I. Study Title: Does Sex Mediate the Association Between Treatment Exposures and Functional Outcomes?

II. Working Group and Investigators:
Primary: Psychology
Secondary: Biostatistics, Chronic Disease

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III. Background and Rationale:

An extensive literature on brain and behavior has documented sex differences in cognition, affect, and structural and functional neuroimaging[1]. Sexual dimorphism in humans is thought to be influenced by both genetic and endocrine factors, similar to other mammalian species. Exposure to sex hormones during critical periods in prenatal or pubertal development impacts the development and functions of neural circuitry[2]. These organizational effects of sex hormones include the transient rise in testosterone during prenatal or early postnatal development that masculinizes and defeminizes neural circuits in males, while the absence of testosterone in females results in development of a female neural phenotype[3-4]. Upon gonadal maturation during puberty, testicular and ovarian hormones act on previously sexually differentiated circuits to facilitate expression of sex-typical behaviors[5].

Sex hormones may also influence changes in brain development. Human neuroimaging studies reveal a linear increase in white matter volume during adolescence, with greater rate of change and larger overall volume of the cerebrum, hippocampus, and amygdala in males compared to females[6-11]. The increase in white matter volume in males has been linked to testosterone and androgen receptor activity[12]. Structural brain MRI studies have also found a negative correlation between estradiol level and age-corrected gray matter volume in adolescent females[13-14].

Many neurodevelopmental, neuropsychiatric, and psychological disorders also show an uneven sex distribution in regard to their prevalence, age at onset, and treatment response[15]. Within the field of pediatric oncology, researchers have identified sex differences across cancer diagnoses and outcomes[16-17]. With respect to cancer type, males are at greater risk for developing Hodgkin's and Non-Hodgkin's lymphomas, acute lymphoblastic leukemia (ALL),

and ependymomas, whereas females have a higher incidence of thyroid carcinomas and malignant melanomas[18-21]. With respect to outcomes, females are at increased risk for developing chronic health conditions and impaired health status[16; 22-23] as well as neurocognitive deficits and emotional distress[34-35]. Females are thought to be particularly vulnerable to CNS-directed therapy relative to males. Male neurodevelopment may serve as a protective factor, as males shows greater white matter volume increases in childhood secondary to hormone activity relative to females[36]. As such, females may be more sensitive to CNS-directed therapy, which directly impacts their relatively lower white matter volume. Similarly, younger age at diagnosis is associated with poorer outcomes[37], raising the interesting possibility that cancer and/or cancer treatments during critical developmental periods alter hormone activity and brain development, resulting in neurocognitive and psychological sequelae.

While sex differences in pediatric oncology have been well-documented, our understanding of the association between sex and neurocognitive and psychosocial outcomes in cancer survivors is less known. To our knowledge, no large-scale study has directly examined the role of sex on neurocognitive, psychological, and quality of life outcomes in long-term survivors of childhood cancers.

IV. Specific Aims/Objectives/Hypotheses:

With better understanding of the sex differences in long-term survivors of pediatric cancer, clinicians can tailor therapies and follow-up interventions to ensure that quality of life is maximized. Therefore, the purpose of this study is three-fold:

Aim 1a: To examine sex differences in neurocognitive, emotional, and quality of life outcomes and impairment rates between survivors and same-sex siblings, as measured by the NCQ, BSI-18, and SF-36.

Hypothesis: Differences between female survivors and female siblings will be larger than differences between male survivors and male siblings for neurocognitive problems, emotional distress, and quality of life.

Aim 1b. To evaluate sex differences in neurocognitive, emotional, and quality of life outcomes and impairment rates among survivors.

Hypothesis: Because white and gray matter development vary by sex[38] and female sex is a risk factor for cancer-related cognitive impairment in pediatric cancer survivors[39], there may be different critical developmental periods during which the male/female brain is more susceptible to injury due to cancer and cancer treatment. It is hypothesized that younger females at time of diagnosis will report worse or greater impairment in neurocognitive function, emotional distress and quality of life compared to same-aged males at time of diagnosis.

