Childhood Cancer Survivor Study Analysis Concept Proposal

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1. **Study Title:** Emotional distress, social resources, and phenotypic aging in adult survivors of childhood cancer

2. **Working Group(s):** Psychology (Primary), Chronic Disease (Secondary)

   Investigators:

Name	Contact information
Kelly Rentscher, PhD	krentscher@mednet.ucla.edu
Kirsten Ness, PT, PhD	kiri.ness@stjude.org
Greg Armstrong, MD, MSCE	greg.armstrong@stjude.org
Kevin Krull, PhD	kevin.krull@stjude.org
Kim Edelstein, PhD	kim.edelstein@uhn.ca
Eric Chow, MD, MPH	ericchow@uw.edu
Tara Brinkman, PhD	tara.brinkman@stjude.org
Wendy Leisenring, ScD	wleisenr@fredhutch.org
Lu Lu, MS	lu.lu@stjude.org
I-Chan Huang, PhD	i-chan.huang@stjude.org
Carrie R. Howell, PhD	chowell@uabmc.edu
Rebecca Howell, PhD	rhowell@mdanderson.org

3. **Background and Rationale:**

   Five-year survival rates for childhood cancer have improved to over 80% over the past several decades.[1] However, treatment of the cancer comes at a cost, with many survivors experiencing late effects that last for the rest of their lives and resemble an aging phenotype, or age-related functional declines thought to be manifestations of aging at the cellular level. Cognitive, physical, and functional symptoms characteristic of an accelerated aging phenotype are more prevalent in childhood cancer survivors than similarly aged peers or siblings, including physiologic frailty,[2–4] cognitive impairment,[5] pain,[6] and limitations in daily activities.[7,8] Specifically, 8-13% of childhood cancer survivors exhibit a physiologic frailty phenotype in early adulthood and 20-32% exhibit pre-frailty.[3,9] These prevalence estimates are comparable to adults aged 65 years and older in the general population, and represent a 2- to 3-fold greater risk compared to peers and siblings.[3,4,9] In addition, 20-48% of survivors exhibit neurocognitive impairment[5,10] and 18-68% experience physical function limitations.[8,11] Not all survivors experience these late effects, suggesting that modifiable behavioral, socioeconomic, and environmental factors may also influence vulnerability. The transition to middle adulthood may represent a period of increased vulnerability in which prolonged or recurring experiences of psychosocial distress may further contribute to accelerated or premature aging trajectories. The proposed research will begin to address this gap by examining the impact of emotional distress and social resources over a 10-year period from early to middle adulthood on an accelerated aging phenotype in childhood cancer survivors and their siblings.

Depression and anxiety symptoms are among the most prevalent emotional comorbidities reported by childhood cancer survivors more than 5 years after diagnosis.[9] Prevalence estimates for clinically elevated emotional distress range from 10–32%, with studies suggesting that survivors experience higher levels of distress than similarly aged peers and siblings.[7,12] Previous research with childhood cancer survivors suggests that elevated levels of emotional distress are uniquely associated with symptoms of phenotypic aging, including frailty,[9] learning and memory problems,[12] poorer physical function, lower vitality, and role disruptions due to physical health.[11,13] In one study, emotional distress accounted for 56% of the variance in physical quality of life after accounting for several socio-demographic and treatment-related factors.[14] However, all of these previous investigations have examined cross-sectional associations between emotional distress and phenotypic aging. Research is needed that investigates longitudinal distress, which may become prolonged or recur over time to cumulatively influence cognitive, physical, and functional declines.[3]

Current theoretical frameworks posit that supportive social relationships can positively influence health by fulfilling basic needs for social connection and providing a buffering resource during times of distress, and importantly, disruptions in social relationships can be an additional source of distress.[15–18] Only two studies to date have examined cross-sectional associations between social relationships and symptoms of phenotypic aging in adult survivors of childhood cancer, finding that survivors who were not married were more likely to be frail and had lower cognitive functioning than those who were married or living as married.[9,11] Given that emotional distress has also been associated with marital status,[11] research that examines the degree to which social relationships—both marital and non-marital—during middle adulthood may moderate associations between emotional distress and phenotypic aging is needed. Recent research has also found that other social resources such as neighborhood socioeconomic status, access to parks, recreational facilities, and grocery stores, and rurality were associated with obesity in adult survivors of childhood cancer;[19] however, associations with phenotypic aging outcomes and have not yet been examined.

