1. STUDY TITLE: Social Isolation and Changes in Cognitive Function in Childhood Cancer Survivors

2. WORKING GROUPS AND INVESTIGATORS

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

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3. BACKGROUND AND RATIONALE

Progress in cancer treatments have made survival into adulthood a reality for most children with a cancer diagnosis today with approximately 500,000 survivors of childhood cancer living in the United States.[1] Survivors often experience behavioral and cognitive deficits as a result of neurotoxic cancer therapy which can alter brain development across the lifespan.[2] The cascading impact of disrupted core cognitive skills of processing speed, attention span, and working memory have been theoretically proposed[3,4] and empirically demonstrated to impact executive functions, academic skills, intellectual outcomes, and adaptive functions.[5,6] Studies have shown that almost half of cancer patients reported social and environmental challenges, including social isolation, and are at risk of neurological and cognitive impairment, faster cognitive decline, and reduced health-related quality of life due to psychological, emotional, and school problems.[7-11] Social isolation is characterized by limited social network or connections with family, friends, and colleagues,[12] and may arise from geographical and physical separation.[13] Social isolation and loneliness was declared as a new epidemic in 2023 and has been associated with an approximately 30% higher risk of early mortality in the general population.[14] Social isolation may be more common for survivors of childhood cancer as prolonged treatment is associated with missed opportunities for engaging in typical activities in youth that facilitate the development of behavioral, social, and cognitive skills.[2]

Survivors have described their cancer journey as isolating due to several reasons including physical symptoms such as fatigue or impaired fitness, undermotivation, and immunocompromised status which can impose restrictions on participation in social activities like sports or hobbies.[7,15-18]

Survivors have expressed that they feel reluctant to "bother" [14] or are concerned about making their support groups feel "uncomfortable or overwhelmed", including members of their family, friends, and even their healthcare team.[18,19] Survivors also report a lack of perceived or actual support from family and friends while simultaneously coping with the challenges of both their professional and personal lives.[18,20-21] Furthermore, while undergoing treatment survivors spend lengthy periods socially isolated, which can make it difficult to re-engage with others post-treatment.[16,22] Studies have shown that survivors have lower rates of marriage or cohabitation and are twice as likely to live dependently compared to their siblings.[23-25]

Risks associated with social isolation are particularly concerning during young adulthood as this period is associated with increased stress due the development of autonomy, vocational and education growth, and developing familial, platonic, and romantic relationships.[19,26] Cancer diagnosis and treatment can detract from some or all these areas, and adolescents and young adults may feel separated and/or different from their peers, thereby contributing to feelings of isolation.[19,20] The negative effects of social isolation are further compounded by subsequent stress and depression which are key biological processes associated with poorer survival.[10] In the general population of adults, social isolation is associated with future cognitive decline, which is particularly salient for survivors of childhood cancer as they are already vulnerable to cognitive difficulties and report experiencing social challenges.[27] Additionally, compared to the general population, survivors have a higher prevalence of chronic health conditions, which may also impact cognitive function and exacerbate social isolation.[28] Several studies have also identified that due to specific deficits in social cognitive skills survivors of brain tumors may be at greatest risk of social isolation compared to other cancer groups.[16,29]

Disparities in health outcomes among survivors have been linked to various neighborhood-level Social Determinants of Health (SDoH), including the Area Deprivation Index (ADI),[30-32] Social Vulnerability Index (SVI)[33-34], persistent poverty,[35,36] and mortgage lending or redlining bias.[37,38] These structural factors are often intertwined with additional risks—for example, persistent poverty counties often overlap with rural areas lacking adequate healthcare,[39] while redlining has historically led to the residential segregation of Black and other marginalized communities in the U.S.,[40] significantly impacting their access to quality care.[41,42] A deeper understanding of how clinical, biological, and psychosocial factors interact with social isolation and survivors' cognitive function and changes in perceived cognitive function is essential to developing targeted interventions.

In the present study, we aim to assess the relation between social isolation and cognitive function and perceived changes in cognitive function in childhood cancer survivors, and to examine the contributions of chronic health conditions and emotional health on this association. This analysis will use recent data on social isolation (FU7) and neurocognitive functioning (NCQ at FU5 and FU7), perceived changes in cognitive function (PROMIS FU7) collected on all survivors enrolled in the CCSS (Original and Expansion cohorts). Results will inform interventions targeting social isolation that may increase the provision of social supports and in turn promote cognitive outcomes.

4. SPECIFIC AIMS AND RESEARCH HYPOTHESES

4.1 Aim 1: Estimate the prevalence and identify predictors of social isolation in adult survivors of childhood cancer (FU7).

4.1.1 *Hypothesis 1a*: Adult survivors of childhood cancer will be more likely to report social isolation compared to sibling controls and normative expectations.

4.1.2 *Hypothesis 1b*: Survivors treated with CNS-directed therapies, particularly survivors of brain tumors, will have the highest prevalence of social isolation compared to other diagnostic/treatment exposure groups.

4.1.3 *Hypothesis 1c*: Survivors who reside in neighborhoods characterized by higher structural inequity and deprivation will be more likely to report social isolation compared to normative expectations.

4.2 Aim 2: Examine associations between social isolation (FU7), cognitive function (difference between FU5 and FU7), and between social isolation and perceived changes in cognitive function (FU7) in adult survivors of childhood cancer.

4.2.1 *Hypothesis 2a:* Greater symptoms of social isolation will be associated with cognitive impairment and negative perception of change in cognitive function.

4.2.2 *Hypothesis 2b*: Survivors who received CNS-directed therapies (i.e., cranial irradiation, intrathecal chemotherapy), particularly survivors of brain tumors, will be more vulnerable to the effect of social isolation on cognitive function and perceived changes in cognitive function compared to other diagnostic/treatment exposure groups.

4.2.3 *Hypothesis 2c*: Survivors who reside in neighborhoods characterized by higher structural inequity and deprivation will be more vulnerable to the effect of social isolation on cognitive function and perceived changes in cognitive function compared to normative expectations.

