

STUDY TITLE

Posttraumatic stress as a unique contributor to behavioral health outcomes and healthcare utilization in adult survivors of childhood cancer

WORKING GROUP AND INVESTIGATORS

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BACKGROUND AND RATIONALE

Survivors of pediatric cancer experience a variety of late-effects, some of which emerge decades after treatment^(1, 2, 3). Although some of these late-effects can be effectively managed with medication, it is estimated that 35% of survivors develop disabilities that significantly impair quality of life^(4, 2). One of the most common late-effects, occurring in approximately 20-40% of survivors, is neurocognitive impairment^(5, 6). Although such late-effects may be mild, they are often pervasive in their influence over a patient's daily life and functioning⁽¹⁾. Posttraumatic Stress is a unique mental health outcome as it is characterized by a) intrusive symptoms, such as recurrent, involuntary thoughts of a stressor; b) avoidance of external cues or reminders of the stressor; c) hypervigilance, a heightened state of sensory arousal and behavioral reactivity. Additionally, the presence of posttraumatic stress often leads to cognitive alterations related to memory and negative beliefs that surround the event and exacerbate symptoms of chronic stress⁽⁷⁾. Studies pertaining to posttraumatic stress in pediatric cancer survivors yield prevalence rates that range from 8-20%^(3, 2, 8, 9, 10, 11). Moreover, survivors in the Childhood Cancer Survivor Study (CCSS) were found to be at four times greater risk of developing posttraumatic stress when compared to siblings, with symptoms often occurring late in adulthood⁽³⁾.

Within the survivor group, posttraumatic stress, maladaptive health beliefs and poor health-related quality of life correspond with predictive variables such as age at diagnosis, with poorer outcomes for those diagnosed in adolescence⁽¹¹⁾. These risk factors have been attributed to the nature of developmental tasks as survivors age and enter adulthood, at which time they must adapt to individuation, independent social functioning, and higher educational or vocational expectations^(3, 10). This demonstrates a reciprocal relationship between cognitive dysfunction and posttraumatic stress as one exacerbates the other. Moreover, young adulthood is the time when late-effects typically become apparent and serve as a reminder of cancer's lasting impact and related limitations^(3, 2, 9, 10). Heightened stress often arises at this time due to increasing uncertainty, a known correlate of posttraumatic stress, as well as the emergence of a level of cognitive maturity to possess awareness of ambiguity^(3, 2, 9, 10). Related outcomes such as failure

to complete high school, unemployment and being unmarried have been demonstrated to significantly correspond with posttraumatic stress in this population ⁽³⁾.

The CCSS includes assessment of neurocognitive impairment, which is correlated with functional deficits including employment and education ^(12, 13). Using the CCSS Neurocognitive Questionnaire, it has been estimated that survivors of non-CNS malignancies are at 50% higher risk of impairment than healthy siblings, particularly in domains related to task efficiency, memory and emotional regulation. Medical complications and treatment variables such as cranial radiation are related to higher prevalence and severity of neurocognitive impairments ⁽¹³⁾. Additionally, there are a number of modifiable factors that contribute to these neurocognitive symptoms including emotional distress and poor sleep quality, each of which is exacerbated by posttraumatic stress ^(12, 14). Sleep disturbances and subsequent fatigue have been found to significantly influence task efficiency and memory, yielding increased risk of impairment comparable to that of high dose radiation ⁽¹⁴⁾. A study examining the specific relation between posttraumatic stress disorder and neurocognitive impairment demonstrates that those with the disorder perceive more severe deficits in functional tasks, attributed to cognitive deficits, despite having fewer medical late effects ⁽⁹⁾. This suggests the role of posttraumatic stress as a critical mediator, beyond organic brain injury.

Although research in the CCSS cohort has shown that most survivors are well adjusted and psychologically healthy, other studies suggest variability in symptom prevalence based on standards of comparison as well as classification of distress ^(15, 16). These inconsistencies can be explained by standard classifications of distress being inappropriate to pediatric cancer survivors ⁽¹⁵⁾. This population is believed to experience distress better characterized by referenced correlates of posttraumatic stress including interpersonal and achievement difficulties, diminished neurocognitive functioning, and a lack of social or emotional support ⁽¹⁵⁾. When distress does occur, it has a significant impact, including increased likelihood of sleep disturbance and limitations in physical activity ^(16, 17). These outcomes are further associated with underlying factors and manifestation of posttraumatic stress, including with health-related limitations as well as diminished social functioning and emotional wellbeing, characterized by depressive symptoms such as hostility and interpersonal sensitivity ^(9, 10).