Recent evidence suggests that cancer treatment can accelerate biological aging in adult cancer survivors by up to 15 years.[20,21] Exposure to cancer treatment is thought to contribute to cellular stress and excess DNA damage that can lead to premature cellular senescence, a permanent state of cell growth arrest.[20–22] Studies with childhood cancer survivors have found that survivors show signs of accelerated biological aging relative to non-cancer controls, including greater gene expression of cellular senescence marker $p16^{INK4a}$, shorter telomere length, and higher circulating markers of inflammation.[2,23,24] Emerging evidence suggests that accelerated biological aging may be a key driver of age-related functional declines;[22,25] therefore, the physical, functional, and cognitive declines observed in childhood cancer survivors may be a manifestation of accelerated aging at the cellular level. In midlife adults without cancer, our group and others have found links between psychological stress and accelerated biological aging, including cellular senescence marker $p16^{INK4a}$, and initial evidence that this can be modified by social connection.[26–28] These findings suggest that psychosocial processes can impact key biological aging pathways; however, whether they contribute to variability in biological and phenotypic aging in childhood cancer survivors has not yet been tested.

The present study will begin to address these gaps by examining the impact of emotional distress and social resources over a 10-year period on accelerated phenotypic aging in childhood cancer survivors compared to sibling controls.

4. Specific Aims and Hypotheses:

Aim 1: Evaluate associations between emotional distress (depression, anxiety, and pain symptoms) and phenotypic aging (physiologic frailty, cognitive function, physical function, role limitations due to physical health problems) in survivors of childhood cancer versus sibling controls.

Hypothesis 1a: Higher depression, anxiety, and pain symptoms across Baseline/Expansion Baseline, FU2, FU4, FU5, and FU7 (when data are available) will be associated with subsequent onset of frailty from Baseline/Expansion Baseline to FU5/FU7, and these associations will be stronger for survivors than siblings.

Hypothesis 1b: Higher depression, anxiety, and pain symptoms across FU2/Expansion Baseline, FU4, FU5, and FU7 (when data are available) will be associated with subsequent onset of cognitive impairment from FU2 to FU5/FU7, and these associations will be stronger for survivors than siblings.

Hypothesis 1c**:** Higher depression, anxiety, and pain symptoms across FU2/Expansion Baseline, FU4, FU5, and FU7 (when data are available) will be associated with poorer physical function and greater role limitations due to physical health at FU5/FU7, and these associations will be stronger for survivors than siblings.

Aim 2. Evaluate the degree to which social resources (social functioning, neighborhood resources, marital status) moderate associations between emotional distress and phenotypic aging in survivors of childhood cancer versus sibling controls.

Hypothesis 2a: Individuals with less disruption in social activities across FU2/Expansion Baseline, FU5, and FU7 (when data are available) will show attenuated associations between depression, anxiety, and pain symptoms and frailty, cognitive and physical function, and role limitations than individuals with greater disruption in social activities.

Hypothesis 2b: Individuals with greater neighborhood resources (neighborhood SES, access to parks, recreational facilities, and groceries stores, rurality) across Baseline/Expansion Baseline and FU6 (or last known follow-up) will show attenuated associations between depression, anxiety, and pain symptoms and frailty, cognitive and physical function, and role limitations than individuals with fewer neighborhood resources.

Exploratory Hypothesis 2c: Individuals who are married or living with a partner as married across Baseline/Expansion Baseline, FU2, FU4, FU5, and FU7 (when data are available) will show attenuated associations between depression, anxiety, and pain symptoms and frailty, cognitive and physical function, and role limitations than individuals who are unmarried.

Analysis Framework:

a. Study Population: This analysis will include CCSS survivors and siblings from the original and expansion (when FU7 data are available) cohorts who meet the following eligibility criteria:

Aim 1a – Frailty:

i. Were at least 18 years old and alive at Baseline/Expansion Baseline

ii. Do not meet criteria for frailty (Section 5.b.i.) at Baseline/Expansion Baseline

iii. Were alive and have outcome data available at FU5 (original cohort) or FU7 (expansion cohort)

iv. Have emotional distress (BSI) data available at Baseline and FU5 (original cohort) or Expansion Baseline (expansion cohort). Data at FU2 and FU4 will also be included in the analyses but are not required for inclusion in the sample.

Based on these criteria, 8,247 survivors and 1,738 siblings will be included in Aim 1a analyses (see Figure 1a for CONSORT diagram).

Aim 1b – Cognitive function:

i. Were at least 18 years old and alive at Baseline/Expansion Baseline

ii. Do not meet criteria for cognitive impairment (T-scores ≥63; Section 5.b.ii.) at FU2

iii. Were alive and have outcome data available at FU5

iv. Have emotional distress (BSI) data available at Baseline and FU5. Data at FU2 and FU4 will also be included in the analyses but are not required for inclusion in the sample.

Based on these criteria, 3,570 survivors and 200 siblings will be included in Aim 1b analyses (see Figure 1b for CONSORT diagram).

Aim 1c – Physical function and role limitations:

i. Were at least 18 years old and alive at Baseline/Expansion Baseline

ii. Were alive and have outcome data available at FU5 (original cohort) or FU7 (expansion cohort)

iii. Have emotional distress (BSI) data available at Baseline and FU5 (original cohort) or Expansion Baseline (expansion cohort). Data at FU2 and FU4 will also be included in the analyses but are not required for inclusion in the sample.

