Study Title: Neurocognitive Predictors of Risky Health Behaviors in Pediatric Cancer Survivors: Distress and Pain as Moderators of Later Substance Use

Primary Working Group: Psychology
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Background and Rationale: Cancer-Related Cognitive Impairment

Besides accidents, cancer is the leading cause of death in children younger than 15 years of age.[1,2] Childhood cancer survival rates have steadily risen in recent years with medical advancements in treatment, so that today 5-year survival rates are over 80%.[3,4,5] However, 30-60% of childhood cancer survivors (CCS) experience cancer-related cognitive impairment (CRCI).[6,7] CRCI can occur as a direct result of cancer involvement to the central nervous system, or an indirect effect of cancer treatments such as irradiation, chemotherapy, and corticosteroid treatment.[6,7,8,9,10,11,12] CRCI can include deficits in executive functioning—the ability to remember, plan, attend to, and integrate information in the process of making decisions. Additionally, CRCI is associated with changes in attention, processing speed, and memory, which can also lead to overall lowered intelligence quotient (IQ) scores and has the potential to impact decision making in survivors of childhood cancer due to these associated impairments.[7,8,10,13,14]

Substance Use Decision Making in Survivorship

Development of the prefrontal cortex, and the associated executive functions that enable decision making, is a process which continues throughout adolescence and into emerging adulthood.[14] Disease and injury affecting the central nervous system (CNS) which occur in childhood may impact decision making that lasts throughout the lifespan, leading to risk. This is particularly true in adolescence when individuals reach a level of maturity and independence in which they must make challenging and complex decisions that can result in negative outcomes but do so with an underdeveloped capacity for executive functioning.

Moreover, adolescence is a time in which experimentation can be expected[14,15]; however, the risk to teens who choose to experiment with substances like alcohol and tobacco is great due to the

cognitive effects that these substances can have during a vulnerable time of brain development.[16] Because CRCI can hinder executive function, it may impact decision making related to risky health behaviors, particularly substance use in adolescence. For instance, Hollen et al.[14] found that in a cohort of 241 cancer-surviving adolescents, executive function impairment was a predictor of lifetime substance use.

Further, impairment in attention has been shown to predict lifetime as well as current tobacco use in adulthood, an obvious threat to the health of pediatric cancer survivors.[14] Executive function impairments were a predictor of smoking in a study of adult survivors of childhood cancer—specifically working memory impairments, childhood attention deficits, and emotion regulation were associated with smoking as adults.[17] Close to half of participants with childhood attention deficits later became smokers in adulthood and were nearly twice as likely to be characterized as current smokers than childhood cancer survivors who had no attention-related problems. [17] It was suggested that survivors were self-medicating with nicotine to improve deficits in attention and help regulate emotion. [17] Indeed, it may be that neurocognitive deficits in emotion regulation would predispose survivors to increased distress, thereby increasing the risk of avoidance coping with substance use due to the lack of cognitive resources for more adaptive coping strategies.

For adolescent cancer survivors, not only is their typical development at risk due to the effects of cancer and its treatment, risks for secondary cancers and other chronic illnesses later in life can be increased by risky health behaviors such as substance use.[14,18] Further, because early initiation of substance use in adolescence is associated with problematic use later in life, decision-making regarding experimentation is also an important factor when considering risk for future substance use disorders.[19] Because substance use behaviors are changeable, understanding the relationship between neurocognitive deficits and substance use decision making in CCS will provide necessary information to direct treatment interventions aimed at decreasing risky decision-making and improving long-term outcomes within this already at-risk population.