Cognitive and emotional wellbeing are known to influence behavioral health with regard to positive health behaviors such as physical activity, and negative health behaviors such as drug and alcohol use ⁽⁵⁾. This is predicted by low personal resiliency, low self-esteem, social withdrawal, poor decision-making, academic problems and neurocognitive impairments ⁽⁵⁾. There is a degree of uncertainty; however, in the influence of emotional distress on healthcare utilization. Some studies show anxiety and depression to have no effect on healthcare utilization, while others find variability between symptoms (i.e. anxiety associated with more survivor care, anxiety and use of antidepressants associated with increased risk-based care, somatization associated with more risk screening) ^(6, 18). A related difference in perceived purpose of healthcare was demonstrated in a study where psychologically healthy cancer survivors reported wanting more clinical than supportive care while those with an increased sense of vulnerability and lower ratings of mental competence demonstrated a preference for supportive care ^(6, 18, 19). Posttraumatic stress may uniquely influence healthcare use and health behaviors via the development of avoidance symptoms as well as a hindrance to awareness and use of self-

management skills^(20, 2). Posttraumatic stress is also associated with more health risk behaviors and fewer positive health behaviors, health-related self-efficacy, and personal responsibility^(8, 20).

A large body of existing research has demonstrated the prevalence of emotional distress and posttraumatic stress in survivors as opposed to the general population as well as sibling controls. Research on influence of posttraumatic stress in medical populations, however, is limited with studies that include small sample sizes and lack of follow-up data. The proposed analysis aims to examine posttraumatic stress as a mediating factor of cognitive, mental and behavioral health outcomes among survivors, utilizing a large and well-characterized sample that permits evaluation of demographic and treatment-related variables.

SPECIFIC AIMS AND RESEARCH HYPOTHESES

Aim 1: To examine the association between posttraumatic stress and concurrent neurocognitive and emotional health conditions in adult survivors of childhood cancer

Hypothesis 1.1: Posttraumatic stress symptoms will be associated with lower perceived neurocognitive functioning in all domains

Hypothesis 1.2: Posttraumatic stress symptoms will be associated with higher emotional distress, perceived cognitive and physical limitations and diminished quality of life

Aim 2: To examine the association between posttraumatic stress and health behaviors (i.e. smoking, physical activity) in adult survivors of childhood cancer

Hypothesis 2.1: Posttraumatic stress symptoms will be associated with more negative health behaviors

Hypothesis 2.2: Posttraumatic stress symptoms will be associated with fewer positive health behaviors

Aim 3: To explore the association between posttraumatic stress and healthcare utilization (i.e. level of general and risk-based care, presence of medical screening) in adult survivors of childhood cancer

Hypothesis 3.1: Participants who report clinically significant avoidance will demonstrate lower healthcare utilization compared to those who report posttraumatic stress without significant avoidance symptoms

Hypothesis 3.2: Participants who endorse clinically significant hypervigilance will demonstrate higher healthcare utilization, compared to those who report posttraumatic stress without this elevation

ANALYSIS FRAMEWORK

Population: This analysis will examine the reports of survivors from the original cohort who completed the 2003 follow-up survey. As the aim of this study is to examine posttraumatic stress

as a unique predictor of outcomes, the portion of survivors who do not show signs of posttraumatic stress will be used as a reference group in the analysis. Siblings will be excluded from the analyses as only 2% of siblings, as compared to 9% of survivors, in this cohort have demonstrated signs of Posttraumatic Stress Disorder ⁽³⁾.

