1. STUDY TITLE: Impact of Chronic Disease on Neurocognitive and Psychosocial Functions

2. WORKING GROUP AND INVESTIGATORS:

2.1. Working Groups: Psychology; Chronic Disease

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3. BACKGROUND AND RATIONALE:

Neurocognitive and psychosocial late effects following treatment of childhood cancer are common sequelae which negatively affect survivors' quality of life. Such late effects are evident across many domains including global intellect, academic abilities, attention and executive functions, fine motor speed and dexterity, memory and learning, and mood.[1-6] In addition to these functional problems, many adult survivors of childhood malignancies develop chronic health conditions. The association between chronic health conditions and neurocognitive and psychosocial outcomes has not been investigated in the Childhood Cancer Survivor Study (CCSS) cohort.

Chronic health conditions, including coronary, pulmonary, and endrocrinological disturbances, have been identified as frequently occurring causes of morbidity in the childhood cancer survivor population.[7-11] The prevalence of having at least one chronic medical condition following treatment for childhood cancer has been found to exceed 70% within the CCSS cohort.[7, 12] The rates of grade 3 or 4 cardiac or pulmonary and Grade 3 endocrine conditions in the CCSS cohort are 3.9%, 2.9, and 7.6, respectively.[13] Survivors are at increased risk of developing a severe or life threatening condition in comparison to their siblings who have not experienced childhood cancer. The aforementioned rates reflect risk ratios of 7.5 (95% CI: 4.8-11.7), 3.1 (95% CI: 2.2-4.4), and 6 (95% CI: 4.5-7.9) for the associated cardiac, pulmonary, and endocrine chronic conditions relative to the sibling cohort.

Serious chronic health impairment has been associated with neurocognitive and psychosocial problems in non-cancer populations. Patients with chronic congestive heart failure have been reported to display significant deficits within the domains of executive function, memory, language, attention, and processing speed.[14] Cardiac patients with cognitive impairments

often experience functional impairment and poorer quality of life including fatigue, poor medication compliance, difficulty completing activities of daily living, and emotional problems.[15-17] Type II diabetes has been associated with decreases in executive functions and processing speed.[18] Patients with chronic obstructive pulmonary disease (COPD) are reported to demonstrate short and long-term memory impairments and difficulties with executive functions such as self-monitoring and attention upon neuropsychological assessment.[19] The unique contribution of chronic health conditions to neurocognitive and psychosocial impairment has not been adequately investigated in the childhood cancer literature.

The aim of this study is to assess the contribution of chronic health status to neurocognitive and psychological functions within the CCSS cohort. Neurocognitive and psychosocial functioning data were collected via the CCSS Neurocognitive Questionnaire (CCSS-NCQ) and the Brief Symptom Inventory (BSI) during the Follow-Up 2003 survey. Chronic health status was assessed as part of the initial baseline CCSS survey in 1995 as well as during the Follow-Up 2000 Survey. Previous CCSS studies have not evaluated the unique contribution of chronic health of the survivor when examining the relation between effects of cancer treatment and neurocognitive and psychosocial outcome. We propose such an investigation.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

4.1. Primary Aim:

4.1.1. To determine the association between chronic medical illness and neurocognitive and emotional functioning among adult survivors of childhood cancer.

4.2. Objectives:

4.2.1. To examine the impact of chronic medical illness on self-reported task efficiency, memory, emotional regulation, and organization skills.

4.2.2. To examine the impact of chronic medical illness on self-reported symptoms of somatization, depression and anxiety.

4.3. Hypotheses:

4.2.1. Survivors with Grade 3 or 4 cardiovascular and/or pulmonary and/or Grade 3 endocrine chronic health conditions will display increased rates of problems with task efficiency, memory, emotional regulation, and organization compared to survivors without chronic illness (Grade 0) and those with mild/moderate chronic illness (Grade 1 or 2).