The Impact of Distress: Anxiety, Depression, Somatization, and Pain as moderators

Survivors of childhood cancers experience mental health issues at greater rates than their healthy siblings.[20] Anxiety, depression, and posttraumatic stress are more commonly diagnosed in CCS than controls.[21] Brinkman et al.[22] found that over 10% of CCS experience clinically significant persistent distress, with 8.9% reporting depressive symptoms, 4.8% reporting anxiety, and 13% reporting somatization that was persistently elevated. Tonorezos and colleagues[23] have similarly found prevalence rates of depression at 11.4%, anxiety at 7.4% and somatization at 13.9%. These symptoms of psychological distress may arise due to uncertainty over treatment, long-term survivorship, or risk of late effects or secondary cancers.[24]

Further, uncertainty regarding an acute, life-threatening illness can be viewed as inherently dangerous, and when adaptive coping resources are insufficient CCS may turn to avoidance as a mechanism to cope.[24] In general, when individuals are experiencing depressive symptoms, they more commonly rely on passive coping such as avoidance in the face of stress.[25] When taxed by pain, the burden of disease, the lengthy period of uncertainty throughout survivorship, or due to the relatively limited coping skills acquired in adolescence, survivors may experience periods in

which coping resources are inadequate, at which time they may lean into substance use to avoid uncertainty and feelings of distress. Finally, although PTSD rates in survivors are low, posttraumatic stress symptoms such as reexperiencing and arousal are common—particularly in adolescent survivors.[26] The stress associated with cancer diagnosis and medical treatment can be overwhelming and traumatic, and cases of cancer-related posttraumatic stress disorder in adults have been associated with distress and reductions in quality of life.[27] Indeed, trauma in childhood has broadly been associated with risk for substance use in adolescence and adulthood. [24]

In sum, survivors of childhood cancers are at risk for impairment in effective decision-making skills due to the developmental impact of cancer and cancer treatments on neurocognitive functions. This, in turn, puts them at increased risk for alcohol and tobacco use in adolescence, a time when these substances can have detrimental effects on brain maturation and habit formation, and potentially increasing the risks of secondary cancers later in life. Identifying the neurocognitive predictors of risky health behaviors such as alcohol and tobacco use in CCS and the role of psychological distress and/or pain in moderating this relationship (i.e., exacerbating the relationship between neurocognitive impairment and substance use), will further expand our capacity to screen for and prevent problematic substance use, as well as assess and treat substance use disorders when they occur within this high-risk group.

Proposed Specific Aims:

1. Determine whether an association exists between neurocognitive impairment on the NCQ (in neurocognitive symptoms associated with task efficiency, emotional regulation, memory, and organization) and substance use (alcohol and tobacco) in survivors and siblings. We will examine these associations cross-sectionally for the entire cohort, and longitudinally for the original cohort.

   Hypothesis: Greater neurocognitive symptoms (i.e., higher scores on the NCQ) will be associated with higher alcohol and tobacco use. Neurocognitive impairment will be associated with increased risk of alcohol and tobacco use. These associations will be more pronounced in survivors than their siblings overall.

2. Determine whether distress (anxiety, depression, and somatization) and/or pain moderates the influence of neurocognitive symptoms or neurocognitive impairment on substance use among survivors and compare with siblings.

   Hypothesis: The relationship between self-reported neurocognitive symptoms or neurocognitive impairment and substance use will be moderated and exacerbated by

clinically significant distress and pain. This relationship will be more pronounced in survivors than their siblings.

Analysis Framework:

A. Study Population: All 5-year childhood cancer survivors and siblings who participated in the Childhood Cancer Survivor Study (CCSS), answering question topics regarding alcohol and tobacco use as follows: For the original cohort, follow-up (FU2) (tobacco items only L.1-L.6), and from 2007 FU4 alcohol items N.1-N.6 and smoking items N.7-N.14; For both the original and expansion cohorts question topics from FU5 (alcohol items N.1-N.6; tobacco items N.7-N.14) will additionally be used. Inclusion will also be based on those survivors who also completed the CCSS-Neurocognitive Questionnaire (CCSS-NCQ) in FU2 for original cohort, and FU5 for expansion cohort, and Brief Symptom Inventory-18 (BSI-18) at baseline FU2 for original cohort, and FU5 surveys for the expansion cohort. Exclusion criteria include those survivors and sibling controls who did not complete the alcohol items (in FU4 for original cohort, or FU5 for original or expansion cohort) and tobacco items (in FU2 or FU4 for original cohort, or FU5 for original or expansion cohort), CCSS-NCQ (in FU2 for original cohort or FU5 for expansion cohort), or BSI-18 (in baseline, FU2, or FU4 for original cohort; or baseline expansion, or FU5 for expansion cohort).