Aim 2:

i. Have social functioning (SF-36), neighborhood resources, and marital status data available for at least 1 timepoint between Baseline/Expansion Baseline and FU7.

b. Outcome Variables: Phenotypic Aging (Aims 1 and 2)

i. **Frailty** will be assessed at Baseline/Expansion Baseline, FU2, and FU5/FU7 using a modified version of the Fried Frailty Index[4,29] based on the following five criteria. outcome.

Low lean muscle mass: Defined as either body mass index (BMI) <18.5 kg/m^2 (Baseline A10 and A11; Expansion Baseline A3 and A4; FU2 7 and 8; FU5 A1 and A2) or unintentional weight loss of ≥ 10 pounds in the past year (Baseline, Expansion Baseline, and FU2 Not available; FU5 A3).

Self-reported exhaustion: Defined as a T-score of ≤40 on the Vitality subscale of the SF-36, which consists of the following 4 items: (1) "How much of the time during the past four weeks did you feel full of life/pep?" (FU2 F1; FU5 P1a); (2) "Did you have a lot of energy?" (FU2 F5; FU5 P1e); (3) "Did you feel worn out?" (FU2 F7; FU5 P1 g); and (4) "Did you feel tired?" (FU2 F9; FU5 P1i). At Baseline and Expansion Baseline, this criterion is defined as a T-score ≥63 on the somatization subscale of the Brief Symptom Inventory, based on significant associations with the SF-36 Vitality subscale in previous

analyses (BSI; Baseline: J17, 18, 26, 27, 29, 31; Expansion Baseline K2, 3, 10, 11, 12, 14).[7,11]

Low energy expenditure: Defined as <383 kilocalories (kcal)/week for males and <270 kcal/week for females, estimated by converting the reported frequency and duration of light, moderate, and vigorous activities into kilocalories using guidelines provided by the Compendium of Physical Activities[4,30,31] (Baseline N9 modified; Expansion Baseline O15 modified; FU2 D1-7; FU5 N15-24)

Slowness/Walking limitations: Defined as a response of "Limited for more than three months" to either of the following 2 items: (1) "Over the last two years, how long has your health limited you in walking uphill or climbing a few flights of stairs?" (Baseline N14c; FU2 E6 modified; FU5 N29c); or (2) "Over the last two years, how long has your health limited you in walking one block?" (Baseline N14e; FU2 E11 modified; FU5 N29e). Note: Baseline and FU2 include similar items from the SF-36.

Weakness: Defined as a response of "Yes, and the condition is still present" to the item "Have you ever been told by a doctor or other health care professional that you have, or have had, weakness or inability to move yours arms?" (Baseline J10; Expansion Baseline J11; FU2 G14; FU5 K11).

Coding: Participants who meet 0–1 criterion are considered robust/non-frail, those who meet 2 criteria are considered pre-frail, and those who meet 3–5 criteria are considered frail. We then create two dichotomous variables to represent participants that are frail (≥ 3 criteria vs. < 3 criteria) and pre-frail (≥ 2 criteria vs. < 2 criteria).

Given that the Baseline/Expansion Baseline include modified items for frailty, sensitivity analyses for Aim 1a will adjust for Baseline/Expansion Baseline frailty, with FU5/FU7 frailty as the primary outcome.

ii. **Cognitive function** will be assessed at FU2, FU5, and FU7 using the CCSS-NCQ[32,33] 8-item Task Efficiency (FU2 J2, 6, 14, 16, 17, 21, 23, 25; FU5 Q2, 5, 11, 12, 13, 16, 18, 20) and 5-item Memory (FU2 J5, 7, 13, 20, 24; FU5 Q4, 6, 10, 15, 19) subscales, which measure neurocognitive concerns over the past 6 months. We focus on these subscales because attention/processing speed and memory are common age-related concerns and most relevant to hypotheses, in order to reduce multiple testing.

Note: Baseline, Expansion Baseline, and FU4 do not include these subscales.

Items for each subscale will be summed to create a subscale score, and subscale scores will be transformed into T-scores (based on sibling norms) for the analysis, with higher scores indicating greater neurocognitive problems.

The primary outcome will be a dichotomous variable, in which T-scores ≥63 (in the top 10^{th} percentile of the sibling reference) are considered clinically meaningful impairment.[5,34] Continuous T-score variables will also be considered in secondary analyses.

Sensitivity analyses for Aim 1b will adjust for FU2 cognitive function, with FU5/FU7 cognitive function as the primary outcome.

iii. **Physical function** will be assessed at FU2, FU5, and FU7 using the SF-36 Physical Functioning subscale (FU2 E3-12; FU5 O3a-j).