4.3 Aim 3: Examine whether social isolation (FU7) mediates the association between chronic health conditions and emotional health symptoms and perceived changes in cognitive function in adult survivors of childhood cancer (FU7).

4.3.1 *Hypothesis 3*: Social isolation will mediate the association between chronic health conditions and poorer emotional health and perceived changes in cognitive function. Specifically, survivors with greater symptoms of social isolation will be more likely to experience greater negative perceived changes in cognitive function in the context of chronic health conditions and poorer emotional health.

4.3.2 *Hypothesis 3b*: Social isolation will mediate the association between chronic health conditions and poorer emotional health and perceived changes in cognitive function. Specifically, survivors who received CNS-directed therapies (i.e., cranial irradiation, intrathecal chemotherapy), particularly survivors of brain tumors, will be more likely to experience greater negative perceived changes in cognitive function compared to other diagnostic/treatment exposure groups.

4.3.3 *Hypothesis 3c*: Social isolation will mediate the association between chronic health conditions and poorer emotional health and perceived changes in cognitive function. Specifically, survivors who reside in neighborhoods characterized by higher structural inequity and deprivation will experience greater symptoms of social isolation and will be more likely to experience greater negative perceived changes in cognitive function

in the context of chronic health conditions and poorer emotional health compared to normative expectations.

5. ANALYSIS FRAMEWORK

5.1 Population: This study will include all eligible survivors in CCSS. Inclusion criteria for the proposed study are follows: at least five years from diagnosis, ≥18 years of age, and completed FU7, including the PROMIS Social Isolation and Cognitive Function measures. With regards to social isolation, we will examine the frequency of self-reported social isolation versus proxy-reported self-isolation and accordingly use either the self-reported social isolation data only (majority of the data is self-reported) or both self- and proxy-reported social isolation if there are no statistically significant differences in the data between both groups of responders for all three aims. Exclusion criteria include genetic or neurodevelopmental disorders associated with neurocognitive impairment related to cancer diagnosis (i.e., Turner syndrome, Klinfelter syndrome).

5.2.1 Aim 1:

Outcome: Social Isolation will be assessed using the *PROMIS Social Isolation instrument*[43] that was administered at FU7 [L20], a four-item scale that assesses perceptions of being avoided, excluded, detached, disconnected from, or unknown by, others. The item bank does not use a time frame (e.g. over the past seven days) when assessing social isolation. Age-standardized T-scores will be used, with higher scores indicating more problems. High social isolation will be defined as a T score>60, which means the survivor's score is at least one standard deviation above the average.

Exposures:

Clinical variables

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

Treatment exposures

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

- Radiation, maximum target dose (maxTD; dose categories, or as a continuous variable if warranted)
  - Cranial (none, <20Gy, ≥20Gy to <30Gy, ≥30Gy)
  - Non-cranial (yes/no)
- Chemotherapy (yes/no, or as a continuous variable if warranted)
  - IV methotrexate
  - Intrathecal methotrexate
  - Cytarabine
  - Vincristine

- Anthracycline equivalent dose
- Alkylating agent equivalent dose
- Corticosteroids
- Platinum agents

- Shunt (yes/no)

Neighborhood-level geocoded SDoH

- Area Deprivation Index[30-31] (ADI) will be evaluated as comparison metric of neighborhood-level socioeconomic adversity, as described by Ehrhardt et al.[32]
- Social Vulnerability Index (SVI), [33-34] a measure of neighborhood-level deprivation, provides data on four SDoH themes including socioeconomic status, household characteristics, racial and ethnic minority status, and housing type and transportation.
- Zip code approximation of Rural-Urban Community Area (RUCA) codes which classifies ZIP code areas using measures of population density, urbanization, and daily commuting.
- Persistent poverty, measure of neighborhood-level structural inequity, as defined by the US Department of Agriculture (USDA) Economic Research Service[44] (ERS) as counties with ≥20% of residents' income falls below the federal poverty level) by the decennial censuses in 1980, 1990, and 2000, as well as in the 2007-2011 American Community Survey. This measure will be categorized as a binary variable: persistent poverty or non-persistent poverty.
- Modern redlining index linked by census tract[37,38] is based on data from the Home Mortgage Disclosure Act data (2007-2013). This index measures the odds ratio of mortgage application denial based on property location and is categorized by levels of mortgage lending bias which include 0-0.5 [least], 0.5-1 [low], 1-2 [moderate], ≥2 [high].
- Medically Underserved Area (MUA), identified by the Health Resources and Services Administration (HRSA),[45] will be used to indicate county-level areas with limited access to primary care services. We will use the Index of Medical Underservice (IMU) score to determine if an area qualifies as MUA (score ≤62.0). IMU consists of four variables: percentage of the population with incomes below poverty, population-to-primary care physician ratio, infant mortality rate, and percentage of the population aged ≥65 years. These medical service areas will be aligned with census tracts and will be evaluated as a modifying/mediating variable.

5.2.2 Aim 2:

Outcomes: Cognitive function will be assessed using the *Neurocognitive Questionnaire (NCQ)* administered at FU5 [Q1-QN33] and FU7 [P1-P33] for both the original and expansion cohorts. We will examine the NCQ at FU7 and the change in the NCQ between FU5 and FU7. The NCQ, which was developed to identify neurocognitive problems in childhood cancer survivors,[46,47] assesses four neurocognitive domains: task efficiency, emotional regulation, organization, and memory. Age-adjusted T-scores will be calculated using sibling norms, and impairment will be defined as a score ≥90th percentile based on sibling distribution. Neurocognitive change in each domain will be defined based on impaired or unimpaired scores at the two time points and will be classified into four categories:

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

This approach is consistent with other CCSS publications for emotional distress,[48] and loneliness.[49] An alternative approach will be considered that defines neurocognitive change as a change of ≥ ±1 standard deviation between FU5 and FU7 and categorized as either "declined", "similar" or "improved" neurocognitive function.[50]

Perceived changes in cognitive function will be assessed using the *PROMIS Cognitive Function instrument*[43] administered at FU7 [L19], a four-item sub-set scale of the PROMIS Cognitive Function item bank that assesses patient-perceived cognitive deficits. Standardized T-scores will be used, and impairment will be defined as a score >60, which means the survivor's score is one standard deviation above the average.