B. Predictor Variables:

1. Neurocognitive symptoms and impairment rates will be assessed with the Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ), a 25-item self-report questionnaire which has been validated for use in childhood cancer survivors to assess four domains of neurocognitive function: task efficiency, emotion regulation, organization, and memory.[28] Participants from the original cohort who participated in FU2 received this version. The revised version (CCSS-NCQ-R), used in FU5 with the expansion cohort, adds 14 items to 19 from the original CCSS-NCQ, increasing sensitivity while allowing longitudinal comparisons;[28] however, only the original 25 items will be used in FU5 for the purposes of this study (J1-25). Participants score each item on a 3-point Likert scale consisting of rating of "never a problem," "sometimes a problem," and "always a problem."[28] Impairment will be defined by a composite score $\leq 10^{th}$ percentile normed on sibling comparison groups as per previous CCSS manuscripts. Scores for each domain will be dichotomized according to impairment (yes/no) and will be pulled from FU2 for the original cohort, and FU5 for the expansion cohort.
2. Distress will be assessed using the Brief Symptom Inventory-18 (BSI-18), an 18-item self-report survey that has been validated to measure three domains of distress:

depression, anxiety, and somatization.[29] Raters use a 5-point scale to endorse items they have experienced throughout the past week related to these domains.[29] Consistent with previous CCSS studies, impairment will be defined by a score ≤ 10th percentile based on standardized norms, and scores will be pulled from FU2 and FU5 (G.1-18). Composite scores for each domain will be dichotomized according to impairment (yes/no).

C. Outcome Variables:

1. Substance Use will be assessed by self-report of alcohol and/or tobacco use from questionnaires provided during FU2 (tobacco items L.1-L.6) or FU4 (alcohol items N.1-N.6; tobacco items N.7-N.14) for original cohort, and FU5 (alcohol items N.1-N.6; tobacco items N.7-N.14) for expansion cohort. Scores for alcohol and tobacco use will be operationalized as ordinal variables consistent with previous CCSS manuscripts (see below).
    a. Alcohol (FU4, N.1-N.6; FU5, N.1-N.6)
        i. Heavy drinking (operationalized as ≥5 drinks/day for women and ≥6 drinks/day for men at least once/month for the past year)
        ii. Risky drinking (operationalized as >3 drinks/day or 7 drinks/week for women, and >4 drinks/day or 14 drinks/week for men)
        iii. Current drinker (operationalized as one or more drinks in the past year)
        iv. No alcohol use (operationalized as <2 drinks in one's lifetime)
    b. Tobacco (FU2, L.1-L.6; FU4, N.7-N.14; FU5, N7-N.14)
        i. Ever smoked (operationalized as exposures to at least 100 cigarettes but no longer smoking)
        ii. Current smoker (operationalized as exposure to at least 100 cigarettes and continually smoking)
        iii. Never smoker (operationalized as exposure to less than 100 cigarettes in one's lifetime)

D. Covariates:

1. Treatment Characteristics
    a. Surgery
        i. Yes
        ii. No
    b. Chemotherapy (yes/no) for the following agents:
        i. antimetabolites
        ii. anthracyclines
        iii. alkylating agents

iv. corticosteroids

c. Radiation (yes/no, location, dosage):
    i. None
    ii. Non-cranial
    iii. > 0Gy to < 20Gy (max dose to brain)
    iv. ≥ 20Gy max dose to brain