Note: Baseline, Expansion Baseline, and FU4 do not include this subscale.

Subscale scores will be transformed into T-scores (based on population norms) for the analysis, with lower scores indicating poorer physical functioning.

The primary outcome will be a dichotomous variable, in which T-scores ≤ 40 (less than 1 SD below the mean) are considered clinically meaningful impairment. Continuous T-score variables will also be considered in secondary analyses.

Sensitivity analyses for Aim 1c will adjust for FU2 physical function, with FU5/FU7 physical function as the primary outcome.

iv. **Role limitations** will be assessed at FU2, FU5, and FU7 using the SF-36 Role Limitations due to Physical Health subscale (FU2 E13-16; FU5 O4a-d).

Note: Baseline, Expansion Baseline, and FU4 do not include this subscale.

Subscale scores will be transformed into T-scores (based on population norms) for the analysis, with lower scores indicating greater role limitations.

The primary outcome will be a dichotomous variable, in which T-scores ≤ 40 (less than 1 SD below the mean) are considered clinically meaningful impairment. Continuous T-score variables will also be considered in secondary analyses.

Sensitivity analyses for Aim 1c will adjust for FU2 role limitations, with FU5/FU7 role limitations as the primary outcome.

c. Predictor Variables: Emotional Distress (Aims 1 and 2)

i. **Depressive symptoms** will be assessed at Baseline/Expansion Baseline, FU2, FU4, FU5, and FU7 (when data are available) using the Brief Symptom Inventory-18 (BSI-18) Depression subscale (Baseline J19, 21, 22, 23, 30, 35; Expansion Baseline K4, 6, 7, 8, 13, 18; FU2 G4, 6, 7, 8, 13, 18; FU4 L4, 6, 7, 8, 13, 18; FU5 L4, 6, 7, 8, 13, 18).

Subscale scores will be transformed into T-scores (based on sex-specific population norms) for the analysis, with higher scores indicating greater depressive symptoms.[35] A dichotomous predictor variable will also be considered, with T-scores ≥63 considered clinically meaningful depression symptoms.

ii. **Anxiety symptoms** will be assessed at Baseline/Expansion Baseline, FU2, FU4, FU5, and FU7 (when data are available) using the Brief Symptom Inventory-18 (BSI-18) Anxiety subscale (Baseline J16, 20, 24, 32, 33, 34; Expansion Baseline K1, 5, 9, 15, 16, 17; FU2 G1, 5, 9, 15, 16, 17; FU4 L1, 5, 9, 15, 16, 17; FU5 L1, 5, 9, 15, 16, 17).

Subscale scores will be transformed into T-scores (based on sex-specific population norms) for the analysis, with higher scores indicating greater anxiety symptoms.[34] A dichotomous predictor variable will also be considered, with T-scores ≥63 considered clinically meaningful anxiety symptoms.

Pain symptoms will be assessed at Baseline/Expansion Baseline, FU2, FU4, FU5, and FU7 (when data are available) using the Brief Symptom Inventory-18 (BSI-18) item

"Pains in your heart or chest" (Baseline J18; Expansion Baseline K3; FU2 G3; FU4 L3; FU5 L3).

Note: Because the somatization subscale is being used to characterize frailty at Baseline/Expansion Baseline, we will examine only the pain item rather than the full somatization subscale.

As a second measure, pain will also be assessed using the 2-item Medical Outcomes Study 36-Item Health Survey Questionnaire (SF-36)[36] Pain subscale, which consists of the following 2 items: (1)"How much bodily pain have you had during the past 4 weeks?" and (2) "During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?" (Baseline: Not available; Expansion Baseline: K21-22; FU2: E21-22; FU4: L21-22; FU5: O7-8).

For analyses that include the SF-36 Pain subscale, subscale scores will be transformed into T-scores (based on population norms) for the analysis, with higher scores indicating greater pain. A dichotomous outcome variable will also be considered, with T-scores ≤40 (less than 1 SD below the mean) considered clinically meaningful impairment.

d. Moderator Variables: Social Resources (Aim 2)

i. **Social functioning** will be assessed at FU2, FU5, and FU7 using the Medical Outcomes Study 36-Item Health Survey Questionnaire (SF-36)[36] Social Functioning subscale, which consists of the following 2 items: (1) "During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?" (FU2 E20; FU5 O6) and (2) "During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?" (FU2 F10; FU5 P2)

Note: Baseline, Expansion Baseline, and FU4 do not include this subscale.