Predictor: Social Isolation will be assessed using the PROMIS Social Isolation instrument[43] as described in Aim 1.

Exposure:

Neighborhood-level geocoded SDoH

- Area Deprivation Index[30-31] (ADI) will be evaluated as comparison metric of neighborhood-level socioeconomic adversity, as described by Ehrhardt et al.[32]
- Social Vulnerability Index (SVI), [33-34] a measure of neighborhood-level deprivation, provides data on four SDoH themes including socioeconomic status, household characteristics, racial and ethnic minority status, and housing type and transportation.
- Zip code approximation of Rural-Urban Community Area (RUCA) codes which classifies ZIP code areas using measures of population density, urbanization, and daily commuting.
- Persistent poverty, measure of neighborhood-level structural inequity, as defined by the US Department of Agriculture (USDA) Economic Research Service[44] (ERS) as counties with ≥20% of residents' income falls below the federal poverty level) by the decennial censuses in 1980, 1990, and 2000, as well as in the 2007-2011 American Community Survey. This measure will be categorized as a binary variable: persistent poverty or non-persistent poverty.
- Modern redlining index linked by census tract[37,38] is based on data from the Home Mortgage Disclosure Act data (2007-2013). This index measures the odds ratio of mortgage application denial based on property location and is categorized by levels of mortgage lending bias which include 0-0.5 [least], 0.5-1 [low], 1-2 [moderate], ≥2 [high].
- Medically Underserved Area (MUA), identified by the Health Resources and Services Administration (HRSA),[45] will be used to indicate county-level areas with limited access to primary care services. We will use the Index of Medical Underservice (IMU) score to determine if an area qualifies as MUA (score ≤62.0). IMU consists of four variables: percentage of the population with incomes below poverty, population-to-primary care physician ratio, infant mortality rate, and percentage of the population aged ≥65 years. These medical service areas will be aligned with census tracts and will be evaluated as a modifying/mediating variable.

5.2.3 Aim 3:

Outcomes: Perceived changs in cognitive function will be assessed using the *PROMIS Cognitive Function instrument*[43] (FU7) as described in Aim 2.

Predictors:

Chronic Health Conditions (CHCs; CTCAE grade 0-4) [D1-I9]. Endocrine, cardiac, pulmonary, neurologic, hearing, vision, we will analyze CHCs with onset before FU7. We will utilize a method developed by Geenen et al,[51] to aggregate chronic health conditions across organ systems taking into account the frequency and grade of conditions. This method will be adapted for CCSS, where chronic conditions are based on self-report and grade 1 conditions are mostly asymptomatic. For survivors who have multiple chronic health conditions within the same organ system, we will use the highest grade within that organ system. This severity/burden score will be classified via the following ordinal categories: none/low (< grade 2 conditions), medium [having (≥1 grade 2) and/or (1 grade 3 condition)], high [having (≥ 2 grade 3 conditions) or (1 grade 4 and 1 grade 3 conditions)], and severe score [(≥ 1 grade 4 events) or (≥ 2 grade 3 conditions and a grade 4 condition)]. This information is also summarized in the table below. Further groupings (e.g., ≤medium vs. high/severe) will be evaluated based on frequency distribution. In addition to the severity of chronic health conditions, we will also use the mean cumulative count.

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	None/low one or more grade 2 event(s) and/or one grade 3 event
None/low	any condition < grade 2*

*adapted from the original method by Geenen, where "low" indicated one or more grade 1 event(s).

Emotional distress (FU7; yes/no; yes if any one of the following is met)

- Anxiety: BSI Anxiety subscale T-score ≥63 [L1-L18]
- Depression: BSI Depression subscale T-score ≥63 [L1-L18]
- Current use of antidepressant and/or anxiolytic medications [C2], as previously defined in CCSS.[34,43]

Mediator: Social Isolation will be assessed using the *PROMIS Social Isolation instrument*[52] (FU7) as described in Aim 1.

Exposure:

Neighborhood-level geocoded SDoH

- Area Deprivation Index[30-31] (ADI) will be evaluated as comparison metric of neighborhood-level socioeconomic adversity, as described by Ehrhardt et al.[32]
- Social Vulnerability Index (SVI), [33-34] a measure of neighborhood-level deprivation, provides data on four SDoH themes including socioeconomic status, household characteristics, racial and ethnic minority status, and housing type and transportation.

- Zip code approximation of Rural-Urban Community Area (RUCA) codes which classifies ZIP code areas using measures of population density, urbanization, and daily commuting.
- Persistent poverty, measure of neighborhood-level structural inequity, as defined by the US Department of Agriculture (USDA) Economic Research Service[44] (ERS) as counties with ≥20% of residents' income falls below the federal poverty level) by the decennial censuses in 1980, 1990, and 2000, as well as in the 2007-2011 American Community Survey. This measure will be categorized as a binary variable: persistent poverty or non-persistent poverty.
- Modern redlining index linked by census tract[37,38] is based on data from the Home Mortgage Disclosure Act data (2007-2013). This index measures the odds ratio of mortgage application denial based on property location and is categorized by levels of mortgage lending bias which include 0-0.5 [least], 0.5-1 [low], 1-2 [moderate], ≥2 [high].
- Medically Underserved Area (MUA), identified by the Health Resources and Services Administration (HRSA),[45] will be used to indicate county-level areas with limited access to primary care services. We will use the Index of Medical Underservice (IMU) score to determine if an area qualifies as MUA (score ≤62.0). IMU consists of four variables: percentage of the population with incomes below poverty, population-to-primary care physician ratio, infant mortality rate, and percentage of the population aged ≥65 years. These medical service areas will be aligned with census tracts and will be evaluated as a modifying/mediating variable.