Outcomes of Interest

The Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ), (items J 1-25) on the 2003 follow-up survivor and sibling questionnaires, is the primary outcome measure of neurocognitive health. This self-report questionnaire contains 25 items on a Likert scale based on frequency of occurrence over the last 6 months ⁽²¹⁾. Responses are scored onto scales representing four areas of functioning: task efficiency, emotional regulation, organization, and memory ^(22, 15). Totals are then converted to t-scores and interpreted based on normative sibling data, with impairment defined as falling into the bottom 10th percentile of siblings ^(21,22). For this analysis, Neurocognitive outcomes are coded according to the distribution as impaired or not impaired. Analyses will examine perceived functioning overall and in each of the domains.

The Brief Symptom Inventory-18 (BSI-18), (G 1-20) on the 2003 follow-up survivor and sibling questionnaires, will serve as a measure of emotional distress. This self-report inventory contains 18 items on a Likert scale based on severity over the past 7 days. Scores are placed onto three dimensions: somatization, depression, and anxiety. A cumulative global distress scale is also calculated ⁽²³⁾. Endorsed items are totaled, converted to t-scores based on community norms and interpreted against a clinical cutoff at the top 10th percentile ⁽²³⁾. Emotional distress will be coded as a high (above clinical cutoff of 65) and moderate-low (below clinical cutoff) experience of overall distress as well as on specific scales of somatization, depression and anxiety.

The Short-Form Survey-36 (SF-36), (E 1-22/F 1-14) on the 2003 follow-up survivor/sibling questionnaires, is a self-report questionnaire designed to measure patient-reported physical and mental health outcomes. It contains 36 items on a Likert scale regarding the presence of various conditions, as well as their frequency and severity, over the last 4 weeks. Items endorsed are scored to the following scales: vitality, physical function, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and general mental health ⁽²⁴⁾. Weighted scores are calculated for each section and transformed into standard T-scores, though z-scores are also available ⁽²⁴⁾. Perceived health-related quality of life will be coded as high-moderate (≥ 60) and low (≤ 40) on each of these scales.

Health Behaviors: Positive and negative health behaviors are present on questionnaires as they pertain to smoking status (L1,2,3,5) and physical activity (3,6). Specific outcomes related to smoking status will include presence and frequency of tobacco use, with frequency measured as fewer than 10 or at least 10 cigarettes a day (L2,3,5) and the presence of smoking cessation attempts (L1,2,5). With regard to physical activity, analyses will examine the frequency of moderate/vigorous exercise (D 3, 4, 6,7) as compared to national recommendations of at least 3 times per week.

Health Care/Medical screening: Adherence to guidelines with regard to routine medical care and screening will be examined. Primary care visits will be examined with regard to average (0-2 visits) or frequent (3+ visits) utilization. Participation in risk-based care and medical screening

will be examined with regard to whether an individual has received this care at least once in the previous year. Questionnaire information regarding the frequency (A3), type (A4,6) and content (A6) of healthcare visits will be used to determine factors associated with use of typical and risk-based healthcare and medical screening.

Predictors

The Posttraumatic Stress Symptom Scale – Self-report, items K1-17 on the 2003 follow-up survivor and sibling questionnaires, will serve as the predictor variable. This self-report questionnaire contains 17 items that represent the symptom criteria of PTSD assessed on a Likert scale based on severity⁽²⁵⁾. A total raw score is determined by number of items endorsed and compared against a clinical cutoff score of 13, which suggests high likelihood of PTSD⁽²⁵⁾. The presence of a likely diagnosis (yes, no) will be coded as the predictor variable.

Data Analysis Plan

Descriptive statistics (including mean, median, standard deviation, percentages, ranges and frequencies) will be calculated for each of the primary outcomes (NCQ, BSI-18, SF-36, Tobacco Consumption, Physical Activity, Medical Screening and Healthcare Use), the primary predictor (Posttraumatic stress) and all covariates (Table 1). Logistic regression models will be constructed between posttraumatic stress and each of the outcome variables including adjustment factors as described below (Tables 2-5). Ordinal logistic regression models will be fit to examine associations between PTSS symptom presentations on a quantitative measure of healthcare utilization (Table 6). For each model described below, confounding factors will be included if their inclusion modifies the association between posttraumatic stress and each outcome of interest by more than 10%.