Aim 2: To identify demographic and treatment factors associated with neurocognitive, emotional and quality of life outcomes and impairment rates in survivors stratified by sex.

Hypothesis 1: Younger age at diagnosis, longer time since diagnosis, CNS radiation exposure, chemotherapy exposures, history of transplant or amputation, relapse or second malignancies, and/or greater number of moderate to severe chronic health conditions (CHCs) affecting cardiovascular, pulmonary, or endocrine functions (i.e., grades 2-4 CHCs as defined by the National Cancer Institute's Common Terminology Criteria for

Adverse Events[40-42]) will predict worse neurocognitive, emotional, and quality of life outcomes in females compared to males.

Hypothesis 2: History of psychoactive medication usage[43] (i.e., anxiolytics, analgesics, or antidepressants), lower educational attainment, unpartnered relationship status, lack of employment, will be associated with greater neurocognitive and emotional difficulties in females as compared to males.

V. Analysis Framework:

Participants:

Survivors and siblings from the original and expansion cohorts who completed the NCQ, SF-36, or BSI-18 will be included in this analysis. Demographic information of survivors and siblings is provided in Table 1. Mean NCQ, BSI-18, and SF-36 scores for male and female survivors and siblings are provided in Table 2.

Measures:

Dependent variables

- CCSS-NCQ
    - Raw scores (NB for the analyst - not the T-scores in the frozen database, as these were generated for survivors by comparing to the general sibling group and are not sex stratified)
        - Composite task efficiency, emotion regulation, organization, memory
        - FU2 J.1-25 (original cohort); FU5 Q.1-33 (expansion cohort; NB please use the 25 items that are the same as those in the original NCQ and not the additional items in the revised NCQ), survivor and sibling cohorts
    - Impairment (yes/no)
        - Impaired = symptom level reported in top 10% of the sex stratified sibling sample on the following domains: Composite, task efficiency, emotion regulation, organization, and memory.
- SF-36
    - Raw score and T-scores
        - Physical functioning, role limitations due to health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, general health
        - FU2 (original cohort); FU5 (expansion cohort); survivors and siblings
    - Impairment
        - Impaired = symptom T score ≤ 40 compared to normative data on the 8 domains (Physical functioning, role limitations due to health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, general health)
- BSI-18
    - T-scores using sex-specific norms
        - Composite (GSI), somatization, depression, anxiety
        - FU2 survivors and siblings (original cohort)

        - FU5 survivors and siblings (expansion cohort)
    - Impairment (yes/no)
        - Impaired = T-scores ≥ 63 on the GSI or at least 2 of the 3 subscales (somatization, depression, anxiety)

- Educational attainment:
    - Original cohort FU2 survivors and siblings, item 12
    - Expansion cohort FU5 survivors and siblings, A4

- Marital/Relationship status:
    - Original cohort FU2, survivors and siblings, item 2
    - Expansion cohort, FU5 survivors and siblings M2

- Employment status:
    - Original cohort, survivors and siblings FU2, item 4
    - Expansion cohort, survivors and siblings FU5, A5

- Medications—history of analgesics, antidepressants, or anxiolytic medications:
    - Original cohort Baseline survivors B.9, B.15
    - Original cohort Baseline siblings B.9, B.15
    - Original cohort FU2 survivors Q8, Q9
    - Original cohort FU2 siblings Q8, Q9
    - Expansion cohort baseline B.9-B.10
    - Expansion sibling baseline B.9-B.10
    - Expansion cohort FU5 survivors C2.9, C2.11
    - Expansion cohort FU5 siblings C2.9, C2.11

Covariates:

- Health behaviors
    - Tobacco use (yes/no):
        - FU2 survivors
        - FU2 siblings
        - FU5 survivors N9
        - FU5 siblings N9
    - Physical activity: yes/no (i.e., meeting CDC guideline of at least 75 mins of vigorous or >150 mins moderate per week; if <75 vigorous and <150 moderate – count vigorous minutes toward moderate total):
        - FU2 D.2-D.7; FU5 N.16-N.21

- Disease variables
    - Age at diagnosis
    - Time since diagnosis
    - Medical conditions
        - Chronic health conditions (number of moderate to severe CTCAE health conditions)

- Relevant CHCs include cardiovascular, pulmonary, endocrine, neurological exceptive cognitive, hematological, secondary malignancy.