Subscale scores will be transformed into T-scores (based on population norms) for the analysis, with lower scores indicating poorer social functioning. A dichotomous outcome variable will also be considered, with T-scores ≤40 (less than 1 SD below the mean) considered clinically meaningful impairment. When data are available at multiple time points, scores will be averaged across time points.

ii. **Neighborhood resources:** will be assessed at Baseline/Expansion Baseline and FU6 (or the last known follow-up) using publicly available data sources of neighborhood factors that are linked geographically to a participant's place of residence. These factors will include: (1) neighborhood socioeconomic status, assessed using the Yost SES Index; (2) access to exercise opportunities, or the percentage of individuals in a given county that have access to parks and recreational facilities; (3) access to healthy food options, or the percentage of people in a census tract that live at least 1 mile from the nearest supermarket for urban areas and at least 10 miles for rural areas; and (4) rurality, categorized as metropolitan, micropolitan, small town, or rural area based on USDA Rural-Urban Commuting Area codes.[19] If data are available at multiple time points, scores will be averaged across time points.

iii. **Marital status:** will be assessed at Baseline, Expansion Baseline, FU2, FU4, FU5, and FU7 by calculating a dichotomous variable representing individuals who are married/living with a partner as married versus those who are

single/widowed/divorced/separated/no longer living as married (Baseline L2; Expansion Baseline M3; FU2 2; FU4 M2; FU5 M2).

If data are available at multiple time points, the variable will represent whether participants were married/living with a partner at any point during the study period. Depending on the distribution of this variable across time points, the proportion of time points in which participants were married/living with a partner during the study period will also be considered.

e. Covariates

i. Age at FU5/FU7

ii. Age at diagnosis

iii. Sex

iv. Race/ethnicity (non-Hispanic white, non-Hispanic Black, Hispanic, other)

v. Treatment exposures: cranial radiation, abdominal radiation, pelvic radiation, cisplatin (≥ 600 mg/m^2), amputation, lung surgery; for radiation, maximum target dose (Gy) will be used for the brain, abdomen, and pelvis body regions.[4]

vi. Obesity (BMI ≥ 30 kg/m^2; never, former, current) at FU5/FU7[4]

vii. Heavy drinking (never, former, current) at FU5/FU7

viii. Smoking status (never, former, current) at FU5/FU7

ix. Grade 3-4 chronic condition at FU5/FU7

5. Statistical Analysis Plan:

a. Preliminary Analyses

To characterize the study sample, descriptive analyses will be conducted for the demographic and clinical variables listed in Table 1. To test for differences between survivors and siblings, t-tests will be conducted for continuous variables and chi-square tests will be conducted for dichotomous variables.

Descriptive analyses will also be performed for the psychosocial and phenotypic aging variables listed in Table 2. To test for differences between survivors and siblings across the follow-up timepoints, ANOVAs will be conducted for continuous variables and chi-square tests will be conducted for dichotomous variables.

A set of correlations will be performed to examine associations between covariates (Section 4.e.) and phenotypic aging variables, and between the emotional distress and phenotypic aging variables.

b. Aim 1: Evaluate associations between emotional distress and phenotypic aging in survivors versus sibling controls

To test Aim 1, hierarchical linear (i.e., multilevel) models will be conducted to account for the nesting of survivors and siblings within families.

First, we will conduct a set of hierarchical generalized linear models that include depression, anxiety, and pain symptoms as the predictor variables, and the dichotomous frailty, pre-frailty, cognitive impairment, physical function, and role limitations variables at FU5/FU7 as the outcome variables, accounting for covariates.

We will also conduct a secondary set of hierarchical linear models that include the continuous cognitive function, physical function, and role limitations variables at FU5/FU7 as the outcome variables, accounting for covariates.

We will examine depression, anxiety, and pain symptoms in the models as follows:

a) Participants' depression, anxiety, and pain score at Baseline/Expansion Baseline
b) Participants' highest depression, anxiety, and pain score across Baseline/Expansion Baseline, FU2, FU4, and FU5/FU7
c) Change in participants' depression, anxiety, and pain scores from Baseline/Expansion Baseline to FU5/FU7 (difference score)
d) The proportion of timepoints that participants have clinically meaningful levels of depression, anxiety, and pain (T-scores ≥63 or >40) across Baseline/Expansion Baseline, FU2, FU4, and FU5/FU7.

   Note: The proportion will be calculated by dividing the number of timepoints that participants have clinically meaningful levels of depression, anxiety, and pain divided by the number of timepoints that participants have data available. A dichotomous variable representing whether participants had clinically elevated symptoms during at least one timepoint will also be considered, depending on the distribution.

The models will also include interaction terms between depression, anxiety, and pain and case status (survivors vs. siblings) to examine potential differences between survivors and siblings. However, considering the potentially low rates of frailty and impairments in cognitive and physical function and role limitations in siblings (i.e., limited power to detect interactions involving case status), logistic and linear regression models will also be used to examine associations between emotional distress and phenotypic aging separately in survivors and siblings.

Sensitivity analyses will adjust for phenotypic aging variables at Baseline/Expansion Baseline (frailty) or FU2 (cognitive function, physical function, role limitations).

c. Aim 2: Evaluate social resources as moderators of the associations between emotional distress and phenotypic aging in survivors versus sibling controls

To test Aim 2, hierarchical generalized linear (i.e., multilevel) models will also be conducted.