Aim 1:

Multivariable logistic regression analysis will be used to examine the impact of posttraumatic stress (yes, no) on emotional health (BSI-18) and health-related quality of life (SF-36) (Table 2). The primary comparison will be with regard to the BSI Global Distress score as well as the SF-36 physical and mental composites. Consideration will also be given; however, to the impact of posttraumatic stress on each component scale of the BSI and SF-36.

Covariates

- Diagnosis (CNS vs. Non-CNS)
- Current age
- Years since diagnosis
- Gender
- Race
- Employment status (item 4)
- Income (items T1,3)
- Marital status (item 2)

Multivariable logistic regression analysis will be conducted to examine the impact of posttraumatic stress (yes, no) on neurocognitive function (NCQ) (Table 3). This outcome will be analyzed with regard to the impact of posttraumatic stress on each domain of the NCQ.

Covariates

- Diagnosis (CNS vs. Non-CNS)
- Age at diagnosis
- Current age
- Gender
- Race
- Income (items T1,3)
- Education level (item 1)
- Chemotherapy
- Radiation

Aim 2:

Multivariable logistic regression analysis will be conducted to examine the impact of posttraumatic stress (yes, no) on tobacco use and physical activity (Table 4).

Covariates

- Diagnosis (CNS vs. Non-CNS)
- Current age
- Years since diagnosis
- Gender
- Race
- Marital status (item 2)
- Education level (item 1)
- Employment status (item 4)
- Income (items T1,3)

Aim 3:

Multivariable logistic regression will examine the impact of posttraumatic stress (PDS yes, no) on number of healthcare visits, risk-based care and participation in medical screening as recommended (Table 5).

Covariates

- Diagnosis (CNS vs. Non-CNS)
- Current age
- Years since diagnosis
- Gender
- Race
- Health Insurance (items M1, 1b)
- Visit for specific physical problems (item A4)
- Education level (item 1)
- Income (items T1,3)

In addition, ordinal and binary logistic regression models will be used to examine the associations of presentations of posttraumatic stress: hypervigilance (PDS subscale elevated/not elevated) and avoidance (PDS subscale elevated/not elevated) with healthcare utilization (defined as a quantitative measure of types of visits and/or screening acquisition, (Table 6)

Covariates

- Diagnosis (CNS vs. Non-CNS)
- Current age
- Years since diagnosis
- Gender
- Race
- Health Insurance (items M1, 1b)
- Visits for specific health problems (item A4, presence of chronic illness)
- Education level (item 1)
- Income (items T1, 3)

Special Considerations: The project will also fulfill the Doctoral Research requirements for Emily Crochet, for which Dr. Van Sickle is the chair. Dr. Van Sickle has taken primary responsibility for this project and Dr. Tyc will also provide support.

Example Tables:

Table 1 – Descriptive statistics of survivor and sibling groups, covariates and outcomes

Variable	Survivors w/o PTSS		Survivors w/o PTSS	
	M	SD	M	SD
Age at Diagnosis				
Age at Baseline				
Age at Follow-Up				
	N	%	N	%
Diagnosis				
- CNS				
- Leukemia				
- Bone				
- Hodgkin’s Disease				
- Kidney (Wilms’)				
- Neuroblastoma				
- Non-Hodgkins Lymphoma				
- Soft Tissue Sarcoma				
Sex				
- Female				
- Male				
Race/Ethnicity				
- White				
- African American				
- Hispanic				
- Other/Not Specified/Unknown				
Educational Attainment				
- < High school				
- High School or GED				
- Occupational Training				
- Bachelor’s Degree				