- Treatment variables
  - Radiation (dose) for cranial, chest, abdomen, pelvis
  - Chemotherapy: antimetabolites (dose), anthracyclines (dose), alkylating agents (dose), corticosteroids (yes/no)
  - Bone marrow transplant (yes/no)
  - Amputation (yes/no)
  - Relapse/SMN (yes/no)

- Sociodemographic variables
  - Age:
    - A.1 Date of birth original, expanded, and sibling baseline and date of survey front cover
  - Race:
    - Baseline original A.4
    - Baseline sibling A.4
    - Expanded cohort baseline A.5
    - Expanded sibling baseline A.5

Analyses:

- Descriptive statistics will be used to characterize the study population for all variables of interest, and comparisons between survivors and siblings will be made using t-tests and chi-square tests as appropriate. Table 1 will show frequencies and percentages for categorical variables and means and SD for continuous variables.
- Table 2 will show mean scores and impairment rates for NCQ, BSI, and SF-36 measures for males and females within each group.

Aim 1: To examine differences in neurocognitive, emotional, and quality of life outcomes between survivors and same-sex siblings (Aim 1a) and sex differences among survivors (Aim 1b), separate linear and logistic regressions will be performed for each outcome (Tables 3-4), adjusting for age:

- Predictors: Sex (male, female); Group (survivors, siblings)
- Outcomes:
  - NCQ T-scores and impairment rates at FU2 (original cohort) and FU 5 (expansion cohort) for composite, task efficiency, emotion regulation, organization, memory
  - BSI-18 T-scores and impairment rates at FU 2 (original cohort) and FU 5 (expansion cohort) for Anxiety, Depression, Somatization subscales. Impairment will be defined as GSI or 2+ subscales T-scores ≥ 63.
  - SF-36 T-scores and impairment rates at FU 2 (original cohort) and FU 5 (expansion cohort) for physical functioning, role limitations due to health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, general health

Aim 2: To identify demographic and treatment factors associated with neurocognitive, emotional and quality of life outcomes in survivors by sex, we will perform linear and logistic regressions stratified by sex (Tables 5-8), adjusting for age.

Of note, age at diagnosis, CNS radiation, disease, chemotherapies, and CHC's are all predictors of neurocognitive outcomes. However, in a developmental model, educational attainment, social relationships, employment and psychoactive medication use is a consequence of neurocognitive and emotional deficits. Also, some of these are pathway processes, so they will need to be examined separately. Therefore, two analyses will be conducted, one with neurocognitive, emotional and quality of life variables as outcomes, and the other with these variables as predictors.

Model 1: age at diagnosis and cancer diagnosis predicting neurocognitive, emotional and quality of life outcomes, adjusting for age.

Model 2: age at diagnosis and treatment exposures (i.e., radiation, chemotherapy) predicting neurocognitive, emotional and quality of life outcomes, adjusting for age

Model 3: Current age and CHCs predicting neurocognitive, emotional and quality of life outcomes, adjusting for age

Model 4: Neurocognitive and emotional outcomes predicting educational attainment, employment, relationship status outcomes

- Predictors:
    - Younger age at diagnosis (age will be analyzed as a categorical variable (<1 year, 1-4 years, 5-9 years, 10-14 years, 15-20 years) to see if there is a critical developmental period in relation to sex differences)
    - Radiation (cranial, non-cranial, none)
    - Chemotherapy exposures (y/n: anthracyclines; alkylating agents; antimetabolites; corticosteroids)
    - Number of grade 3-4 chronic health conditions
    - Brain tumor diagnosis
    - History of transplant or amputation.

To evaluate whether sex moderates the relationship between significant variables identified from Aim 2 and NCQ, BSI, and SF-36 responses. A moderation analysis will be performed similar to those conducted previously in CCSS (e.g., Armstrong NEJM paper, Turcotte JAMA paper) (Table 9).

