Use (yes/no)					
Healthcare use	No Healthcare (yes/no)					
	General Healthcare (yes/no)					
	Long-term Survivorship Care (yes/no)					
	Emergent Care (yes/no)					

Each health behavior and healthcare use domain represents a unique model. Models will be adjusted for treatment exposures and sociodemographic identified by elastic net.

Table 5 (continued). Proposed table for Aim 3: Identify the extent to which healthcare utilization and risky health behaviors mediate the association between neurocognitive functioning and burden and global CHC Burden.

Neurocognitive Burden *Non-Clinically Elevated Distress		
Health behaviors	Smoking status (current/ never or former)	
	≤9 MET Hours (yes/no)	
	Heavy/Risky Alcohol Use (yes/no)	
Healthcare use	No Healthcare (yes/no)	
	General Healthcare (yes/no)	
	Long-term Survivorship Care (yes/no)	
	Emergent Care (yes/no)	

Each health behavior and healthcare use domain represents a unique model. Models will be adjusted for treatment exposures and sociodemographic identified by elastic net.

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