

1. STUDY TITLE: *Adolescent behavior problems, health behavior, and social outcomes in the Childhood Cancer Survivor Study.*

2. WORKING GROUP AND INVESTIGATORS:

2.1. Working Group: Prevention and Control

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3. BACKGROUND AND RATIONALE:

Impaired psychosocial functioning has been identified as an important risk factor for poor health behavior, reduced social competence, and reduced utilization of health care in various medical populations. Depression and social isolation, for examples, are reported to increase risk for cardiovascular disease^{1,2} and obesity,^{3,4} and may be associated with insufficient exercise and physical activity.⁵⁻⁷ Attention deficits are a recognized risk factor for school failure,^{8,9} under employment,^{10,11} and lower income.¹¹ Attention deficits may also be associated with increased risk for obesity.^{12,13} Similarly, antisocial behavior, above and beyond its connection with attention deficits, is associated with increase risk for school failure,⁹ and may increase risk for obesity.^{14,15}

Adolescence is a developmental period when many behavioral and cognitive patterns are established and engrained. When attention problems and/or antisocial behaviors persist during adolescence, adverse behavioral patterns frequently continue into adulthood.^{9,16} Thus, it is important to identify the determinants of adult outcomes so that appropriate interventions may be developed and tested in high risk groups.

Behavioral problems in childhood are often assessed via parent report. A commonly used and standardized instrument for this purpose is the Child Behavior Checklist (CBCL),¹⁷ which assesses both internalizing and externalizing behavioral symptoms. The Behavior Problem Index (BPI) is a subset of questions from the CBCL that was collected, via parent report, during the Baseline Childhood Cancer Survivor Study (CCSS) assessment for adolescents younger than 18 years of age. In a recent analysis of the factor structure of the BPI in CCSS, five primary factors were identified: depression/anxiety, headstrong behavior, attention deficit, social withdrawal, and antisocial behavior.¹⁸ In this analysis, survivors demonstrated

increased risk ratios for depression/anxiety, attention deficit, and antisocial behavior as compared with siblings. Leukemia and CNS survivors were at significantly higher risk for adverse outcomes compared to other diagnostic groups.

Given the increased prevalence of emotional and behavioral problems in these adolescent cancer survivor groups, and the established association between these problems and poor health behavior and reduced social competence in the general population it is reasonable to question whether psychological symptoms in adolescence predict future adverse behavior and outcomes. This concept proposal aims to address this question by associating the parent-reported BPI factors at baseline with self-reported health behavior, social competence, and health care utilization data collected on the same adolescents at Follow-Up 2. Of the 2,979 adolescents whose parents completed the BPI during Baseline, 1,670 (56%) completed Follow-Up 2 on themselves. Within this sample, 45% are survivors of leukemia and 12% are survivors of CNS tumors. Thus, 57% of the sample should be at increased risk for behavioral problems as evidenced by the BPI.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

4.1. Primary Aim:

- 4.1.1. To examine the association between adolescent psychosocial symptoms and future health behaviors, social competence, and health care utilization among young adult survivors of childhood cancer.

4.2. Objectives:

- 4.2.1. To examine the impact of baseline symptoms of depression/anxiety, headstrong behavior, attention deficit, social withdrawal, and antisocial behavior on health behaviors.
- 4.2.2. To examine the impact of baseline symptoms of depression/anxiety, headstrong behavior, attention deficit, social withdrawal, and antisocial behavior on future obesity.
- 4.2.3. To examine the impact of baseline symptoms of depression/anxiety, headstrong behavior, attention deficit, social withdrawal, or antisocial behavior on future social competence.
- 4.2.4. To examine the impact of baseline symptoms of depression/anxiety, headstrong behavior, attention deficit, social withdrawal, or antisocial behavior on future health care utilization.

4.3. Hypotheses:

- 4.3.1. Symptoms of depression/anxiety, attention deficit, and social withdrawal in adolescence will predict future health behaviors. Specifically, we expect increased depression/anxiety, increased attention deficits, and increased social withdrawal to be predictive of decreased physical activity, increased tobacco use, and decreased sun screen use at Follow-Up 2.
- 4.3.2. Symptoms of depression/anxiety, attention deficit, and social withdrawal in adolescence will predict future obesity. Specifically, we expect increased

depression/anxiety, increased attention deficits, and increased social withdrawal to be predictive of increased BMI at Follow-Up 2.

4.3.3. Symptoms of attention deficits, social withdrawal, and antisocial behavior in adolescence will predict social competence at Follow-Up 2. Specifically, we expect increased attention deficits and increased antisocial behavior to predict decreased educational attainment, unemployment, and decreased personal income. We also expect increased social withdrawal to be predictive of being unmarried and to be living with one's parents.