- Predictors: The significant variables from Aim 2
- Moderator: Sex
- Outcomes: NCQ, BSI, SF-36

Figures/Tables:

Table 1. Demographic and clinical characteristics of survivors of childhood cancer and sibling groups.

Characteristics	Survivors			Siblings		
	Males N (%)	Females N (%)	p	Males n N (%)	Females N (%)	p
Race						
White						
Black						
Other						
Ethnicity						
Hispanic						
Non-Hispanic						
Age at baseline survey						
18-29 yrs						
30-39 yrs						
40-54 yrs						
Education						
1-8 years						
9-12 years						
Completed high school/GED						
Training after HS other than college						
Some college						
College graduate						
Post-graduate level						
Current tobacco use						
Yes						
Current physical activity meeting CDC guidelines						
Yes						
Physically Active (% meeting CDC guidelines)						
Yes						
Employment status						
Working full-time						
Working part-time						
Not seeking paid work						
Unemployed						
Retired						
Student						
Relationship status						
Single						
Married/living as married						

Widowed						
Divorced						
Separated						
Age at diagnosis						
< 1 yr						
1-4 yrs						
5-9 yrs						
10-14 yrs						
15-20 yrs						
Cancer diagnosis						
Leukemia						
CNS malignancy						
Hodgkin lymphoma						
Non-Hodgkin lymphoma						
Kidney tumors						
Neuroblastomas						
Soft tissue sarcoma						
Bone tumors						
Chemotherapy						
Antimetabolites						
Anthracyclines						
Alkylating agents						
Corticosteroids						
Radiation treatment						
Cranial						
Non-cranial						
None						
Chronic health conditions						
Psychoactive medication use						
Clinically significant psychiatric symptomatology[1]						
Yes						

[1] (GSI or at least two BSI subscales > 63)

Table 2. Reported neurocognitive problems, emotional distress, and quality of life and impairment rates in survivor and sibling groups, by sex.

	Mean T-Score[1] (SD)				Impairment rate (%)		
	Males		Females		Males		Fem
	Siblings	Survivors	Siblings	Survivors	Siblings	Survivors	Survivors
NCQ							
Composite							
Task Efficiency							
Emotion Regulation							

Organization							
Memory							
BSI-18							
GSI							
Depression							
Anxiety							
Somatization							
SF-36							
Physical Functioning							
Health role limitations							
Emotional role limitations							
Energy/Fatigue							
Emotional well-being							
Social functioning							
Pain							
General Health							

[1] T scores based on data from same-sex siblings

Table 3. Multivariate regressions exploring associations between sex and self-reported neurocognitive, emotional, and QOL functioning in survivors and siblings, adjusted for age.

	Males					**Females**						
	Survivors	**Siblings**				**Survivors**	**Siblings**					
	β (SE)	*β (SE)*	*Mean Difference*	*95% CI*	*p*[a]	*β (SE)*	*β (SE)*	*Mean Difference*	*95% CI*	*p*[a]	*Difference of Differences*	*p*[b]
NCQ												
Composite												
Task Efficiency												
Emotional Regulation												
Organization												
Memory												
BSI-18												
GSI												
Depression												
Anxiety												
Somatization												
SF-36												
Physical functioning												
Health role limitations												
Emotional role												

limitations												
Energy/Fatigue												
Emotional well-being												
Social functioning												
Pain												
General Health												

[a] These are p values from comparing survivors with same-sex siblings.
[b] These are p values from comparing the survivor-sibling differences between the sexes.

Table 4. Logistic regressions exploring associations between sex and impairment rates in self-reported neurocognitive, emotional, and QOL functioning in survivors, relative to siblings, adjusted for age.

	Males		**Females**		
	OR (95% CI)	*p*	*OR (95% CI)*	*p*	*Diffe M*
NCQ					
Task Efficiency					
Emotional Regulation					
Organization					
Memory					
BSI-18					
GSI					
Depression					
Anxiety					
Somatization					
SF-36					
Physical functioning					
Health role limitations					
Emotional role limitations					
Energy/Fatigue					
Emotional well-being					
Social functioning					
Pain					
General Health					

[a] These are p values from comparing the differences between survivors by sex.

