1. CCSS Analysis Concept Proposal: Physical and Psychological Symptom Profiles of Survivors of Childhood Cancer and their Siblings: Links to Health Behaviors and Health Care Utilization.

2. Working Group: Psychology (Primary); Cancer Control (Secondary); Epidemiology & Biostatistics (Secondary)

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3. Background:

Treatment advances in pediatric cancer have resulted in improved survival rates over the last several decades,[1] yet symptom burden remains a significant issue for childhood cancer survivors (CCS). Nearly 62% of CCS report at least one chronic condition,[2] 31-100% report fatigue,[3] and 5-59% report pain.[4,5] Other patient reported outcomes include cardiac symptoms (17%), pulmonary symptoms (7.3%), motor movement difficulties (17.7%), and sensory abnormalities (34.2%).[6]

In addition to physical complaints, CCS are more likely to experience mental health problems compared to healthy siblings,[7] and this may be related to the presence of physical symptom burden. It is well documented that symptom burden impacts psychological well-being and overall quality of life for CCS.[3,4,6] For example, chronic pain among survivors is linked to

depression, anxiety, and reduced vitality.[8] Survivors who experienced fatigue are more likely to report depressive symptoms.[3,9] Of course, the nature of this relation is reciprocal, and psychological functioning can indeed influence or exacerbate reports of physical symptoms.[10] Associations between physical symptoms and psychological symptoms are complex and heterogeneous within CCS.[11] That is, not all survivors who experience physical distress also experience psychological distress and vice versa. However, those with comorbid physical and psychological symptom burden likely require more intensive interventions to improve quality of life outcomes.[11]

Physical and psychological symptoms impact health care utilization (HCU).[12] While insurance status and income are important determinants of HCU among CCS,[13,14] some research has pointed to increased HCU among survivors who experience more chronic health symptoms or psychological distress.[12,15] Though some HCU is appropriate given the presentation of symptomology, increased psychological distress may impact utilization among cancer survivors as it can influence emergency room visits, hospitalizations, and hospital readmission rates.[16] However, these findings are not consistent, as some research within CCS does not find psychological distress and somatic complaints to predict HCU.[14,17] Inconsistency within this research may point to heterogeneity in the range of physical and psychological burdens CCS experience and highlights the importance of examining how the combination of these symptoms may inform patterns of HCU.

Problematic health behaviors (e.g., smoking, alcohol use, physical inactivity) are also related to ongoing physical and psychological symptom burden in CCS.[18] For example, CCS who reported pain,[18] fatigue,[3,18] or psychological distress[18,19] were less likely to engage in physical activity. Other health risk behaviors such as smoking, drug use, and binge drinking, tend to be higher among survivors who experience ongoing symptom burden.[20,21] These findings are particularly problematic for CCS, as they are at increased risk of developing chronic and life threatening health conditions,[7] calling for the need to systematically examine the shared impact of symptom burden on lifestyle behaviors.

Taken together, physical and psychological symptoms among CCS tend to co-occur and cumulative effects are linked to problematic health care utilization[12] and health behaviors.[18] Identifying distinct subgroups of individuals based on physical and psychological symptom profiles may help illuminate those CCS most at risk for symptom burden and elucidate links to health care utilization and health behaviors. Importantly, comparing findings between CCS to individuals without history of pediatric cancer may help ascertain which factors are unique to the pediatric cancer experience. The proposed concept seeks to accomplish this through the aims noted below. Findings from this research may lead to the development of modular based interventions to help address symptom burden more comprehensively rather than targeting symptoms in isolation, ultimately leading to improved health care utilization and behaviors among CCS.

4. Primary Aims and Hypotheses

1. To identify latent profiles of survivors with similar psychological and physical symptoms (per self-report at Baseline).
   Hypothesis 1: Unique profiles with various combinations of physical and psychological symptoms will emerge.[11]

2. To compare the pattern of profiles between survivors and siblings.
   Hypothesis 2. A latent profile analysis (LPA) using equality constraints will indicate meaningful differences between survivors and siblings.