4.3.4. Symptoms of depression/anxiety and social withdrawal in adolescence will predict future health care utilization. Specifically, we expect increased depression/anxiety and increased social withdrawal to predict decreased frequency of physician contact and decreased frequency of dental visits.

5. ANALYSIS FRAMEWORK:

5.1. Outcome(s) of interest: The primary outcomes of interest are social competence, health behaviors, obesity, and health care utilization. We plan to conduct the following analyses:

5.1.1. Separate regression analyses will be conducted for each outcome variable, using symptoms of depression/anxiety, headstrong behavior, attention deficit, social withdrawal, and antisocial behavior during adolescence as predictors. Behavioral symptoms will be taken from the adolescent Baseline data, with factor scores calculated as previously established.¹⁸ Outcomes will be taken from Follow-Up 2.

5.1.1.1. Logistic regression analysis will be used for outcome variables currently classified into non-ordinal categories:

- Current employment status (Employed - Yes/No)
- Current marital status (Married – Yes/No)
- Current living arrangements (Living Independently – Yes/No)

5.1.1.2. Ordinal regression will be used for outcome variables currently classified into other categories:

- Educational level
- Income
- Frequency of other tobacco use
- Frequency of sun screen use
- Frequency of physician contact
- Frequency of dental visits

These variables will also be re-formatted into binary categories and analyzed with logistic regression to calculate odds ratios. Insurance status will also be used as a covariate for health care utilization.

5.1.1.3. Linear regression will be used to examine the association between behavioral problems and outcome variables available in integer format:

- Minute/week of vigorous/moderate physical activity
- BMI
- Cigarettes/day

These outcome variables will also be re-formatted into binary categories and analyzed with logistic regression to calculate odds ratios.

- 5.1.2. Mediators and moderator of outcome will be examined by including diagnosis (i.e. Leukemia, CNS Tumor, Hodgkin's Disease, Non-Hodgkin's Lymphoma, Wilms' Tumor, Neuroblastoma, and Soft Tissue Sarcoma), cancer therapy (i.e. cranial radiation vs. non-cranial radiation; CNS chemotherapy vs. non-CNS chemotherapy), sex, special education, and psychotropic medication history (i.e. antidepressants, stimulants, etc...) as covariates. Marital status, employment, educational level, body mass index, and smoking at baseline will also be used as covariates of outcome.
- 5.1.3. Related to the specific hypotheses, the following analyses will be conducted:
- 5.1.3.1. Symptoms of depression/anxiety, attention deficit, and social withdrawal in adolescence will predict future health behaviors.
- Physical activity outcome: Predictors = depression/anxiety, attention deficits, and social withdrawal; Covariates = diagnosis, cranial irradiation, CNS chemotherapy, sex, psychotropic medication.
 - Tobacco use outcome: Predictors = depression/anxiety, attention deficits, and social withdrawal; Covariates = diagnosis, cranial irradiation, CNS chemotherapy, sex, psychotropic medication, smoking at baseline.
 - Sun screen use outcome: Predictors = depression/anxiety, attention deficits, and social withdrawal; Covariates = diagnosis, cranial irradiation, CNS chemotherapy, sex, psychotropic medication.
- 5.1.3.2. Symptoms of depression/anxiety, attention deficit, and social withdrawal in adolescence will predict future obesity.
- BMI outcome: Predictors = depression/anxiety, attention deficits, and social withdrawal; Covariates = diagnosis, cranial irradiation, CNS chemotherapy, sex, psychotropic medication, BMI at baseline.
- 5.1.3.3. Symptoms of attention deficits, social withdrawal, and antisocial behavior in adolescence will predict social competence at Follow-Up 2.
- Educational attainment outcome: Predictors = attention deficits and antisocial behavior; Covariates = diagnosis, cranial irradiation, CNS chemotherapy, sex, psychotropic medication, educational level at baseline, history of special education.
 - Employment outcome: Predictors = attention deficits and antisocial behavior; Covariates = diagnosis, cranial irradiation, CNS chemotherapy, sex, psychotropic medication, employment at baseline, history of special education.
 - Personal income outcome: Predictors = attention deficits and antisocial behavior; Covariates = diagnosis, cranial irradiation, CNS chemotherapy, sex, psychotropic medication, employment, history of special education.
 - Marital status outcome: Predictor = social withdrawal; Covariates = diagnosis, cranial irradiation, CNS chemotherapy, sex, psychotropic medication, marital status at baseline.
 - Living arrangement outcome: Predictor = social withdrawal; Covariates = diagnosis, cranial irradiation, CNS chemotherapy, sex, psychotropic medication, employment at baseline, marital status at baseline.
- 5.1.3.4. Symptoms of depression/anxiety and social withdrawal in adolescence will predict future health care utilization.