5.4 Covariates

- BMI (at FU7) [A1-A2]
  - Underweight (BMI < 18.5)
  - Normal (BMI ≥ 18.5 and < 25)
  - Overweight (BMI ≥ 25 and <30)
  - Obese (BMI ≥30)

Sociodemographic factors (at FU7)

- Age at evaluation
- Age at diagnosis
- Sex
- Race/ethnicity
  - White, non-Hispanic
  - Black, non-Hispanic
  - Other
- Employment [A7]
  - Full-time
  - Part-time
  - Retired/disabled/unemployed
- Educational attainment [A6]
  - < High school, completed high school
  - Training after high school/some college, college graduate/post-graduate
- Marital status [A10]

- History of marriage (yes/no; yes if married, living with partner as married, widowed, divorced, separated or no longer living as married)

- Independent living [A9]
  - Yes (yes/no; yes if live with spouse/partner, live alone, live with roommates)
- Health insurance [A16]
  - Yes (yes/no; yes if yes, Canadian resident)

Health-related factors (at FU7)

- Physical activity (yes/no met CDC guidelines) [M15-M21]
- Alcohol use (yes/no for heavy/risky drinking) [M1-M6]
- Smoking status (current/ever, never) [M7-M11]
- Pain (yes/no; yes if any one of the following is met):
  - Headaches (migraines, severe headaches) still present [J3-J4]
  - Moderate to very severe bodily pain [N7-N8]

6. ANALYTIC APPROACH

Frequency distributions will be generated to categorize relevant outcome variables, predictors, and covariates according to a prior and/or reasonable groupings. Descriptive statistics including means, standard deviation, medians, ranges, frequencies, and percentages will be calculated for all outcomes, predictors, and covariates. With regards to social isolation, we will examine the frequency of self-reported social isolation versus proxy-reported social isolation and accordingly use either the self-reported social isolation data only (majority of the data is self-reported) or both self- and proxy-reported social isolation if there are no statistically significant differences in the data between both groups of responders for all three aims.

Aim 1: Estimate the prevalence and identify predictors of social isolation in adult survivors of childhood cancer (FU7).

Prevalence estimates of social isolation will be generated for survivors and siblings. The analysis will examine the prevalence of social isolation at a few different thresholds such as 1 SD, 1.5 SD, 2 SD (Table 2). A generalized linear model for high social isolation (defined as a score >60) will evaluate the association of exposures described above with social isolation (Table 3). If the outcomes are rare, logistic regression will be used, otherwise a log-link and Poisson errors will be used to model prevalence ratios. Associations of social isolation with primary diagnoses and treatment exposures will be included in separate models to avoid problems due to collinearity of childhood cancer diagnosis and treatments. Reported prevalence of social isolation will be compared to healthy sibling comparators in models adjusted for age at follow-up, sex, race/ethnicity, BMI, neighborhood-level geocoded SDoH, and sociodemographic factors (employment, educational attainment, marital status, and health insurance status). In sensitivity analyses, models will be adjusted for independent living (as an additional indicator of social support) in place of marital status, due to significant overlap between the two variables that precluded inclusions of both in the main models. Finally, prevalence ratios (PRs) and odds ratios (ORs) as a function of age and corresponding 95% confidence intervals will be generated to compare risk of social isolation between survivors and siblings. We will also stratify the results by stages of adulthood including young adult, middle adulthood (40 to mid-60s), and late adulthood (mid-60s and beyond).

Aim 2: Examine associations between social isolation (FU7), changes in cognitive function (difference between FU5 and FU7), and perceived changes in cognitive function in adult survivors of childhood cancer (FU7).

Multivariable multinomial regression models will be used to investigate associations between social isolation (predictor) and neurocognitive functioning (outcome). As previously mentioned, high social isolation will be defined as a score >60. Models will be adjusted a priori for sex, race/ethnicity, age at diagnosis, treatment exposures, BMI, neighborhood-level geocoded SDoH, employment, educational attainment, marital status, and health insurance status at FU7 (Table 4). Since each neighborhood-level SDoH metric represents a theoretically different concept, and it is not yet known which is most strongly associated with survivors' outcomes, each metric will be analyzed independently. Due to limitations in available geocoding data—particularly for older geocodes—our primary analytic approach will include all geocoded addresses reported by CCSS participants from the year 2000 onward. For each participant, the geocode corresponding to the highest level of neighborhood-level structural inequity and deprivation will be used in analyses to capture exposure to any recent disadvantage. Additionally, sensitivity analyses will be performed to compare results using the most recent versus the earliest available geocode, to explore the effects of exposure timing (e.g., during young adulthood vs. childhood/adolescence).

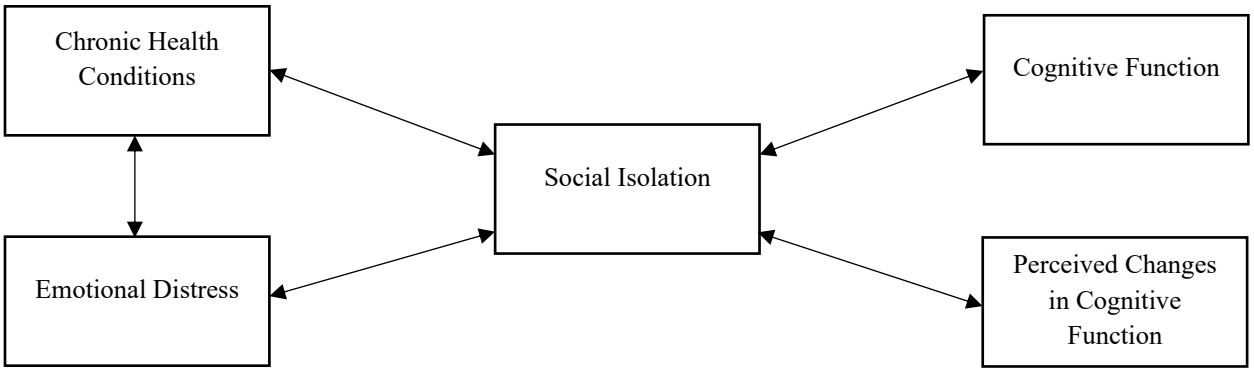
Trajectories of neurocognitive functioning will be defined as changes in NCQ impairment between FU5 and FU7 as previously described (i.e., persistent, resolved or new-onset neurocognitive impairment vs. stable unimpaired neurocognitive functioning in the primary approach; "declined" or "improved" vs. "similar" in the alternative approach), using separate models for each NCQ domain score (task efficiency, emotional regulation, organization, and memory). We will also examine NCQ scores as measured at FU7 (Table 5). Alternatively, generalized linear models will be used to determine the relative risk of new-onset impairment at follow-up in each domain among survivors who did not report impairment in that domain at baseline. Additionally, cognitive functioning will also be defined using the PROMIS Cognitive Function instrument administered at FU7, impairment will be defined as a score >60. For both the NCQ and PROMIS Cognitive Function measures, we will compare survivors with self-completed versus proxy-completed questionnaires to examine potential bias in the analysis. We will also stratify the results by stages of adulthood.