Note. For Tables 5-8, we will run separate models to examine potential effects of cancer diagnosis and treatment exposures with age at diagnosis. We will also run separate models to examine effects of age at survey and CHCs on outcomes.

Table 5a. Logistic regression exploring medical and demographic variables associated with cognitive impairment in cancer survivors stratified by sex, relative to siblings.

	Males															Females													
	COMP			TE			ER			ORG			MEM			COMP			TE			ER			ORG			MEM		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Race																														
White																														
Black brif																														
Other																														
Ethnicity																														
Hispanic																														
Other																														
Age at baseline																														
18-29																														
30-39																														
40-54																														
Current tobacco use																														
Yes																														
Physically Active (meeting CDC guidelines)																														
Yes																														
Age at dx																														
<1 yr																														
1-4 yrs																														
5-9 yrs																														
10-14 yrs																														
15-15 yrs																														
Cancer dx																														
Leukemia																														
CNS malignancy																														
Hodgkin lymphoma																														
Non-Hodgkin lymphoma																														
Kidney tumor																														
Neuroblastoma																														
Soft tissue sarcoma																														
Bone tumor																														
Chemotherapy																														
Antimetabolites																														
Anthracyclines																														
Alkylating agents																														
Corticosteroids																														
Radiation tx																														
Cranial																														

Non-cranial																														
None																														
Psychoactive medication usage																														
Yes																														
# of grade 3-4 CHC																														
0																														
1																														
>1																														
Cancer dx (Model 2, includes the same covariates as above except cancer treatment)																														
Leukemia																														
CNS malignancy																														
Hodgkin lymphoma																														
Non-Hodgkin lymphoma																														
Kidney tumor																														
Neuroblastoma																														
Soft tissue sarcoma																														
Bone tumor																														

Table 5b. Multivariate regression exploring medical and demographic variables associated with cognitive symptoms in cancer survivors and siblings, stratified by sex. Data are beta coefficients, standard errors in parentheses.

	COMP			**TE**			**ER**			**ORG**			**MEM**			**COMP**			**TE**			**ER**			**ORG**			**MEM**		
	Survivors	Sibs	p	Survivors	Sibs	p	Survivors	Sibs	p	Survivors	Sibs	p	Survivors	Sibs	p	Survivors	Sibs	p	Survivors	Sibs	p	Survivors	Sibs	p	Survivors	Sibs	p	Survivors	Sibs	p
Race																														
White																														
Black																														
Other																														
Ethnicity																														
Hispanic																														
Other																														
Age at baseline																														
18-29																														
30-39																														
40-54																														
Current tobacco use																														
Yes vs no																														
Physically Active (meeting CDC guidelines)																														
Yes vs no																														
Age at dx																														
<1 yr																														
1-4 yrs																														
5-9 yrs																														
10-14 yrs																														
15-15 yrs																														
Chemotherapy																														
Antimetabolites																														

Anthracyclines																															
Alkylating agents																															
Corticosteroids																															
Radiation tx																															
Cranial																															
Non-cranial																															
None																															
Psychoactive medication usage																															
Yes vs no																															
# of grade 3-4 CHCs																															
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Cancer dx (Model 2; includes same covariates as above except cancer treatment)																															
Leukemia																															
CNS malignancy																															
Hodgkin lymphoma																															
Non-Hodgkin lymphoma																															
Kidney tumor																															
Neuroblastoma																															
Soft tissue sarcoma																															
Bone tumor																															

Table 6a. Logistic regression exploring medical and demographic variables associated with significant emotional distress in cancer survivors stratified by sex relative to siblings.