- Frequency of physician visits outcome: Predictors = depression/anxiety and social withdrawal; Covariates = diagnosis, cranial irradiation, CNS chemotherapy, sex, psychotropic medication.
- Frequency of dental visits outcome: Predictors = depression/anxiety and social withdrawal; Covariates = diagnosis, cranial irradiation, CNS chemotherapy, sex, psychotropic medication.

5.2. Subject population:

5.2.1. Adolescent Baseline Data

5.2.1.1. Inclusion criteria

- Cancer survivors whose parents completed BPI and who themselves completed Follow-Up 2.
- Cancer survivors who were 12-17 years of age at Baseline.

5.2.1.2. Exclusion criteria

- Stroke (F9)
- Cerebral Palsy (J1)
- Paralysis (J2)
- Mental Retardation (J3)
- Epilepsy (J4)

5.2.1.3. Variables

- Cancer Diagnosis
- Radiation Therapy Variable (Dichotomous: CRT vs Non-CRT; no localization or intensity required)
- Chemotherapy Variable (Dichotomous: CNS vs Non-CNS; CNS=IV/IT Methotrexate and Corticosteroids; Non-CNS=all others)
- Age (A1)
- Sex (A2)
- Baseline BMI (A10, A11)
- Baseline Psychopharmacology (B8(15))
- BPI (J19, J20, J21)
- Baseline Marital Status (L2)
- Baseline Smoker (N1) – Yes/No
- Baseline Other Tobacco Use (N2) – Yes/No
- Baseline Grade Level (O1)
- Baseline Special Education (O3)
- Baseline Employed (O7)

5.2.2. Follow-Up 2 Data

5.2.2.1. Inclusion criteria

- Cancer survivors whose parents completed the Behavior Problems Index in the Baseline CCSS Questionnaire and who themselves completed the Follow-Up 2 Questionnaire (n=1,670).

5.2.2.2. Variables

- Current Education Completed (1)
- Current Marital Status (2)

- Current Living Arrangement (3)
- Current Employment (4)
- Current BMI (7, 8)
- Number times seen physician (A3)
- Number times seen physican for cancer (A5)
- Use Sun screen (C11)
- Min/wk vigorous exercise (D3, D4)
- Min/wk moderate exercise (D6, D7)
- Tobacco (L1) – Yes/No
- Cigarettes/Day (L3)
- Other Tobacco (L6)
- Insurace (M1) Covariate
- Dental visits (O17)
- Current Psychopharm (Q8)
- Current Personal Income (S3)

5.3. Explanatory variables.

- Psychotropic medications at and after baseline functioning (previously coded by and available from Ann Mertens).
- Cranial radiation (yes vs. no)
- Chemotherapy (CNS vs. Non-CNS)

5.4. Examples of specific tables and figures:

Descriptive Statistics at Follow Up 2

	No	%
Sex		
Female		
Male		
Age		
<i>Intervals TBD</i>		
Diagnosis		
Leukemia		
CNS		
HD		
NHL		
Wilms'		
Neuroblastoma		
Soft tissue sarcoma		

Current Social Competence

	No	%
Education		
9-12 years		
High school grad		
Post HS Training		
College		
Post Grad		
Employment		
Working FT		
Working PT		
Caring for home		
Unemployed		
Unable to work		
Student		
Income		
< 20,000		
20,000-39,999		
40,000-59,999		
60,000-79,999		
80,000-99,999		
≥ 100,000		
Living Arrangement		
Spouse/Partner		
Parents		
Roommate		
Brother/Sister		
Other relative		
Alone		
Marital Status		
Single		
Married		
Living as married		
Divorced/Separated		

Current Health Care Utilization

	No	%
Physician care in last 2 yrs		
None		
1-2 times		
3-4 times		
5-6 times		
7-10 times		
11-20 times		
> 20 times		
Cancer-related care in last 2 yrs		
None		
1-2 times		
3-4 times		
5-6 times		
7-10 times		
11-20 times		
> 20 times		
Dental Care in last yr		
No		
Yes		
Health Insurance		
Yes		
No		
Canadian Resident		

Current Health Characteristics

	No	%
BMI Classification		
Underweight		
Normal Range		
Overweight		
Obese		
Exercise		
None	#	%
Moderate Physical Activity	Min/wk	
Vigorous Physical Activity	Min/wk	
Tobacco Use		
None		
Cigarettes		
Chew		
Snuff		
Pipe		
Cigars		
Sun Protection		
Sunscreen		
Protective Clothing		
Use Hat		
Limit Exposure		
Stay in Shade		

Odds ratios for the prediction of social competence in adults by behavior problems during adolescence.

	<i>College Graduate</i>			<i>Full-time Employment</i>			<i>Income*</i>			<i>Married</i>			<i>Living Independently</i>		
	OR	95% CI	p	OR	95% CI	P	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Dep/Anx															
Headstrng															
Attent Def															
Social W/D															
Antisocial															
Total															

* Cut-off level will be determined following review of data distribution.