2. Patient Characteristics
    a. Cancer Diagnosis
        i. Leukemia
        ii. CNS tumors
        iii. Hodgkin
        iv. Non-Hodgkin
        v. Neuroblastoma
        vi. Wilms
        vii. Soft tissue sarcoma
        viii. Osteosarcoma
    b. Age at diagnosis (in years from baseline expansion, original, and sibling)
        i. < 10 years
        ii. ≥ 10 years
    c. Age at questionnaire
    d. Pain (J.3, J.4, J.9 expanded survivor baseline; J.6, J.7, J.13 original survivor and sibling baseline; FU2 G.19; FU4 L.21; FU5 L.20)
        i. No pain
        ii. Mild
        iii. Moderate
        iv. Severe
        v. Very severe
    e. Antidepressant/stimulant/analgesic medication use (yes/no for each category)
3. Sociodemographic Variables
    a. Sex assigned at birth (A.2 from baseline original, expansion, sibling)
        i. Male
        ii. Female
    b. Race/ethnicity (A.5, A.5a for expanded baseline, A.4, A.4a for original and sibling baseline)
        i. Asian
        ii. Black

iii. White
iv. Hispanic
v. Other

c. Educational attainment (R.1-R.2 expanded baseline, O.1-O.2 original and sibling baseline)
    i. < 12 yrs
    ii. High school graduate/GED
    iii. Some college
    iv. College graduate/post graduate
d. Marital/relationship status (M.2-M.3 for expanded baseline, L.1-L.2 for original and sibling baseline)
    i. Never married
    ii. Married/living with partner
    iii. Widowed/divorced/separated
e. Household income (FU2, S.1; FU5, A.7)
    i. Zero
    ii. < $19,999
    iii. $20,000-39,999
    iv. $40000-59999
    v. > $60,000

E. Statistical Analyses: Frequency distribution tables will be utilized to describe and compare participant variables for outcomes, predictors, and covariates. Means and standard deviations will be calculated for substance use among survivors overall, sibling controls, survivors with and without neurocognitive impairment, survivors with neurocognitive impairment and distress, and survivors with reported neurocognitive impairment without distress (Table 1).

1. Specific Aim 1: To investigate the relationships between CCSS-NCQ symptoms or NCQ impairment for each domain (task efficiency, emotional regulation, memory, and organization) and severity of alcohol and tobacco use. First, we will use ANOVA to examine the marginal association between the domain scores and the alcohol/tobacco use categories, and Chi-squared test to examine whether the impairment proportions for each domain is associated with the alcohol/tobacco use categories (Tables 2 & 3). We will then decide to use either NCQ symptom score or NCQ impairment (yes/no) as the predictor variable of interest in the following multivariable analysis.

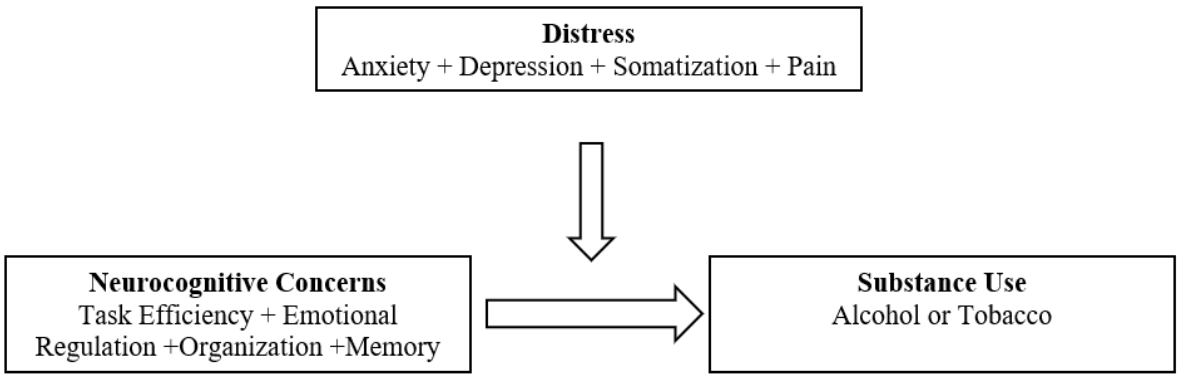
We will use generalized estimation equations for multinomial outcomes (alcohol and tobacco use categories), accounting for the within-family correlation between sibling controls and survivors, to estimate the odds of an alcohol/tobacco-use level vs. the reference level in association with each domain impairment, testing the potential effect modifications by the survivor-control status, adjusting for other covariates listed in d), in a single model for each of alcohol use and tobacco use. Because substance use can also begin in adolescence, to examine whether associations between neurocognitive symptoms and substance use exist even in those diagnosed at younger ages we will treat age as a categorical variable (< 10, ≥ 10 years) and examine its effect modification on the association. Covariates and effect modification that are not statistically significant at 0.05 level will be eliminated from the model.