4.2.2. Survivors with Grade 3 or 4 cardiovascular and/or pulmonary and/or Grade 3 endocrine chronic health problems will display increased rates of problems with somatization, depression, and anxiety compared to survivors without chronic illness (Grade 0) and those with mild/moderate chronic illness (Grade 1 or 2).

5. METHODS:

5.1. Population: Cancer survivors who completed the baseline survey, who provided sufficient baseline questionnaire data to allow determination of chronic conditions grades[7], and who were 18 or older at Follow-Up 2003 and completed both the NCQ and the BSI on

the 2003 Follow-Up Survey. Survivors who answered yes to question J3 on the Baseline survey (Mental Retardation) are not eligible.

5.2. Outcomes of interest: The primary outcomes of interest are neurocognitive functions as assessed by the NCQ domains of Task Efficiency, Emotional Regulation, Organization, and Memory and psychosocial functions as assessed with BSI scales of Somatization, Depression, and Anxiety.

- BSI (G1-G18) scores for Somatization, Depression, and Anxiety subscales as continuous outcomes.
- NCQ (J1-25) scores for Task Efficiency, Emotional Regulation, Organization, and Memory subscales as continuous outcomes.

5.3. Independent variables:

- Chronic Illness grading using NCI Common Terminology Criteria for Adverse Events for Cardiovascular, Pulmonary, and Endocrine conditions, specifically using the max grade per chronic condition in each organ category for the participant. (CCSS Late Effects Database variables any, any34, multiple)
- Cancer Diagnosis (nine categories including leukemia, CNS tumor, Hodgkin, Non-Hodgkin lymphoma, Wilms' tumor, Neuroblastoma, soft tissue sarcoma, Ewing's sarcoma, and osteosarcoma)
- Chemotherapy Variables (Data categorized as continuous or categorical variables identifying cumulative amounts: Anthracyclines, Alkylating Agents, Antimetabolites including Methotrexate, Bleomycin). Alkylating agent dose score[20] and anthracycline dose score will be used for those agents and cumulative doses will be used for antimetabolites including methotrexate and bleomycin.
- Radiation Variables (Data categorized as continuous variables identifying cumulative treatment amounts: CRT hypothalamic/pituitary, heart, lung, ovarian/uterine, testicular; no localization required)
- Surgery Variables for surgeries during treatment (Dichotomous: Brain, Lung; do not include biopsies, no localization required). Appropriate ICD-9 codes including 162 (malignant neoplasm of trachea, bronchus, or lung), 191 (malignant neoplasm of brain), 192 (192.0-192.3; malignant neoplasm of other and unspecified parts of nervous system), 196 (secondary and unspecified malignant neoplasm of lymph nodes) will be used when reviewing surgical procedures for inclusion.
- Sex (A2 – Baseline survey)
- Age/Time Variables (Continuous, modeled 2 at a time)
    - Baseline Age (A1)
    - Age at Diagnosis
    - Age at Follow-up 2003
    - Time Since Diagnosis
- Health Insurance Status (Q2 – Baseline survey)

5.4 Statistical Modeling

5.4.1. Descriptive statistics including means, standard deviations, medians ranges, frequencies, and percents will be calculated for the outcomes of interest (BSI and NCQ), for chronic disease status, and for demographic and treatment factors. These data will be presented as shown in Tables I and II. Data will be examined for normality. If the data are markedly non-normally distributed, consideration will be given to transform the variables or remove extreme outliers.