Aim 3: Examine whether social isolation (FU7) mediates the association between chronic health conditions and emotional health symptoms and perceived changes in cognitive function in adult survivors of childhood cancer (FU7).

We will utilize path analysis as shown in the figure below to determine the contributions of social isolation to the associations between chronic health conditions and emotional distress and perceived changes in cognitive function in adult survivors of childhood cancer. We are proposing that social isolation mediates the relation between chronic health conditions and emotional health symptoms and our outcome, perceived change in cognitive function, adjusting for age at follow-up, sex, race/ethnicity, BMI, neighborhood-level geocoded SDoH, and personal sociodemographic factors (employment, educational attainment, marital status, and health insurance status). Since each neighborhood-level SDoH metric represents a theoretically different concept, and it is not yet known which is most strongly associated with survivors' outcomes, each metric will be analyzed independently. Due to limitations in available geocoding data—particularly for older geocodes—

our primary analytic approach will include all geocoded addresses reported by CCSS participants from the year 2000 onward. For each participant, the geocode corresponding to the highest level of neighborhood-level structural inequity and deprivation will be used in analyses to capture exposure to any recent disadvantage. Additionally, sensitivity analyses will be performed to compare results using the most recent versus the earliest available geocode, to explore the effects of exposure timing (e.g., during young adulthood vs. childhood/adolescence). The double-headed arrows represent a bidirectional "path" between the outcomes, where the variables are thought to exert an influence on each other. No assumptions regarding causal inference are made between variables thought to covary. We will also examine the contribution of diagnosis and treatment exposures as covariates in the model.

Path Analysis Diagram



The program figures will be used to write the R programming code. The output will provide a test of the null hypothesis as well as goodness of fit statistics. A model with an ideal fit to the data would reflect some if not all of the following: the absolute values of entries in the normalized residual matrix should not exceed 2.00, the *p*-value associated with the model chi-square test should exceed .05 and be closer to 1.00, the comparative fit index and the non-normed fit index should both exceed .9 and be closer to 1.00, the R^2 value for each endogenous variable should be relatively large, and the absolute value of the *t* statistics for each path coefficient should exceed 1.96, and the standardized path coefficients should exceed .05.[53] The output will also provide estimates and significance tests for the path coefficients, variances, and covariances; these are the parameters of interest in path analysis. Depending upon the fit between the model and the data, modification indices will indicate how the model should be revised for a better fit (Table 6).

Table 1. Sociodemographic and clinical characteristics at FU7 of childhood cancer survivors.

	Total sample (N =)	**CNS-directed therapies (n =)**	**Non-CNS-directed therapies (n =)**
	n (%)	**n (%)**	**n (%)**
Sex			
Male			
Female			
Race/Ethnicity			
White, non-Hispanic			
Black, non-Hispanic			
Other			
Age at assessment, years			
18-29			
30-39			
40-49			
50+			
Age at diagnosis, years			
0-4			
5-9			
10-14			
15-21			
Diagnosis			
Leukemia			
CNS tumors			
Hodgkin lymphoma			
Non-Hodgkin lymphoma			
Neuroblastoma			
Wilms' tumor			
Soft tissue sarcoma			
Bone tumor			
Cranial radiation, Gy			
None			
<20			
≥20 to <30			
≥ 30			
Non-cranial radiation			
Yes			
No			
IT Methotrexate			
IV Methotrexate, g/m2			
Median (IQR) dose			
None			
>0 to <40			
≥ 40			

Cytarabine			
Yes			
No			
Anthracycline, mg/m2			
Median (IQR) dose			
None			
1-249			
≥250			
BMI			
Underweight			
Normal			
Overweight			
Obese			
Physical activity			
Smoking			
Alcohol drinking			
Emotional distress			
Pain			
Vitality			
Chronic conditions			
None/low			
Medium			
High			
Severe			

Note. CNS-directed therapies include cranial radiation and intrathecal methotrexate.
Note. BMI, Body Mass Index; Gy, grey; IQR, interquartile range; IT, intrathecal; IV intravenous.

Table 2 (Aim 1)**.** Prevalence of social isolation in childhood cancer survivors and siblings.

	Survivors (N =)		**Siblings (N =)**		
	n	**%**	**n**	**%**	**PR (95% CI)**
Social Isolation					
1 SD					
1.5 SD					
2 SD					

Note. Models will be adjusted a priori for age at follow-up, sex, race/ethnicity, BMI, employment, educational attainment, marital status, and health insurance status at FU7.
Note. CI, confidence interval; PR, prevalence ratio.

Table 3 (Aim 1)**.** Associations between exposures and social isolation.