a. Predictors: NCQ symptoms (raw scores), or NCQ impairment (yes/no)
b. Interaction: NCQ symptoms or NCQ impairment x Group (survivors vs siblings)
c. Outcomes: Alcohol or Tobacco use severity
d. Covariates: Sociodemographic, diagnosis, and treatment variables listed above

2. Specific Aim 2: Determine whether the relationship between neurocognitive symptoms or neurocognitive impairment and substance (alcohol and/or tobacco) use in childhood cancer survivors is moderated by distress (See Figure 1). This analysis will utilize CCSS-NCQ data from FU2 for the original cohort and FU5 for the expansion cohort; BSI-18, from FU2 for the original cohort, and FU5 for the expansion cohort; and alcohol and tobacco use items from FU4 in the original cohort and FU5 in the expanded cohort (Figures 2 & 3).
    a. Predictors: NCQ symptoms (raw scores) or NCQ impairment (yes/no)
    b. Moderators: BSI-18 significant symptoms (i.e., scores above cut-off) for GSI, Depression, Anxiety, Somatization, and pain as listed above
    c. Outcomes: Alcohol and tobacco usage
    d. Covariates: As listed above,

We will add the binary variable distress level (high/low), the interaction between distress level and the NCQ impairment in each domain, the interaction between distress level and survivor status, and test if the interaction between distress level and the NCQ impairment in each domain is different between survivors and siblings, using the above final model.

Figure 1. *Moderating Model: Distress on Alcohol and/or Tobacco Use in Survivors with Neurocognitive Concerns*



Note: The moderation model will be tested for both alcohol and tobacco use.

Special Considerations: None

Suggested Tables

Table 1. *Descriptive Statistics.*

	Survivors		p	Siblings		p
	N	*%*		N	%	
Age at Diagnosis						
<1						
1-4						
5-9						
10-14						
15-20						
Age at Questionnaire						
Sex						
Female						
Male						
Race/Ethnicity						
Asian						
Black						
White						
Hispanic						
Other						
Education						
<12 yrs						
High school graduate						
Some college						
College graduate						
Household income						

- Zero
- <$19,999
- $20,000-39,999
- $40,000-59,999
- Over $60,000

Marital/Relationship status
- Ever married
  - Yes
  - No
- Currently married
- Living as married
- Widowed

Neurocognitive Concerns
- Task Efficiency
- Emotional Regulation
- Organization
- Memory

Tobacco Use
- Ever Smoked
- Current Smoker
- Never Smoker

Alcohol Use
- Heavy
- Risky
- Current
- None

Distress
- Anxiety
- Depression
- Somatization

Treatment Characteristics
- Surgery
- Chemotherapy
  - Antimetabolites
  - Anthracyclines
  - Alkylating agents
- Corticosteroids
- Radiation
  - None
  - Non-cranial
  - Cranial >0Gy to <20Gy
  - Cranial ≥20Gy