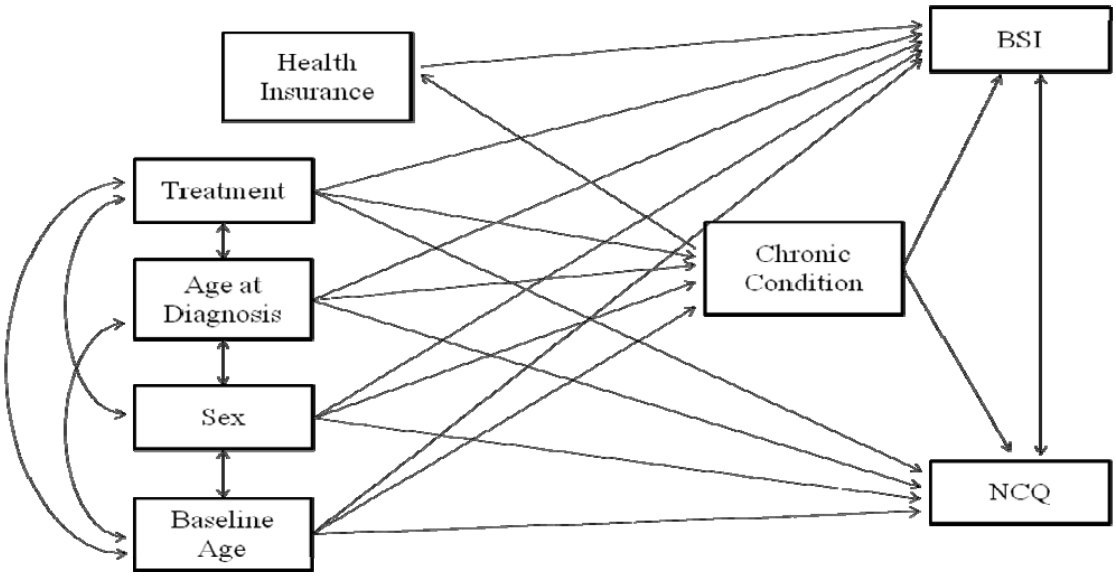
5.4.2. Because the proposed associations are complex and because we hypothesize that chronic disease status is in fact a mediator of the association between demographic and treatment factors and either emotional or cognitive health, we will utilize path analysis as shown in the figures below to determine associations between treatment and demographic factors, chronic disease status and our two primary outcomes of interest. All of the variables in our proposed model are manifest (observed). We are proposing that treatment and demographic factors are antecedent to chronic disease status and that our outcomes, emotional and neurocognitive health, are consequent variables in the model. The single-headed straight arrows represent a unidirectional "path", where the variable at the point of origin is exerting an influence on the variable that the arrow is pointing toward. The double-headed arrow represents a bidirectional "path" between the outcomes, where the variables are thought to exert an influence on each other. The curved, double-headed arrows represent a covariance or correlation between two variables. No assumptions regarding causal inference are made between variables thought to covary.

5.4.2.1. The data will be examined to assure that the necessary conditions for path analysis are present. These conditions include interval or ratio-level measurement, minimal numbers of values, normally distributed data, linear and additive relationships, absence of multicollinearity, absence of measurement error, inclusion of all nontrivial causes, overidentified model, and minimal number of observations.[21]