Similarly, we will conduct a set of hierarchical generalized linear models to examine interactions between depression, anxiety, and pain symptoms and social resources (social functioning, neighborhood resources, marital status) on phenotypic aging, accounting for covariates. We will also conduct a secondary set of hierarchical linear models that include the continuous cognitive function, physical function, and role limitations variables at FU5/FU7 as the outcome variables, accounting for covariates.

These models will also include interaction terms between depression, anxiety, and pain symptoms, social resource variables, and case status (survivors vs. siblings) to examine potential differences between survivors and siblings. However, considering the potentially low rates of

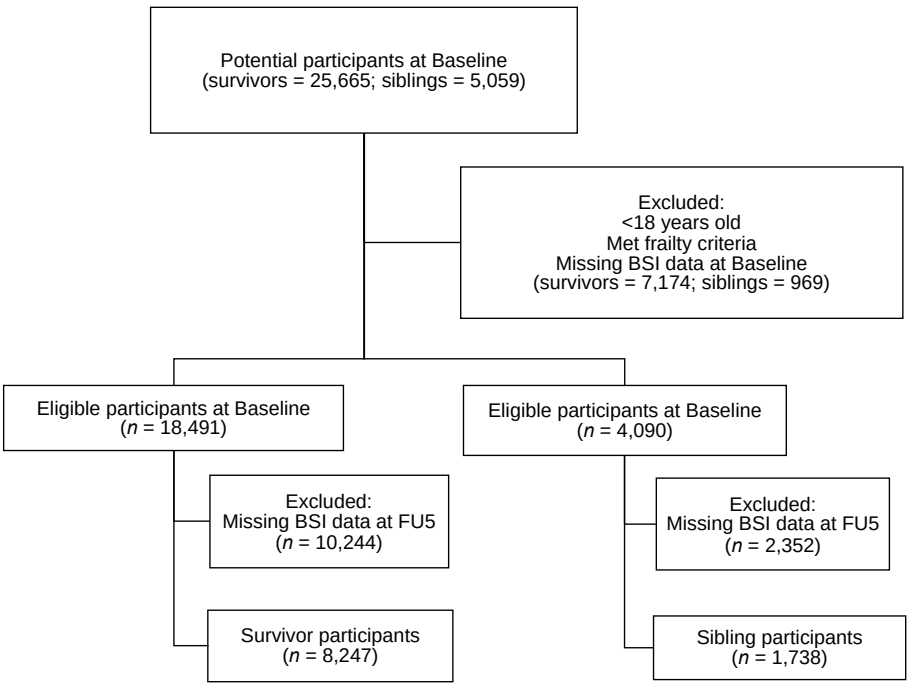
frailty and impairments in cognitive and physical function and role limitations in siblings (i.e., limited power to detect interactions involving case status), logistic and linear regression models will also be used to examine associations between emotional distress, social resources, and phenotypic aging separately in survivors and siblings.

Sensitivity analyses will adjust for phenotypic aging variables at Baseline/Expansion Baseline (frailty) or FU2 (cognitive function, physical function, role limitations).

Figure 1. CONSORT Diagram for the Childhood Cancer Survivor Study (CCSS).

CONSORT diagram showing the sample of childhood cancer survivors and siblings for (a) Aim 1a and (b) Aim 1b analyses. Participants were excluded if they were younger than 18 years of age at Baseline, met criteria for frailty at baseline (Aim 1a) or cognitive impairment at FU2 (Aim 1b), or were missing BSI data at FU2 or FU5.

(a)



(b)