Cancer Diagnosis
- Leukemia
- CNS malignancy
- Hodgkin lymphoma
- Non-Hodgkin lymphoma
- Neuroblastoma
- Wilms
- Soft tissue sarcoma

Osteosarcoma	
Pain	
No pain	
Mild	
Moderate	
Severe	
Very Severe	
Antidepressant	
Simulant	
Analgesic	

Table 2a. *Association between Neurocognitive score and Alcohol Use Severity*

Mean (sd)	Heavy Use	Risky Use	Current Use	No Use	p-value
1. Task Efficiency					
2. Emotion Regulation					
3. Organization					
4. Memory					

Table 2b. *Association between Neurocognitive Impairment and Alcohol Use Severity*

Impairment (%)	Heavy Use	Risky Use	Current Use	No Use	p-value
1. Task Efficiency					
2. Emotion Regulation					
3. Organization					
4. Memory					

Table 3a. *Association between Neurocognitive and Tobacco Use Severity*

Mean (sd)	Ever Smoker	Never Smoker	Current Smoker
1. Task Efficiency			
2. Emotion Regulation			
3. Organization			
4. Memory			

Table 3b. *Association between Neurocognitive Impairment and Tobacco Use Severity*

Impairment (%)	Ever Smoker	Never Smoker	Current Smoker
1. Task Efficiency			
2. Emotion Regulation			
3. Organization			
4. Memory			

Figure 2. *Moderating Effect of Distress on Tobacco Use in Survivors with Neurocognitive Concerns*