	Social Isolation OR (95% CI)
Model 1: Diagnosis	
Siblings	1.00 (-)
Leukemia	
CNS tumors	
Hodgkin lymphoma	
Non-Hodgkin lymphoma	
Neuroblastoma	
Wilms' tumor	
Soft tissue sarcoma	
Bone tumor	
Model 2: Treatment exposure	
Treatment modality	
Chemotherapy	
Radiation therapy	
Both	
IV Methotrexate, g/m^2	
Median (IQR) dose	
None	
>0 to <40	
≥ 40	
Cytarabine	
Yes	
No	
Anthracycline, mg/m^2	
Median (IQR) dose	
None	
1-249	
≥250	
Cranial radiation, Gy	
None	
<20	
≥20 to <30	
≥ 30	
Non-cranial radiation	
Yes	
No	
Shunt	
Yes	
No	
Model 3: Neighborhood-level geocoded SDoH	
ADI	
Least disadvantaged 80%	

The other most disadvantaged 20%	
SVI	
Least disadvantaged 80%	
The other most disadvantaged 20%	
Urbanization using RUCA codes	
Persistent poverty	
Modern redlining index	
Least	
Low	
Moderate	
High	
MUA	

Note. Models will be adjusted a priori for age at follow-up, sex, race/ethnicity, BMI, employment, educational attainment, marital status, and health insurance status at FU7.

Note. ADI, Area Deprivation Index; CNS, central nervous system; COI, Child Opportunity Index; Gy, grey; IQR, interquartile range; IT, intrathecal; IV, intravenous; MUA, Medically Underserved Area; RUCA, Rural-Urban Commuting Area Codes; SVI, Social Vulnerability Index.

Table 4 (Aim 2)**.** Multinomial regression examining associations between social isolation, cognitive function, and perceived changes in cognitive function in adult survivors of childhood cancer.

	Neurocognitive functioning trajectories from change in NCQ at FU5 and FU7												**PROMIS Cognitive Function at FU7**
	Persistent impairment				**New-onset impairment**				**Resolved impairment**				**Impaired**
	TE	**ER**	**Org**	**Mem**	**TE**	**ER**	**Org**	**Mem**	**TE**	**ER**	**Org**	**Mem**	
	RR (95% CI)	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
Social Isolation at FU7													

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

Note. Separate models for each neurocognitive outcome; adjusted a priori for sex, race/ethnicity, age at diagnosis, treatment exposures, BMI, neighborhood-level geocoded SDoH, employment, educational attainment, marital status, and health insurance status at FU7.

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

Table 5 (Aim 2)**.** Multinomial regression examining associations between social isolation, cognitive function, and perceived changes in cognitive function in adult survivors of childhood cancer at FU7.

	Neurocognitive functioning trajectories from NCQ (FU7)												**PROMIS Cognitive Function (FU7)**
	Persistent impairment				**New-onset impairment**				**Resolved impairment**				**Impaired**
	TE	**ER**	**Org**	**Mem**	**TE**	**ER**	**Org**	**Mem**	**TE**	**ER**	**Org**	**Mem**	
	RR (95% CI)	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
Social Isolation													

Note. Persistent impairment = impaired to impaired; new-onset impairment = non-impaired to impaired; resolved impairment; impaired to non-impaired; stable non-impairment as reference group.
Note. Separate models for each neurocognitive outcome; adjusted a priori for sex, race/ethnicity, age at diagnosis, treatment exposures, BMI, neighborhood-level geocoded SDoH, employment, educational attainment, marital status, and health insurance status at FU7.
Note. CI, confidence interval; ER, Emotional regulation; Mem, Memory; Org, Organization; RR, relative risk; TE, Task efficiency.

Table 6 (Aim 3)**.** Fit indices for the path model of the contributions of chronic health conditions and emotional health to associations between social isolation and perceived changes in cognitive function in adult survivors of childhood cancer (FU7).

	Initial model	**Final model**
χ^2		
Degrees of freedom		
P-value		
χ^2 ratio		
GFI		
AGFI		
SRMR		
RMSEA estimator		
CFI		
NNFI		

Note. For health status in the initial model, this will include physical activity, smoking, and alcohol consumption.
Note. The model will be adjusted a priori for sex, race/ethnicity, age at diagnosis, treatment exposures, BMI, neighborhood-level geocoded SDoH, employment, educational attainment, marital status, and health insurance status at FU7.
Note. Acceptable values: *p*-value for χ^2 >0.05; χ^2 ratio <2.0; Goodness of Fit Index (GFI) ≥0.85; GFI adjusted for degrees of freedom (AGFI) ≥0.80; standardized root mean square residual (SRMR) ≤0.10; root mean square error of approximation (RMSEA) ≤0.08; Comparative Fit Index (CFI) ≥0.90; Bentler–Bonett Non-normed Index (NNFI) ≥0.90.