Odds ratios for the prediction of health behaviors in adults by behavior problems during adolescence.

	<i>Physical Exercise*</i>			<i>Smoking*</i>			<i>Non-smoke Tobacco*</i>			<i>Sun Screen Use*</i>		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Dep/Anx												
Headstrng												
Attent Def												
Social W/D												
Antisocial												
Total												

* Cut-off level will be determined following review of data distribution.

Odds ratios for the prediction of health care utilization in adults by behavior problems during adolescence.

	<i>General Physical Care*</i>			<i>Cancer Related Care*</i>			<i>Dental Care*</i>		
	OR	95% CI	p	OR	95% CI	P	OR	95% CI	p
Dep/Anx									
Headstrng									
Attent Def									
Social W/D									
Antisocial									
Total									

* Cut-off level will be determined following review of data distribution.

6. SPECIAL CONSIDERATION:

6.1. Given the availability of statistical support to Dr. Krull at St. Jude Children’s Research Hospital, we believe that we can complete the statistical procedures ourselves and, thus, not add to the list awaiting 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 publications committee for review.

7. REFERENCES:

1. Urizar GG, Jr., Sears SF, Jr. Psychosocial and cultural influences on cardiovascular health and quality of life among Hispanic cardiac patients in South Florida. J Behav Med 2006;29(3):255-68.

2. Luttik ML, Jaarsma T, Moser D, Sanderman R, van Veldhuisen DJ. The importance and impact of social support on outcomes in patients with heart failure: an overview of the literature. *J Cardiovasc Nurs* 2005;20(3):162-9.
3. Cuijpers P, Schoevers RA. Increased mortality in depressive disorders: a review. *Curr Psychiatry Rep* 2004;6(6):430-7.
4. Lauder W, Mummery K, Jones M, Caperchione C. A comparison of health behaviours in lonely and non-lonely populations. *Psychol Health Med* 2006;11(2):233-45.
5. Mental health in the United States: health risk behaviors and conditions among persons with depression--new Mexico, 2003. *MMWR Morb Mortal Wkly Rep* 2005;54(39):989-91.
6. Vickers KS, Nies MA, Patten CA, Dierkhising R, Smith SA. Patients with diabetes and depression may need additional support for exercise. *Am J Health Behav* 2006;30(4):353-62.
7. Sallis JF, Prochaska JJ, Taylor WC. A review of correlates of physical activity of children and adolescents. *Med Sci Sports Exerc* 2000;32(5):963-75.
8. Faraone SV, Biederman J, Mennin D, Gershon J, Tsuang MT. A prospective four-year follow-up study of children at risk for ADHD: psychiatric, neuropsychological, and psychosocial outcome. *J Am Acad Child Adolesc Psychiatry* 1996;35(11):1449-59.
9. Faraone SV, Biederman J, Spencer T, et al. Attention-deficit/hyperactivity disorder in adults: an overview. *Biol Psychiatry* 2000;48(1):9-20.
10. Biederman J, Faraone SV, Spencer TJ, Mick E, Monuteaux MC, Alardi M. Functional impairments in adults with self-reports of diagnosed ADHD: A controlled study of 1001 adults in the community. *J Clin Psychiatry* 2006;67(4):524-40.
11. Biederman J, Faraone SV. The effects of attention-deficit/hyperactivity disorder on employment and household income. *MedGenMed* 2006;8(3):12.
12. Campbell BC, Eisenberg D. Obesity, attention deficit-hyperactivity disorder and the dopaminergic reward system. *Coll Antropol* 2007;31(1):33-8.
13. Hubel R, Jass J, Marcus A, Laessle RG. Overweight and basal metabolic rate in boys with attention-deficit/hyperactivity disorder. *Eat Weight Disord* 2006;11(3):139-46.
14. Johnson JG, Cohen P, Kasen S, Brook JS. Personality disorder traits evident by early adulthood and risk for eating and weight problems during middle adulthood. *Int J Eat Disord* 2006;39(3):184-92.
15. Pickering RP, Grant BF, Chou SP, Compton WM. Are overweight, obesity, and extreme obesity associated with psychopathology? Results from the national epidemiologic survey on alcohol and related conditions. *J Clin Psychiatry* 2007;68(7):998-1009.
16. Mannuzza S, Klein RG. Long-term prognosis in attention-deficit/hyperactivity disorder. *Child Adolesc Psychiatr Clin N Am* 2000;9(3):711-26.
17. Achenbach TM. *Manual for the Child Behavior Checklist*. Burlington: University of Vermont, Department of Psychiatry; 1991.
18. Schultz KA, Ness KK, Whitton J, et al. Behavioral and social outcomes in adolescent survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol* 2007;25(24):3649-56.