3. To identify demographic and medical predictors of symptom latent profile for survivors.
   Hypothesis 3. Sex, income-level, insurance status, and brain tumor diagnosis will be associated with profile membership.[22]

4. To evaluate the association between latent profiles at Baseline and healthcare utilization and health behaviors (physical activity, sedentary behavior, smoking, etc.) at Follow-up 2 (original cohort) and Follow-up 5 (expansion cohort) surveys.
   Hypothesis 4a: Survivors in profiles characterized by elevated levels of both psychological and physical symptom burden will demonstrate decreased physical activity, increased likelihood of smoking behaviors, and increased problematic drinking behaviors.
   Hypothesis 4b: Profiles characterized by elevated psychological and physical symptoms will be associated with higher health care utilization.

5. Analysis Framework

A. Study Population.

All 5-year survivors and siblings who participated in the CCSS Baseline when at least 18 years old, and completed either Follow-up 2 (original) or Follow-up 5 (expansion) surveys.

B. Variables of Interest

1. Latent Profile Analysis
   a. Number of endorsed Hearing/vestibular Symptom
      i. Item C4-Tinnitus or ringing in the ear? (present/not present)
      ii. Item C5- Persistent dizziness or vertigo? (present/not present)
   b. Number of endorsed Cardiac Symptom
      i. Item F3- Irregular heartbeat or palpitations? (present/not present)
      ii. Item F17-Does exercise cause severe chest pain, shortness of breath, or irregular heart beat? (present/not present)
   c. Number of endorsed Respiratory System
      i. G.6 Asthma
      ii. G.8 Chronic cough or shortness of breath for greater than one month?
      iii. G.13 Any other breathing or lung problems?
   d. Number of endorsed Brain and Nervous System Symptom
      i. Item J8-Problems with balance, equilibrium, or ability to reach for or manipulate objects? (present/not present)
      ii. Item J9-Tremors or problems with movement? (present/not present)
      iii. Item J12- Decreased sense of touch? (present/not present)

iv. Abnormal sensation in arms, legs, or back? (present/not present)

e. Number of endorsed Pain Symptoms
    i. Item J13-Prolonged pain in arms, legs, or back? (present/not present)
    ii. Item J36-Current pain as a result of cancer? (yes/no)
f. Somatic Symptoms
    i. Somatic subscale score from the Brief Symptom Inventory (Items J16-J35)
        1. Start as continuous, may be categorized in final analyses as Present, T ≥ 63); Not present T≤62
g. Anxiety Symptoms
    i. Anxiety subscale score from the Brief Symptom Inventory (Items J16-J35)
        1. Start as continuous, may be categorized in final analyses as Present, T ≥ 63); Not present T≤62
    ii. Item J37-Current anxiety/fears resulting from cancer; Start as continuous, may be categorized in final analyses as:
        1. Present, = Medium, A lot, Very Much
        2. Not present= Small amount, No anxiety
h. Depression Symptoms
    i. Somatic subscale score from the Brief Symptom Inventory (Items J16-J35)
        1. Start as continuous, may be categorized in final analyses as Present, T ≥ 63); Not present T≤62

2. Proposed Predictors of the Latent Cluster Analysis
    a. Item A2- Sex
    b. Item A4- Race
    c. Age at primary cancer diagnosis (in years)
    d. Age at time of assessment (in years)
    e. Item O1-Highest level of schooling achieved at the time of Baseline (may be collapsed in analyses)
        i. 1 to 8 years
        ii. 9-12 years
        iii. Completed high school
        iv. Training after high school
        v. Some college
        vi. College graduate
        vii. Post-graduate level
    f. Item Q8- Household Income (may be collapsed in analyses)
        i. Less than $9,999
        ii. $10,000-19,999
        iii. $20,000-39,999
        iv. 40,000-59,999
        v. Over $60,000

g. Item L2- Marital Status (may be collapsed in analyses, living with partner vs. not living with partner)
    i. Married
    ii. Living as Married
    iii. Widowed
    iv. Divorced
    v. Separated or no longer living as married
h. Item Q2-Insurance Coverage (yes/no/Canadian; yes and Canadian grouped in analyses)
i. Treatment exposures:
    i. Treatment-related surgery, excluding biopsies (yes/no)
    ii. Chemotherapy (yes/no)
        1. Alkylating agents
        2. Anthracycline
        3. Platinum agents
        4. Vinca alkaloids
        5. Retinoic acid
        6. Methotrexate
        7. Corticosteroids
    iii. Radiation Body Region (yes/no)
        1. Brain
        2. Chest
        3. Abdomen
        4. Pelvis
j. Diagnosis (Note: to reduce redundancy, treatment exposure and diagnosis will be examined in two separate, parallel models to determine which factors may be more relevant for consideration in the final model)
    i. Leukemia
    ii. CNS Tumor
    iii. Hodgkin's Lymphoma
    iv. Non-Hodgkin's Lymphoma
    v. Neuroblastoma
    vi. Wilms tumor
    vii. Soft tissue sarcoma
    viii. Bone Tumor