	Males												**Females**											
	GSI			**Depression**			**Anxiety**			**Somatization**			**GSI**			**Depression**			**Anxiety**			**Somatization**		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Race																								
White																								
Black																								
Other																								
Ethnicity																								
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Other																									
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40-54																									
Current Tobacco Use																									
Yes																									
Physical activity (meeting CDC guidelines)																									
Yes																									
Age at dx																									
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1-4 yrs																									
5-9 yrs																									
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15-20 yrs																									
Cancer dx																									
Leukemia																									
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Hodgkin lymphoma																									
Non-Hodgkin lymphoma																									
Kidney tumor																									
Neuroblastoma																									
Soft tissue sarcoma																									
Bone tumor																									
Chemotherapy																									
Antimetabolites																									
Anthracyclines																									
Alkylating agents																									
Corticosteroids																									
Radiation treatment																									
Cranial																									
Non-cranial																									
None																									

Psychoactive medication usage																								
Yes or no																								
# of grade 3-4 CHC																								
0																								
1																								
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Table 6b. Multivariable regression exploring medical and demographic variables associated with significant emotional distress in cancer survivors stratified by sex relative to siblings.

	Males										**Females**									
	GSI			**Depression**			**Anxiety**		**SOM**		**GSI**		**Depression**			**Anxiety**			**SOM**	
	Survivors	Sibs		Survivors	Siblings		Survivors	Siblings	Survivors	Siblings	Survivors	Siblings	Survivors	Siblings		Survivors	Siblings		Survivors	Siblings
	B (SE)	B (SE)	p	B (SE)	B (SE)	p	B (SE)	B (SE)	p	B (SE)	B (SE)	B (SE)	p	B (SE)	B (SE)	p	B (SE)	B (SE)	p	B (SE)	B (SE)	p
Race																						
White																						
Black																						
Other																						
Ethnicity																						
Hispanic																						
Other																						
Age at baseline																						
18-29																						
30-39																						
40-54																						
Current Tobacco Use																						
Yes vs no																						
Physical activity (meeting CDC guidelines)																						
Yes vs no																						
Age at dx																						
<1 yr																						
1-4 yrs																						
5-9 yrs																						
10-14 yrs																						

15-20 yrs									
Chemotherapy									
Antimetabolites									
Anthracyclines									
Alkylating agents									
Corticosteroids									
Cancer Diagnosis									
Leukemia									
CNS									
Hodgkin Lymphoma									
Non-Hodgkin lymphoma									
Kidney tumor									
Neuroblastoma									
Soft tissue sarcoma									
Bone tumor									
Radiation treatment									
Cranial									
Non-cranial									
None									
Psychoactive medication use									
Yes vs no									
# of grade 3-4 CHCs									
0									
1									
>1									

Table 7a. Logistic regression exploring medical and demographic variables associated with impaired quality of life in cancer survivors stratified by sex relative to siblings.

	Males																**Females**													
	Physical fx		Health role limitations		Emotional role limitations		Energy		Emotional well-being		Social		Pain		General health		Physical fx		Health role limitations		Emotional role limitations		Energy		Emotional well-being		Social		Pai	
	OR (95% CI)	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*O (9 C*	
Race																														

White																														
Black																														
Other																														
Ethnicity																														
Hispanic																														
Other																														
Age at baseline																														
18-29																														
30-39																														
40-54																														
Current tobacco use																														
Yes																														
Physical activity (meeting CDC guidelines)																														
Yes																														
Age at dx																														
<1 yr																														
1-4 yrs																														
5-9 yrs																														
10-14 yrs																														
15-20 yrs																														
Cancer dx																														
Leukemia																														
CNS malignancy																														
Hodgkin lymphoma																														
Non-Hodgkin lymphoma																														
Kidney tumor																														
Neuroblastoma																														
Soft tissue sarcoma																														
Bone tumor																														
Chemotherapy																														
Antimetabolites																														
Anthracyclines																														
Alkylating agents																														
Corticosteroids																														
Radiation treatment																														
Cranial																														
Non-cranial																														
None																														
Psychoactive medication usage																														
Yes																														
# of grade 3-4 CHCs																														
0																														
1																														

>1																													

Table 7b. Multivariable regression exploring medical and demographic variables associated with impaired quality of life in cancer survivors stratified by sex relative to siblings.