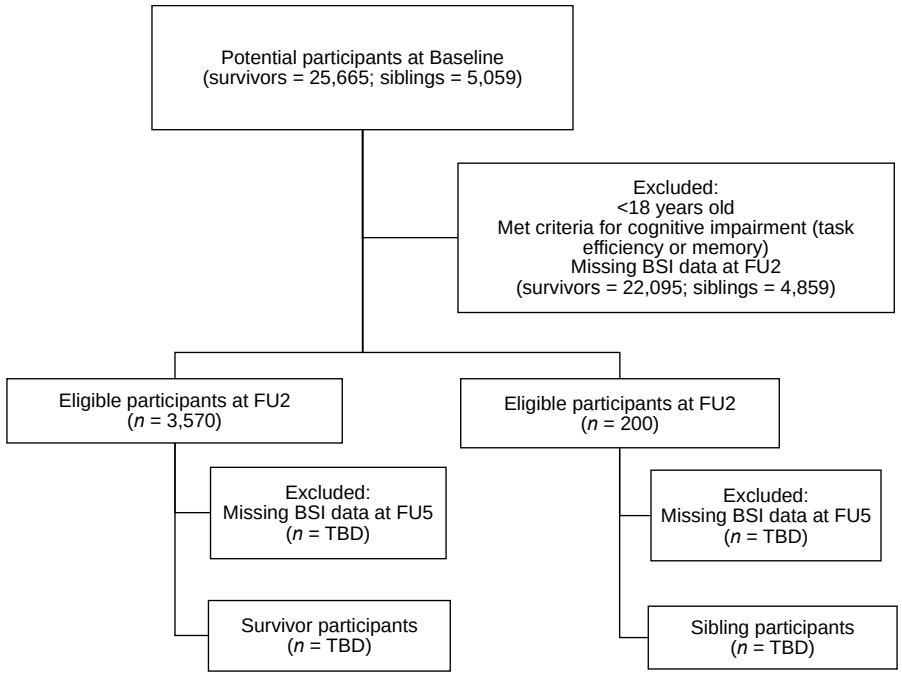


Table 1. Demographic and clinical characteristics of childhood cancer survivors and siblings			
Characteristic	Childhood cancer survivors (n = ###)	Siblings (n = ###)	p-value
Age at Diagnosis, *M (SD)*			
Age at FU5/FU7, *M (SD)*			
Sex, *n* (%)			
Female			
Male			
Race/ethnicity, *n* (%)			
Non-Hispanic white			
Non-Hispanic Black			
Hispanic			
Other			
Employment status, *n* (%)			
Employed			
Unemployed or looking for job			
Student or retired			
Not specified			
Education, *n* (%)			
Less than high school			
High school graduate			
College graduate			
Post-graduate			
Not specified			
Health insurance, *n* (%)			
Yes			
No			
Obesity at FU5/FU7 (BMI $\geq$ 30 kg/m^2), *n* (%)			
Never			
Former			
Current			
Heavy drinking at FU5/FU7, *n* (%)			

Never			
Former			
Current			
Smoking status at FU5/FU7, *n* (%)			
Never			
Former			
Current			
Grade 3-4 chronic condition at FU5/FU7			
Cancer diagnosis, *n* (%)			
Treatment exposures, *n* (%)			
Cranial radiation			
Abdominal radiation			
Pelvic radiation			
Amputation			
Lung surgery			

Table 2. Psychosocial and phenotypic aging variables in childhood cancer survivors and siblings.								
	Baseline/Expansion		Follow-up 2		Follow-up 4		Follow-up 5/7	
Variable	Survivors (*n* = ####)	Siblings (*n* = ####)	Survivors (*n* = ####)	Siblings (*n* = ####)	Survivors (*n* = ####)	Siblings (*n* = ####)	Survivors (*n* = ####)	Siblings (*n* = ####)
Emotional distress								
BSI Depression symptoms, *M (SD)*								
BSI Anxiety symptoms, *M (SD)*								
BSI Pain symptoms, *M (SD)*								
Social functioning								
SF-36 Social functioning, *M (SD)*								
Neighborhood resources, *M (SD)*								
Marital status, *n* (%)								
Married or living as married								
Non-married								
Phenotypic aging								
Frailty, *n* (%)								
Robust/Non-frail					-	-		
Pre-frail					-	-		
Frail					-	-		
Cognitive function								
Task efficiency, *M (SD)*					-	-		
Memory, *M (SD)*					-	-		
SF-36 Physical function, *M (SD)*					-	-		
SF-36 Role limitations, *M (SD)*					-	-		

Table 3. Hierarchical generalized linear models with interactions between emotional distress, social resources, and case status (survivors vs. siblings) predicting frailty and pre-frailty				
	Frailty (≥ 3 criteria)		Pre-frailty (≥ 2 criteria)	
Models	*Coeff* (95% CI)	*p*-value	*Coeff* (95% CI)	*p*-value
1. Depression				
Case status				
Depression*Case status				
2. Depression				
Case status				
Social functioning				
Depression*Case status				
Depression*Social functioning				
Case status*Social functioning				
Depression*Social functioning*Case status				
3. Depression				
Case status				
Neighborhood resources				
Depression*Case status				
Depression*Neighborhood resources				
Case status*Neighborhood resources				
Depression*Neighborhood resources*Case status				
4. Depression				
Case status				
Marital status				
Depression*Case status				
Depression*Marital status				
Case status*Marital status				
Depression*Marital status*Case status				
5. Anxiety				
Case status				
Anxiety*Case status				
6. Anxiety				

Case status				
Social functioning				
Anxiety*Case status				
Anxiety*Social functioning				
Case status*Social functioning				
Anxiety*Social functioning*Case status				
7. Anxiety				
Case status				
Neighborhood resources				
Anxiety*Case status				
Anxiety*Neighborhood resources				
Case status*Neighborhood resources				
Anxiety*Neighborhood resources*Case status				
8. Anxiety				
Case status				
Marital status				
Anxiety*Case status				
Anxiety*Marital status				
Case status*Marital status				
Anxiety*Marital status*Case status				
9. Pain				
Case status				
Pain*Case status				
10. Pain				
Case status				
Social functioning				
Pain*Case status				
Pain*Social functioning				
Case status*Social functioning				
Pain*Social functioning*Case status				
11. Pain				