3. Longitudinal Correlates associated with latent clusters at Follow-up 2 or 5
    a. Healthcare Utilization
        i. A1. During this two-year period, which of the following health care providers did you see?
        ii. A2. Where did you receive healthcare?
        iii. A3. During past 2 years, how many times see physician?
        iv. A5. How many of these visits were related to your previous cancer or similar illness?

v. Categorize variable as followed:
    1. No health care if A3= None.
    2. General Health Care = A3-A5, If A1= Physician, Nurse
    3. General Survivor Care= A5
    4. Emergent Care= A2 Endorsement of ER or Urgent Care Center

b. Health Behaviors
    i. Alcohol
        1. Item N6- During the last 12 months, how often did you have 5 or more (males) or 4 or more (females) drinks containing any kind of alcohol in a single day?
            a. Start continuous; may categorize as heavy drinking
            b. Heavy drinking ≥5 days of binge drinking per month
    ii. Smoking
        1. Item N1d. Do you smoke now (yes/no)
        2. Item N1. Have you smoked at least 100 cigarettes in your entire life?
        3. Categorize N1 and N1d as followed:
            a. Never smokers, N1d= No AND N1= No
            b. Former smokers N1= Yes AND N1d= No
            c. Current Smokers, N1d= Yes AND N1=Yes
    iii. Physical Activity
        1. Item D1. Past month, did you participate in physical activity?
        2. Item D3. Days per week vigorous physical activity?
        3. Item D4. Total mins vigorous physical activity?
        4. Item D6. Days per week moderate physical activity?
        5. Item D7. Total mins moderate physical activity?
        6. Calculate time spent physical activities per week
            a. Time Vigorous per week= D3XD4
            b. Time Moderate per week=D6XD7

4. Other Descriptive Variables for Table 1.

C. Statistical Analyses

Aim 1: Latent profile analysis will be conducted to empirically derive physical and psychological symptom classes using the following categories of variables (See Section B1 for more details): hearing symptoms, cardiac symptoms, sensory/movement symptoms, pain symptoms, somatic symptoms, anxiety symptoms, depression symptoms. This analysis will be conducted with the CCS group only. The model will be specified with uncorrelated indicators and freely estimated variances across classes. However, factors may be constrained pending model convergence. The Bayesian information criterion (BIC)[23], will be used to determine model fit for each number of classes estimated, with lower BIC values indicating better model fit[24]. The Lo-Mendell-Rubin[25] and the Bootstrap Likelihood Ration Test[26] will be used to compare model improvement between neighboring classes (e.g., 2 class solution vs. 3 class solution, 3 class

solution vs. 4 class solution). A significant *p*-value derived from these tests indicates statistically significant improvement in fit by the addition of a class[24].

Aim 2. To compare the pattern of profiles between survivors and siblings, an LPA using equality restraints[27] will be employed to determine how well the sibling LPA matches to the CCS profiles.

Aim 3. For the CCS group only, to determine if significant associations exist between demographic and medical factors with latent profiles developed in Aim 1, the three-step approach[28] will be used. The three-step approach allows covariates to be tested as predictors of latent classes in a multinomial logistic regression while maintaining the probabilistic nature of the latent profile variable. In the first step, the model is estimated using only the latent profile indicators (which is achieved through Aim 1). In the second step, the most likely class variable is created for each subject. Finally, the most likely class is regressed on the predictor variable taking into account the probability of misclassification of the class assignment generated in step 2. Depending on the statistical software package used, these steps can be conducted simultaneously. To reduce redundancy, treatment exposure and diagnosis will be examined separately in two parallel models to determine which factors may be more relevant for consideration in the final model

Aim 4. The frequency of health care utilization and health behaviors will be compared across latent profiles will be tested again using the three-step approach[28]; however these variables will be specified as distal outcomes for the survivor group only.