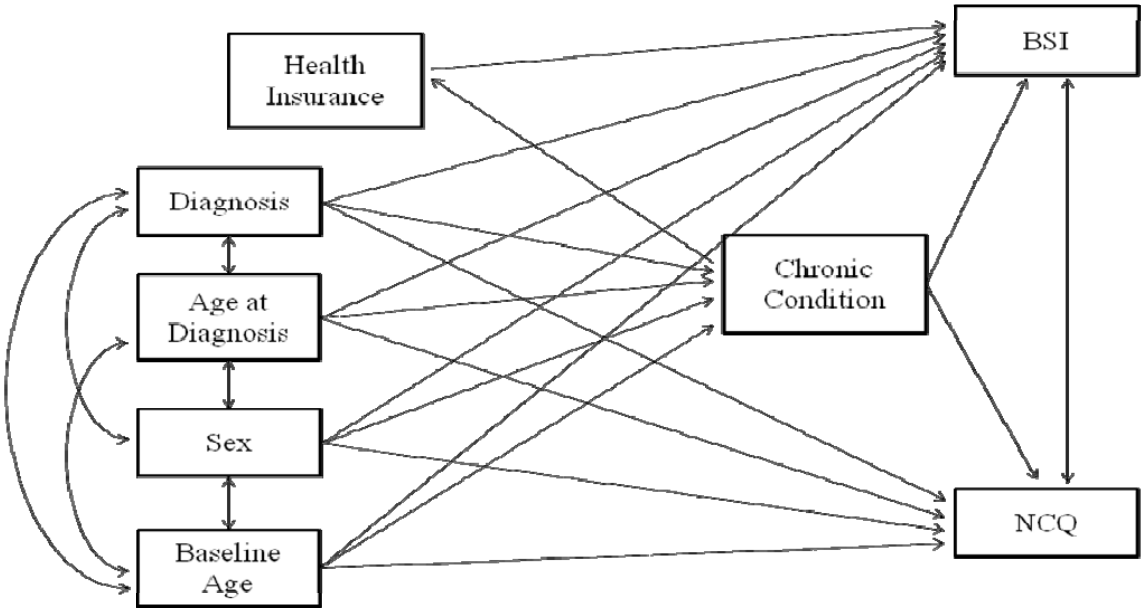
An overview of the path analysis process follows. The initial step includes preparation of detailed program figures which describe relationships between all variables and identifies the parameters to be estimated (See below).

Path analysis program figures

Path Analysis Diagram for Treatment Model



Path Analysis Diagram for Diagnosis Model



The program figures will be used to write the SAS programming code. The analysis will be conducted using PROC CALIS in SAS. This procedure is used for path analysis as well as for several other types of analyses. Statements representing the models depicted above will be included in the CALIS program (i.e., the LINEQS input statement for model specification). The output from the PROC CALIS procedure 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 R2 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.[21] The output from PROC CALIS 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.

5.6. Examples of specific tables:

Table I

Descriptive Statistics at Baseline

	Mean	SD	Median	Range	N	%
Sex						
Male						
Female						
Age at Diagnosis						
0-4						
5-9						
10-14						
15-21						
Age at Baseline						
Health Insurance						
Yes, Canadian						
No						
Diagnosis						
Leukemia						
CNS						
HD						
NHL						
Wilms'						
Neuroblastoma						
Soft Tissue Sarcoma						
Ewing's Sarcoma						
Osteosarcoma						
Treatment						
Chemotherapy						
Anthracycline						
Alkylating Agent						
Anti-metabolite						
Bleomycin						
Radiation						
Hypothalamic/Pituitary						
Heart						
Lung						
Ovarian/Uterine						
Testicular						
Brain Surgery						
Yes						
No						
Lung Surgery						
Yes						
No						
Chronic Health Condition						
No Condition (Grade 0)						
Cardiovascular Grade 1						

Cardiovascular Grade 2	
Cardiovascular Grade 3	
Cardiovascular Grade 4	
No Condition (Grade 0)	
Endocrine Grade 1	
Endocrine Grade 2	
Endocrine Grade 3	
Endocrine Grade 4	
No Condition (Grade 0)	
Pulmonary Grade 1	
Pulmonary Grade 2	
Pulmonary Grade 3	
Pulmonary Grade 4	
Any Condition	
Grade 0 - Grade 2	
Grade 3 or 4	
Multiple Health Conditions	
≥2	
3	

Table II

Descriptive Statistics at Follow-Up 2

	Mean	SD	Median	Range	N	%	%Impaired
BSI							
Somatization							
Depression							
Anxiety							
NCQ							
Task Efficiency							
Emotional Regulation							
Organization							
Memory							

6. SPECIAL CONSIDERATION:

6.1. Given that Dr. Jain will be working with Dr. Ness at St. Jude Children's Research Hospital, we believe that we can complete the statistical procedures ourselves and, thus, not add to the list at the Statistical Centers. However, we will have a member of the statistical coordinating center review all analyses and methods during the process and prior to sending the paper to the publication committee for review.

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