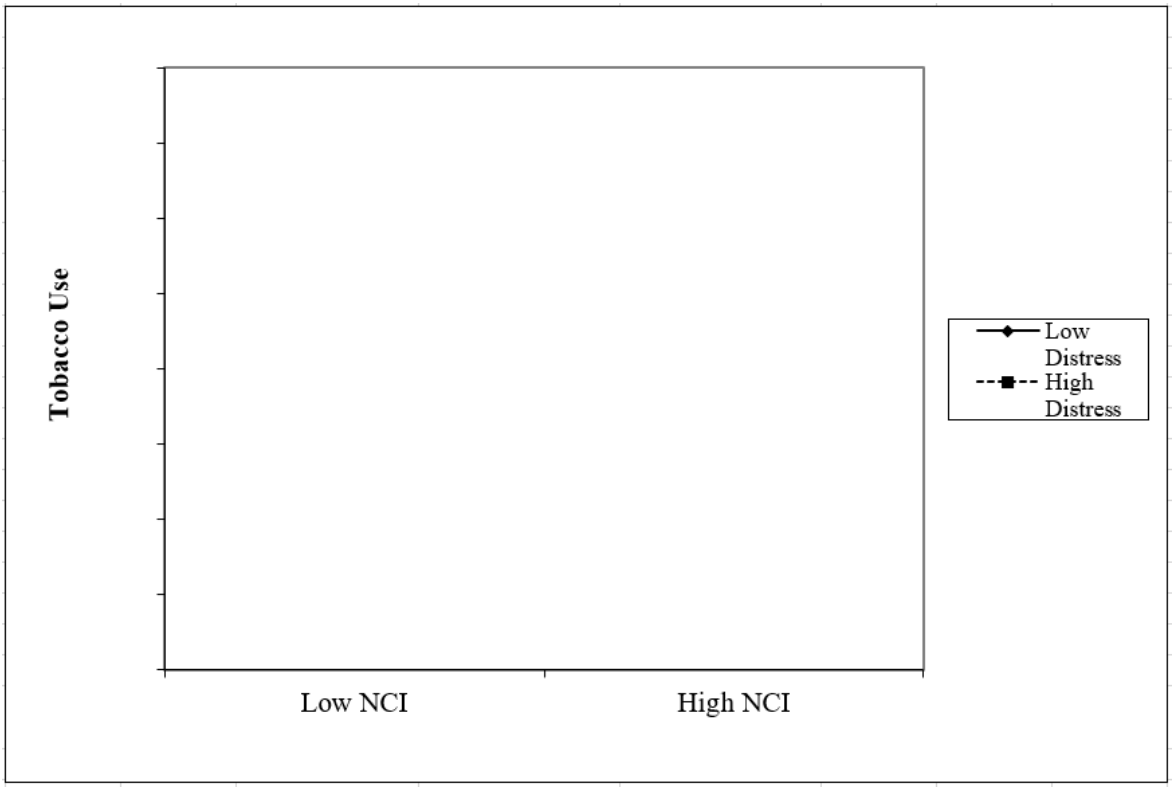
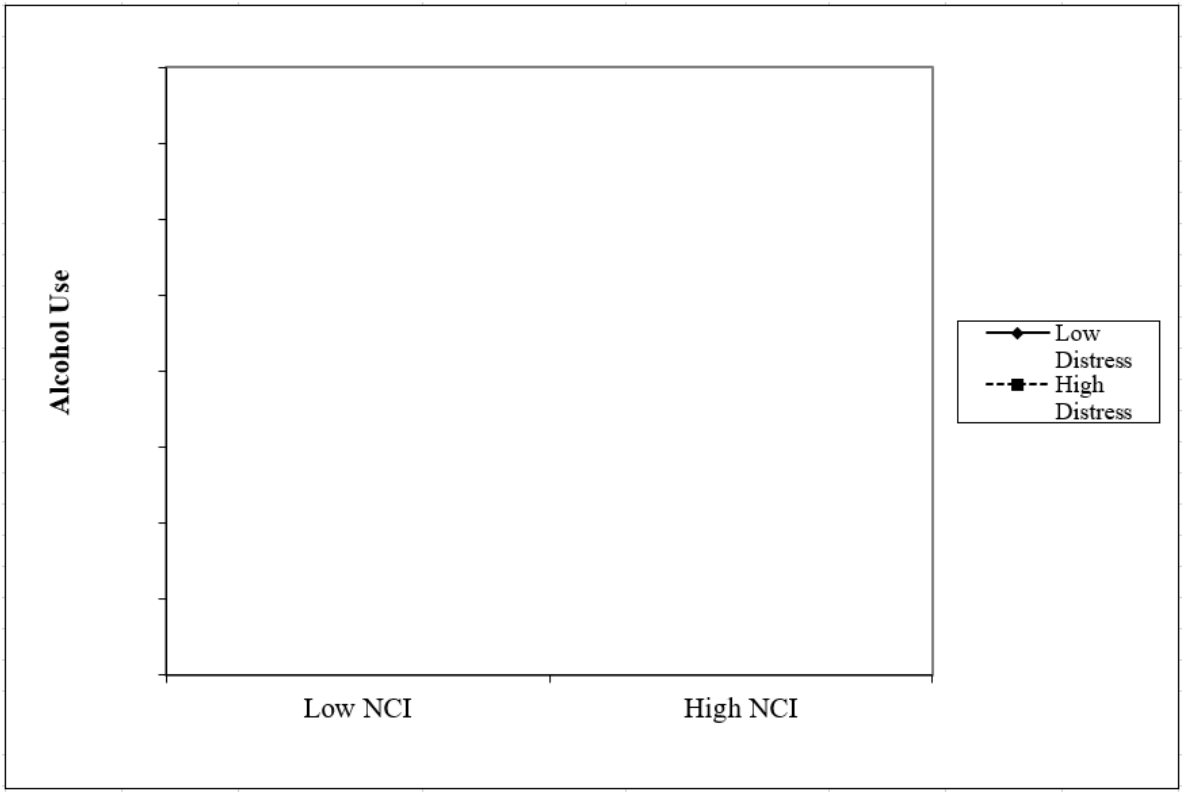


Figure 3. *Moderating Effect of Distress on Alcohol Use in Survivors with Neurocognitive Concerns*



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