	Males																					Females																				
	PF			HEA			EMO			ENE			SOC			Pain			GH			PF			HEA			EMO			ENE			SOC			Pain			GH		
	Sur	Sibs		Sur	Sibs		Sur	Sibs		Sur	Sibs		Sur	Sibs		Sur	Sibs		Sur	Sibs		Sur	Sibs		Sur	Sibs		Sur	Sibs		Sur	Sibs		Sur	Sibs		Sur	Sibs		Sur	Sibs	
	β (SE)	*β (SE*	*p*	*β (SE)*	*β (SE*	*p*	*β (SE)*	*β (SE*	*p*	*β (SE)*	*β (SE*	*p*	*β (SE)*	*β (SE*	*p*	*β (SE)*	*β (SE*	*p*	*β (SE)*	*β (SE*	*p*	*β (SE)*	*β (SE*	*p*	*β (SE)*	*β (SE*	*p*	*β (SE)*	*β (SE*	*p*	*β (SE)*	*β (SE*	*p*	*β (SE)*	*β (SE*	*p*	*β (SE)*	*β (SE*	*p*	*β (SE)*	*β (SE*	*P*
Race																																										
White																																										
Black																																										
Other																																										
Ethnicity																																										
Hispanic																																										
Other																																										
Age at baseline																																										
18-29																																										
30-39																																										
40-54																																										
Current tobacco use																																										
Yes vs no																																										
Physical activity meeting CDC guidelines																																										
Yes vs no																																										
Age at dx																																										
<1 yr																																										
1-4 yrs																																										
5-9 yrs																																										
10-14 yrs																																										
15-20 yrs																																										
Cancer dx																																										
Leukemia																																										
CNS malignancy																																										

Hodgkin lymphoma																																										
Non-Hodgkin lymphoma																																										
Kidney tumor																																										
Neuroblastoma																																										
Soft tissue sarcoma																																										
Bone tumor																																										
Chemotherapy																																										
Antimetabolites																																										
Anthracyclines																																										
Alkylating agents																																										
Corticosteroids																																										
Radiation treatment																																										
Cranial																																										
Non-cranial																																										
None																																										
Psychoactive medication usage																																										
Yes vs no																																										
# of grade 3-4 CHCs																																										
0																																										
1																																										
>1																																										

Table 8a. Logistic regression exploring the relationship between education, marital status, and employment status and elevated emotional distress in survivors stratified by sex relative to siblings.

	Males	**Females**

	College graduate		Married/living as married		Employed full-time		College graduate		Married/living as married		Employed full-time	
	OR (95% CI)	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*
BSI-18												
GSI												
Depression												
Anxiety												
Somatization												

Table 8b. Logistic regression exploring the relationship between education, marital status, and employment status and poor quality of life in survivors relative to siblings, stratified by sex.

	Males						Females					
	College graduate		Married/living as married		Employed full-time		College graduate		Married/living as married		Employed full-time	
	OR (95% CI)	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*
SF-36												
Physical fx												
Emotional role limitations												
Energy												
Emotional well-being												
Social												
Pain												
General health												

Table 8c. Logistic regression exploring the relationship between education, marital status, and employment status and neurocognitive impairment in survivors relative to siblings stratified by sex.

	Males						**Females**					
	College graduate		**Married/living as married**		**Employed full-time**		**College graduate**		**Married/living as married**		**Employed full-time**	
	OR (95% CI)	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*	*OR (95% CI)*	*p*
NCQ												
Composite												
Task efficiency												
Emotional Regulation												
Organization												

Table 9. Analysis of sex as a moderator between significant demographic, disease, and treatment effects and self-reported neurocognitive, emotional, and quality of life functioning.

	Path a sig. variables → functioning without sex effect		**Path b: Sex → neurocognitive, emotional, and QOL functioning**		**Mediation path a*b**		
	β	*p*	*β*	*p*	*value*	*95% CI*	*p*
NCQ							
Composite							
Task Efficiency							
Emotion Regulation							
Organization							
Memory							
BSI-18							
GSI							
Depression							

Anxiety							
Somatization							
SF-36							
Physical functioning							
Health role limitations							
Emotional role limitations							
Energy/Fatigue							
Emotional well-being							
Social functioning							
Pain							
General Health							

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