References

1. Bhatia S, Tonorezos ES, Landier W. Clinical care for people who survive childhood cancer: a review. JAMA. 2023 Sep 26;330(12):1175-86. PMID: 37750876.
2. Brown TT, Jernigan TL. Brain development during the preschool years. Neuropsychology review. 2012 Dec;22:313-33. PMCID: PMC3511633.
3. Palmer SL, Glass JO, Li Y, Ogg R, Qaddoumi I, Armstrong GT, Wright K, Wetmore C, Broniscer A, Gajjar A, Reddick WE. White matter integrity is associated with cognitive processing in patients treated for a posterior fossa brain tumor. Neuro-oncology. 2012 Sep 1;14(9):1185-93.
4. Wolfe KR, Madan-Swain A, Kana RK. Executive dysfunction in pediatric posterior fossa tumor survivors: a systematic literature review of neurocognitive deficits and interventions. Developmental neuropsychology. 2012 Feb 1;37(2):153-75.
5. King TZ, Ailion AS, Fox ME, Hufstetler SM. Neurodevelopmental model of long-term outcomes of adult survivors of childhood brain tumors. Child Neuropsychology. 2019 Jan 2;25(1):1-21.
6. Szymanski KA, Pincus JE, King TZ. Relationships between cognitive flexibility performance and adaptive behavior outcomes in survivors of pediatric brain tumor. The Clinical Neuropsychologist. 2025 Jan 2;39(1):129-58.
7. Elkefi S, Trapani D, Ryan S. The role of digital health in supporting cancer patients' mental health and psychological well-being for a better quality of life: A systematic literature review. International Journal of Medical Informatics. 2023 Aug 1;176:105065.
8. Wright P, Smith A, Booth L, Winterbottom A, Kiely M, Velikova G, Selby P. Psychosocial difficulties, deprivation and cancer: three questionnaire studies involving 609 cancer patients. British journal of cancer. 2005 Sep;93(6):622-6.
9. Gerber NU, Zehnder D, Zuzak TJ, Poretti A, Boltshauser E, Grotzer MA. Outcome in children with brain tumours diagnosed in the first year of life: long-term complications and quality of life. Archives of disease in childhood. 2008 Jul 1;93(7):582-9.
10. Pennington KP, Schlumbrecht M, McGregor BA, Goodheart MJ, Heron L, Zimmerman B, Telles R, Zia S, Penedo FJ, Lutgendorf SK. Living Well: Protocol for a web-based program to improve quality of life in rural and urban ovarian cancer survivors. Contemporary clinical trials. 2024 Sep 1;144:107612.
11. Gudenkauf LM, Antoni MH, Stagl JM, Lechner SC, Jutagir DR, Bouchard LC, Blomberg BB, Glück S, Derhagopian RP, Giron GL, Avisar E. Brief cognitive–behavioral and relaxation training interventions for breast cancer: A randomized controlled trial. Journal of consulting and clinical psychology. 2015 Aug;83(4):677.
12. Ng IKS. The ‘loneliness’ epidemic: a new social determinant of health? Internal Medicine Journal. 2024;54(3):365–7. Available from: https://doi.org/10.1111/imj.16356
13. Wakefield CE, Sansom-Daly UM, McGill BC, McCarthy M, Girgis A, Grootenhuis M, Barton B, Patterson P, Osborn M, Lowe C, Anazodo A. Online parent-targeted cognitive-behavioural therapy intervention to improve quality of life in families of young cancer survivors: study protocol for a randomised controlled trial. Trials. 2015 Dec;16:1-2.
14. Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. Perspectives on psychological science. 2015 Mar;10(2):227-37.
15. Tometich DB, Welniak T, Gudenkauf L, Maconi ML, Fulton HJ, Martinez Tyson D, Zambrano K, Hasan S, Rodriguez Y, Bryant C, Li X. “I couldn't connect the wires in my

brain.” Young adult cancer survivors' experience with cognitive functioning. Psycho-Oncology. 2024 Mar;33(3):e6309.
16. Nicklin E, Velikova G, Hulme C, Rodriguez Lopez R, Glaser A, Kwok-Williams M, Boele F. Long-term issues and supportive care needs of adolescent and young adult childhood brain tumour survivors and their caregivers: a systematic review. Psycho-Oncology. 2019 Mar;28(3):477-87.
17. Sodergren SC, Husson O, Robinson J, Rohde GE, Tomaszewska IM, Vivat B, Dyar R, Darlington AS, EORTC Quality of Life Group. Systematic review of the health-related quality of life issues facing adolescents and young adults with cancer. Quality of Life Research. 2017 Jul;26:1659-72.
18. Vance YH, Eiser C, Horne B. Parents’ views of the impact of childhood brain tumours and treatment on young people’s social and family functioning. Clinical child psychology and psychiatry. 2004 Apr;9(2):271-88.
19. Jin Z, Griffith MA, Rosenthal AC. Identifying and meeting the needs of adolescents and young adults with cancer. Current oncology reports. 2021 Feb;23:1-0.
20. Goossens J, Delbaere I, Beeckman D, Verhaeghe S, Van Hecke A. Communication difficulties and the experience of loneliness in patients with cancer dealing with fertility issues: a qualitative study. In Oncology nursing forum 2015 Jan 1 (Vol. 42, No. 1).
21. Warner EL, Kent EE, Trevino KM, Parsons HM, Zebrack BJ, Kirchhoff AC. Social well-being among adolescents and young adults with cancer: a systematic review. Cancer. 2016 Apr 1;122(7):1029-37.
22. Boydell KM, Stasiulis E, Greenberg M, Greenberg C, Spiegler B. I'll show them: the social construction of (in) competence in survivors of childhood brain tumors. Journal of Pediatric Oncology Nursing. 2008 May;25(3):164-74.
23. Brinkman TM, Recklitis CJ, Michel G, Grootenhuis MA, Klosky JL. Psychological symptoms, social outcomes, socioeconomic attainment, and health behaviors among survivors of childhood cancer: current state of the literature. Journal of Clinical Oncology. 2018 Jul 20;36(21):2190-7.
24. Janson C, Leisenring W, Cox C, Termuhlen AM, Mertens AC, Whitton JA, Goodman P, Zeltzer L, Robison LL, Krull KR, Kadan-Lottick NS. Predictors of marriage and divorce in adult survivors of childhood cancers: a report from the Childhood Cancer Survivor Study. Cancer epidemiology, biomarkers & prevention. 2009 Oct 1;18(10):2626-35.
25. Kunin-Batson A, Kadan-Lottick N, Zhu L, Cox C, Bordes-Edgar V, Srivastava DK, Zeltzer L, Robison LL, Krull KR. Predictors of independent living status in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Pediatric blood & cancer. 2011 Dec 15;57(7):1197-203.
26. Penn A, Kuperberg A. Psychosocial support in adolescents and young adults with cancer. The Cancer Journal. 2018 Nov 1;24(6):321-7.
27. Lara E, Caballero FF, Rico-Uribe LA, Olaya B, Haro JM, Ayuso-Mateos JL, Miret M. Are loneliness and social isolation associated with cognitive decline? International journal of geriatric psychiatry. 2019 Nov;34(11):1613-22.
28. Guglielmi V, Colangeli L, Parrotta ME, Ciammariconi A, Milani I, D'Adamo M, Sbraccia P, Capoccia D. Social isolation and loneliness in non-communicable chronic diseases: Impact of COVID-19 pandemic, population aging and technological progress. Nutrition, Metabolism and Cardiovascular Diseases. 2025 Mar 15:104015.