D. Proposed Study Tables

Table 1. *Demographic Information*

	Survivors # (%)	Siblings # (%)
Sex		
Female		
Male		
Age at Survey Assessment		
Mean (Standard Deviation)		
Range		
Age at Diagnosis		
Mean (Standard Deviation)		
Range		
Race/Ethnicity		
Non-Hispanic black		
Non-Hispanic white		
Hispanic		
Other		
Diagnosis		
Leukemia		-
CNS Tumor		-
Hodgkin's Lymphoma		-
Non-Hodgkin's Lymphoma		-
Neuroblastoma		-
Wilms tumor		-
Soft tissue sarcoma		-
Bone Tumor		-
Treatment Modalities		
Received Radiation		-
Cranial		-
Chest		-
Abdomen		-
Pelvic		-

Table 1 *Demographic Information (Continued)*

	Survivors # (%)	Siblings # (%)
Received Chemotherapy		
Alkylating agents		-
Anthracycline		-
Platinum agents		-
Vinca alkaloids		-
Retinoic acid		-
Methotrexate		-
Corticosteroids		-
Insurance Status (% with “yes” or Canadian)		
Income		
Less than $10,000		
$10,000-$19,999		
$20,000-$39,999		
$40,000-$59,999		
Over $60,000		
Marital Status		
Married		
Living as Married		
Widowed		
Divorced		
Separated or no longer living as married		
Education Level		
1 to 8 years		
9-12 years		
Completed high school		
Training after high school		
Some college		
College graduate		
Post-graduate level		

Table 2 *Comparison of Model Fit for Latent Profiles*

N-Classes	Akaike Information	Bayesian Information Criterion	Entropy	Lo-Mendell-Rubin	Bootstrap Likelihood Ratio Test	N-Class Size Range
2						
3						
4						
5						
6						
…						

Table 3 *Means and Standard Deviations for Symptoms Across Profiles*

	Latent Class 1		Latent Class 2		Latent Class 3		Latent Class 4	
	M	SD	M	SD	M	SD	M	SD
Hearing Symptoms								
Cardiac Symptoms								
Brain/Nervous System Symptoms								
Pain Symptoms								
Somatic Symptoms								
Anxiety Symptoms								
Depression Symptoms								

Table 4 *Parameter and Predictor Estimates for Co-Variates*

	Odds Ratio	Confidence Interval	Two-Tailed P-Value
Parameterization using Reference Class 1			
Class 2			
Demographics			
Sex (Male vs. Female)			
Non-Hispanic Black			
Non-Hispanic White			
Hispanic			
Other			
Age at Assessment			
Insurance Status			
Income			
Education Level			
Marital Status			
Medical (or Treatment Modalities)			
Leukemia			
Lymphoma			
Central Nervous System Tumor			
Solid Tumor			
Class 3			
Demographics			
Sex (Male vs. Female)			
Non-Hispanic Black			
Non-Hispanic White			
Hispanic			
Other			
Age at Assessment			
Insurance Status			
Income			
Education Level			
Marital Status			
Medical (or Treatment Modalities)			
Leukemia			
Lymphoma			
Central Nervous System Tumor			
Demographics			
Sex (Male vs. Female)			
Non-Hispanic Black			
Non-Hispanic White			
Hispanic			
Other			
Age at Assessment			
Insurance Status			
Income			
Education Level			
Marital Status			
Medical (or Treatment Modalities)			
Leukemia			
Lymphoma			
Central Nervous System Tumor			
Solid Tumor			

Table 5 *Health Outcomes Across Latent Classes*

	Latent Class 1		Latent Class 2		Latent Class 3		Latent Class 4		Chi-Square Comparisons
	M	SD	M	SD	M	SD	M	SD	*
Healthcare Utilization									
No Healthcare									1,2,4>3
General Healthcare									3>1
Survivor-Specific Care									
Emergent Care									
Health Behaviors									
Risky Drinking									
Never Smoker									
Past Smoker									
Current Smoker									
Vigorous PA									
Moderate PA									

Note. PA= Physical Activity; *p at least <.05

Analysis note: If using the three-step approach in Mplus, chi-square comparisons tests are conducted using the auxiliary function (e.g., du3step). Table will be modified if an alternative comparison test is used (e.g., exporting profile membership to conduct multivariate modeling).

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