Case status				
Neighborhood resources				
Pain*Case status				
Pain*Neighborhood resources				
Case status*Neighborhood resources				
Pain*Neighborhood resources*Case status				
12. Pain				
Case status				
Marital status				
Pain*Case status				
Pain*Marital status				
Case status*Marital status				
Pain*Marital status*Case status				

Table 4. Hierarchical generalized linear models with interactions between emotional distress, social resources, and case status (survivors vs. siblings) predicting cognitive impairments in task efficiency and memory				
	Impairment in task efficiency		Impairment in memory	
Models	*Coeff* (95% CI)	*p*-value	*Coeff* (95% CI)	*p*-value
1. Depression				
Case status				
Depression*Case status				
2. Depression				
Case status				
Social functioning				
Depression*Case status				
Depression*Social functioning				
Case status*Social functioning				
Depression*Social functioning*Case status				
3. Depression				
Case status				
Neighborhood resources				
Depression*Case status				
Depression*Neighborhood resources				
Case status*Neighborhood resources				
Depression*Neighborhood resources*Case status				
4. Depression				
Case status				
Marital status				
Depression*Case status				
Depression*Marital status				
Case status*Marital status				
Depression*Marital status*Case status				
5. Anxiety				
Case status				
Anxiety*Case status				

6. Anxiety				
Case status				
Social functioning				
Anxiety*Case status				
Anxiety*Social functioning				
Case status*Social functioning				
Anxiety*Social functioning*Case status				
7. Anxiety				
Case status				
Neighborhood resources				
Anxiety*Case status				
Anxiety*Neighborhood resources				
Case status*Neighborhood resources				
Anxiety*Neighborhood resources*Case status				
8. Anxiety				
Case status				
Marital status				
Anxiety*Case status				
Anxiety*Marital status				
Case status*Marital status				
Anxiety*Marital status*Case status				
9. Pain				
Case status				
Pain*Case status				
10. Pain				
Case status				
Social functioning				
Pain*Case status				
Pain*Social functioning				
Case status*Social functioning				
Pain*Social functioning*Case status				

11. Pain				
Case status				
Neighborhood resources				
Pain*Case status				
Pain*Neighborhood resources				
Case status*Neighborhood resources				
Pain*Neighborhood resources*Case status				
12. Pain				
Case status				
Marital status				
Pain*Case status				
Pain*Marital status				
Case status*Marital status				
Pain*Marital status*Case status				

Table 5. Hierarchical generalized linear models with interactions between emotional distress, social resources, and case status (survivors vs. siblings) predicting impairment in physical function and role limitations				
	Impairment in physical function		Impairment in role limitations	
Models	*Coeff* (95% CI)	*p*-value	*Coeff* (95% CI)	*p*-value
1. Depression				
Case status				
Depression*Case status				
2. Depression				
Case status				
Social functioning				
Depression*Case status				
Depression*Social functioning				
Case status*Social functioning				
Depression*Social functioning*Case status				
3. Depression				
Case status				
Neighborhood resources				
Depression*Case status				
Depression*Neighborhood resources				
Case status*Neighborhood resources				
Depression*Neighborhood resources*Case status				
4. Depression				
Case status				
Marital status				
Depression*Case status				
Depression*Marital status				
Case status*Marital status				
Depression*Marital status*Case status				
5. Anxiety				
Case status				
Anxiety*Case status				

6. Anxiety				
Case status				
Social functioning				
Anxiety*Case status				
Anxiety*Social functioning				
Case status*Social functioning				
Anxiety*Social functioning*Case status				
7. Anxiety				
Case status				
Neighborhood resources				
Anxiety*Case status				
Anxiety*Neighborhood resources				
Case status*Neighborhood resources				
Anxiety*Neighborhood resources*Case status				
8. Anxiety				
Case status				
Marital status				
Anxiety*Case status				
Anxiety*Marital status				
Case status*Marital status				
Anxiety*Marital status*Case status				
9. Pain				
Case status				
Pain*Case status				
10. Pain				
Case status				
Social functioning				
Pain*Case status				
Pain*Social functioning				
Case status*Social functioning				
Pain*Social functioning*Case status				

11. Pain				
Case status				
Neighborhood resources				
Pain*Case status				
Pain*Neighborhood resources				
Case status*Neighborhood resources				
Pain*Neighborhood resources*Case status				
12. Pain				
Case status				
Marital status				
Pain*Case status				
Pain*Marital status				
Case status*Marital status				
Pain*Marital status*Case status				

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