<ul style="list-style-type: none"> - Post-graduate <p>Employment Status</p> <ul style="list-style-type: none"> - Employed - Unemployed - Student <p>Household Income</p> <ul style="list-style-type: none"> - < 20,000 - 20,000-39,999 - 40,000 – 59,999 - 60,000+ <p>Marital Status</p> <ul style="list-style-type: none"> - Single/never married - Married or living as married - Divorced or separated <p>Treatment Type</p> <ul style="list-style-type: none"> - Surgery only - Any chemotherapy - Any radiation - Any chemotherapy & radiation <p>Health Insurance</p> <ul style="list-style-type: none"> - Yes - No - Yes w/ limitations <p>Posttraumatic Stress</p> <ul style="list-style-type: none"> - Yes, with highest elevation on hypervigilance - Yes, with highest elevation on avoidance - Yes, with highest elevation on intrusive - No <p>Clinical Distress, BSI-18</p> <ul style="list-style-type: none"> - High cumulative - High somatization - High depression - High Anxiety <p>Health-related quality of life (SF-36)</p> <ul style="list-style-type: none"> - Physical Composite - Mental Composite - Vitality - Bodily pain - General health perception - Emotional role functioning - Social role functioning <p>Smoking Status</p> <ul style="list-style-type: none"> - Never smoker - Former smoker - Current smoker <p>Frequency of use among smokers</p> <ul style="list-style-type: none"> - 9 or fewer cigarettes per day - 10+ cigarettes per day 		
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<p>Previous Cessation Attempts</p> <ul style="list-style-type: none"> - 0 attempts - 1 attempt - 2+ attempts <p>Physical Activity</p> <ul style="list-style-type: none"> - Moderate exercise 1-2x per week - Moderate exercise 3+ times weekly - Vigorous exercise 1-2x per week - Vigorous exercise 3+x weekly <p>Primary care visits in 2 yr period</p> <ul style="list-style-type: none"> - 0 visits - 1-2 visits - 3+ visits <p>Risk-based care visits in 2 yr period</p> <ul style="list-style-type: none"> - 0 visits - 1-2 visits - 3+ visits <p>Medical Screening (yes/no in last year)</p> <ul style="list-style-type: none"> - Echocardiogram - Colonoscopy - Bone Density test - Mammogram (for women) - Pap smear (for women) 		
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All multivariable models displayed below will also include relevant adjustment factors, to be determined during analyses. Tables will indicate what adjustments were made for each outcome in footnotes.

Table 2: A multivariable logistic regression analysis of posttraumatic stress on BSI-18 and SF-36 scores

	PTSS (n)	No PTSS (n)	OR (95% CI)	P value
<p>BSI-18 Total</p> <ul style="list-style-type: none"> - High - Moderate/ Low 				
<p>SF-36 Physical Composite</p> <ul style="list-style-type: none"> - High/ Moderate - Low 				
<p>SF-36 Mental Composite</p> <ul style="list-style-type: none"> - High/Moderate - Low 				

Table 3: A multivariable logistic regression analysis of posttraumatic stress on NCQ scores

	PTSS (n)	No PTSS (n)	OR (95% CI)	P value
NCQ- Task Efficiency				

- Impaired - Not Impaired				
NCQ – Emotional Regulation - Impaired - Not Impaired				
NCQ – Memory - Impaired - Not Impaired				
NCQ – Organization - Impaired - Not Impaired				

Table 4: A multivariable logistic regression analysis of posttraumatic stress on health behaviors

	PTSS (n)	No PTSS (n)	OR (95% CI)	P value
Exercise - ≤ 3x per week - ≥ 3x per week				
Smoking Status - Ever smoked - Never smoked				
Smoking Frequency (cigarettes per day) - 9 or fewer - 10 or more				
Cessation Attempts - 0 attempts - 1 or more				

Table 5: a multivariable logistic regression analysis of posttraumatic stress on healthcare utilization

	PTSS (n)	No PTSS (n)	OR (95% CI)	P value
Primary Care Visits - 0-2 visits - 3+ visits				
Risk-Based Care - Yes - No				

Participation in medical screening - Yes - No				
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Table 6: Multivariable Ordinal and Binary logistic regression of particular representations of posttraumatic stress (PDS- elevated hypervigilance, PDS – elevated avoidance) on healthcare utilization

	PDS – hypervigilance (elevated)		PDS – avoidance (elevated)	
	N (%)	OR ^a (95% CI) p-value	N (%)	OR ^a (95% CI) p-value
Primary Care Visits - 0 - 1-2 visits - 3+ visits				
Risk Based Care Visits - 0 - 1-2 visits - 3+ visits				
Participation in medical screening (yes/no)				

^a Odds Ratios derived from ordinal proportional odds regression models for number of care visits and from binary logistic regression models for screening participation. Goodness of fit for the proportional odds model will be assessed and if the odds are not proportional across outcome categories, a generalized ordinal regression model will be fit and separate ORs will be reported.

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