29. Maunsell E, Pogany L, Barrera M, Shaw AK, Speechley KN. Quality of life among long-term adolescent and adult survivors of childhood cancer. Journal of Clinical Oncology. 2006 Jun 1;24(16):2527-35.
30. Kind AJ, Buckingham WR. Making neighborhood-disadvantage metrics accessible—the neighborhood atlas. The New England journal of medicine. 2018 Jun 28;378(26):2456.
31. Kind AJ, Jencks S, Brock J, Yu M, Bartels C, Ehlenbach W, Greenberg C, Smith M. Neighborhood socioeconomic disadvantage and 30-day rehospitalization: a retrospective cohort study. Annals of internal medicine. 2014 Dec 2;161(11):765-74.
32. Ehrhardt MJ, Liu Q, Dixon SB, Caron E, Redd D, Shelton K, Huang IC, Bhakta N, Ness KK, Mulrooney DA, Brinkman TM. Association of modifiable health conditions and social determinants of health with late mortality in survivors of childhood cancer. JAMA Network Open. 2023 Feb 1;6(2):e2255395-.
33. Flanagan BE, Gregory EW, Hallisey EJ, Heitgerd JL, Lewis B. A social vulnerability index for disaster management. Journal of homeland security and emergency management. 2011 Jan 5;8(1).
34. Singh GK. Area deprivation and widening inequalities in US mortality, 1969–1998. *American journal of public health* 2003; 93(7): 1137-43.
35. Moss JL, Pinto CN, Srinivasan S, Cronin KA, Croyle RT. Persistent poverty and cancer mortality rates: an analysis of county-level poverty designations. Cancer Epidemiology, Biomarkers & Prevention. 2020 Oct 1;29(10):1949-54.
36. Moss JL, Pinto CN, Srinivasan S, Cronin KA, Croyle RT. Enduring cancer disparities by persistent poverty, rurality, and race: 1990-1992 to 2014-2018. JNCI: Journal of the National Cancer Institute. 2022 Jun 1;114(6):829-36.
37. Beyer KM, Zhou Y, Laud PW, McGinley EL, Yen TW, Jankowski C, Rademacher N, Namin S, Kwarteng J, Beltrán Ponce S, Nattinger AB. Mortgage lending bias and breast cancer survival among older women in the United States. Journal of Clinical Oncology. 2021 Sep 1;39(25):2749-57.
38. Beyer KM, Zhou Y, Matthews K, Bemanian A, Laud PW, Nattinger AB. New spatially continuous indices of redlining and racial bias in mortgage lending: links to survival after breast cancer diagnosis and implications for health disparities research. Health & place. 2016 Jul 1;40:34-43.
39. Streeter RA, Snyder JE, Kepley H, Stahl AL, Li T, Washko MM. The geographic alignment of primary care Health Professional Shortage Areas with markers for social determinants of health. PloS one. 2020 Apr 24;15(4):e0231443.
40. Rothstein R. The color of law: A forgotten history of how our government segregated America. Liveright Publishing; 2017 May 2.
41. Haas JS, Earle CC, Orav JE, Brawarsky P, Keohane M, Neville BA, Williams DR. Racial segregation and disparities in breast cancer care and mortality. Cancer. 2008 Oct 15;113(8):2166-72.
42. Dai D. Black residential segregation, disparities in spatial access to health care facilities, and late-stage breast cancer diagnosis in metropolitan Detroit. Health & place. 2010 Sep 1;16(5):1038-52.
43. Intro to PROMIS [Internet]. Available from: https://www.healthmeasures.net/explore-measurement-systems/promis/intro-to-promis

44. US Department of Agriculture. Descriptions and maps: county economic types, 2015 edition. 2017. https://www.ers.usda.gov/data-products/county-typology-codes/descriptions-and-maps (accessed September 3 2025).
45. Health Resources and Services Administration. Medically Underserved Areas/Populations. 2015. https://bhw.hrsa.gov/loans-scholarships/nhsc (accessed September 3 2025).
46. Krull KR, Gioia G, Ness KK, et al: Reliability and validity of the Childhood Cancer Survivor Study Neurocognitive Questionnaire. Cancer 113:2188-97, 2008
47. Kenzik KM, Huang IC, Brinkman TM, et al: The Childhood Cancer Survivor Study-Neurocognitive Questionnaire (CCSS-NCQ) revised: item response analysis and concurrent validity. Neuropsychology 29:31-44, 2015
48. Daniel LC, Wang M, Mulrooney DA, Srivastava DK, Schwartz LA, Edelstein K, Brinkman TM, Zhou ES, Howell RM, Gibson TM, Leisenring W. Sleep, emotional distress, and physical health in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. Psycho-oncology. 2019 Apr;28(4):903-12.
49. Papini C, Fayad AA, Wang M, et al: Emotional, behavioral, and physical health consequences of loneliness in young adult survivors of childhood cancer: Results from the Childhood Cancer Survivor Study. Cancer, 2023
50. Van Kessel E, Snijders TJ, Baumfalk AE, et al: Neurocognitive changes after awake surgery in glioma patients: a retrospective cohort study. Journal of Neuro-Oncology 146:97-109, 2020
51. Geenen MM, Cardous-Ubbink MC, Kremer LC, van den Bos C, van der Pal HJ, Heinen RC, Jaspers MW, Koning CC, Oldenburger F, Langeveld NE, Hart AA. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. Jama. 2007 Jun 27;297(24):2705-15.
52. Brinkman TM, Ullrich NJ, Zhang N, et al: Prevalence and predictors of prescription psychoactive medication use in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Journal of Cancer Survivorship 7:104-14, 2013
53. Brinkman TM, Zhang N, Ullrich NJ, et al: Psychoactive medication use and neurocognitive function in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor study. Pediatric Blood & Cancer 60:486-93, 2013