

Childhood Cancer Survivor Study (U24 CA55727)

Report of the Psychology Working Group Kevin Krull, PhD

CCSS Investigator Meeting
Williamsburg, VA
June 9-10, 2010

- Overview of standardized instruments
- Manuscript – recently published and drafted/under review
- Approved concepts in progress
- New concepts in development
- Future priorities

Standard Psychological Instruments

- Medical Outcomes Survey Short Form – 36 (SF-36)
 - General health, well-being, quality of life over past month
 - Nationally representative normative sample
 - Scales
 - Physical and Mental summary scales
 - Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, Mental Health
- Brief Symptom Inventory – 18 (BSI-18)
 - Emotional distress over prior 7 days
 - Nationally representative normative sample
 - Scales
 - Global Distress
 - Depression, Anxiety, Somatization

- Post-Traumatic Stress Disorder
 - DSM-IV categorical classification
 - 17 symptoms over 3 categories (1-3-2)
 - Re-experience/intrusion, avoidance, increased arousal
 - “Distress” (BSI-18) or “functional impairment” (SF-36 Role Emotional)
- Post-Traumatic Growth Inventory
 - Positive life change associated with traumatic event
 - Scales
 - New Possibilities, Relating to Others, Personal Strength, Spiritual Change, Appreciation of Life

- **CCSS-Neurocognitive Questionnaire (NCQ)**
 - Self-reported neurocognitive problems
 - EFA and CFA in CCSS
 - CCSS Sibling Cohort norms
 - Scales
 - Task Efficiency, Memory, Organization, Emotional Regulation

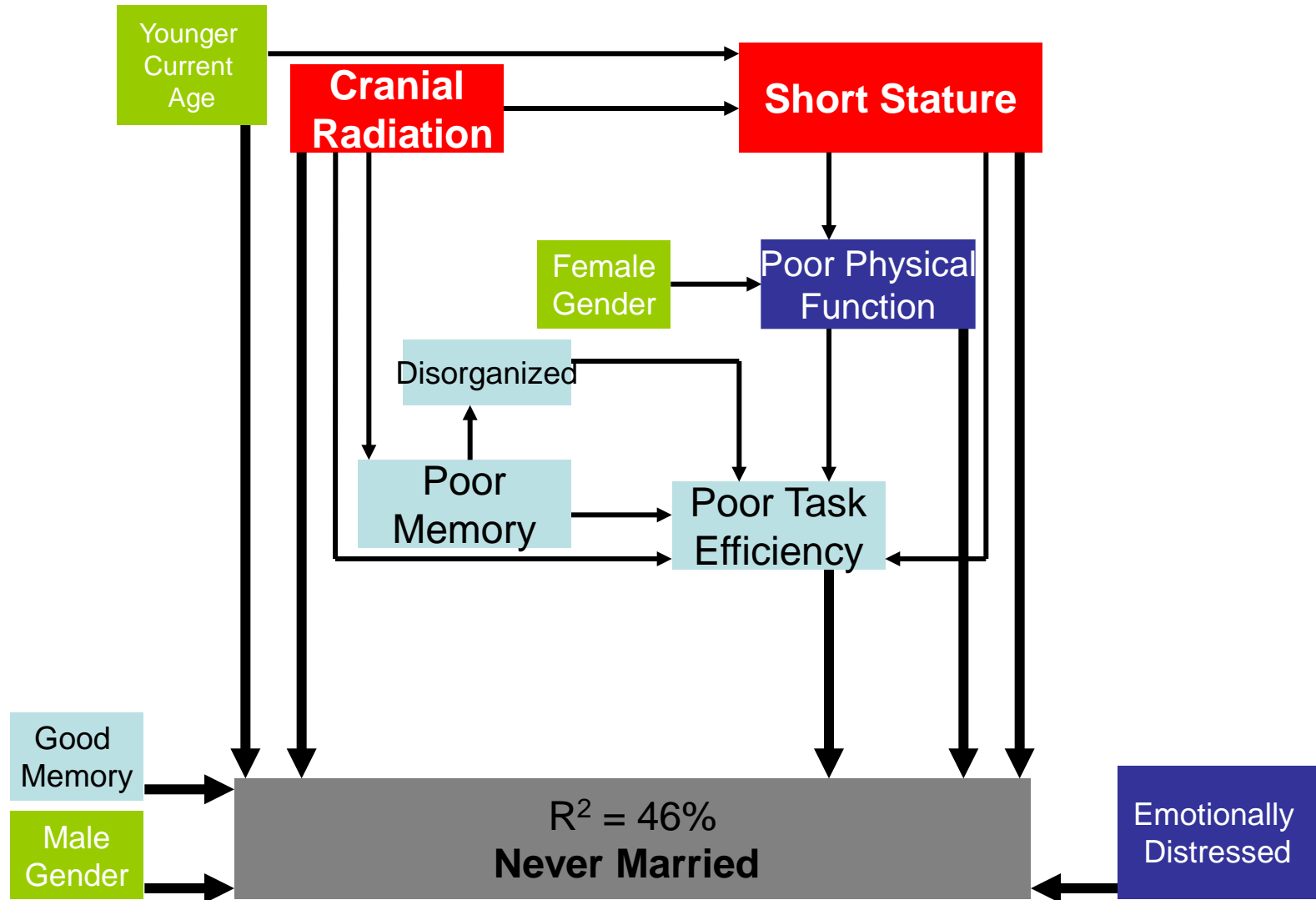
Manuscript Completed / Drafted

Marriage and Divorce

Janson C, Cox C, Termuhlen A, Leisenring W, Whitton J, Goodman P, Mertens AC, Zeltzer L, Robison LL, Krull KR, Kadan-Lottick N. Predictors of marriage and divorce among adult survivors of childhood cancers. *Cancer Epidemiol Biomarkers Prev*, 2009; 18(10):2626-35.

- Aims:
 - To estimate rate of marriage and divorce in adult survivors of childhood cancer
 - To examine predictors of marriage and divorce
- Methods:
 - 2003 Follow-up survey
 - BSI-18, CCSS-NCQ
 - Structural Equation Modeling (SEM)

Graphic representation of structural equation modeling of predictors of never-married status in CCSS cases

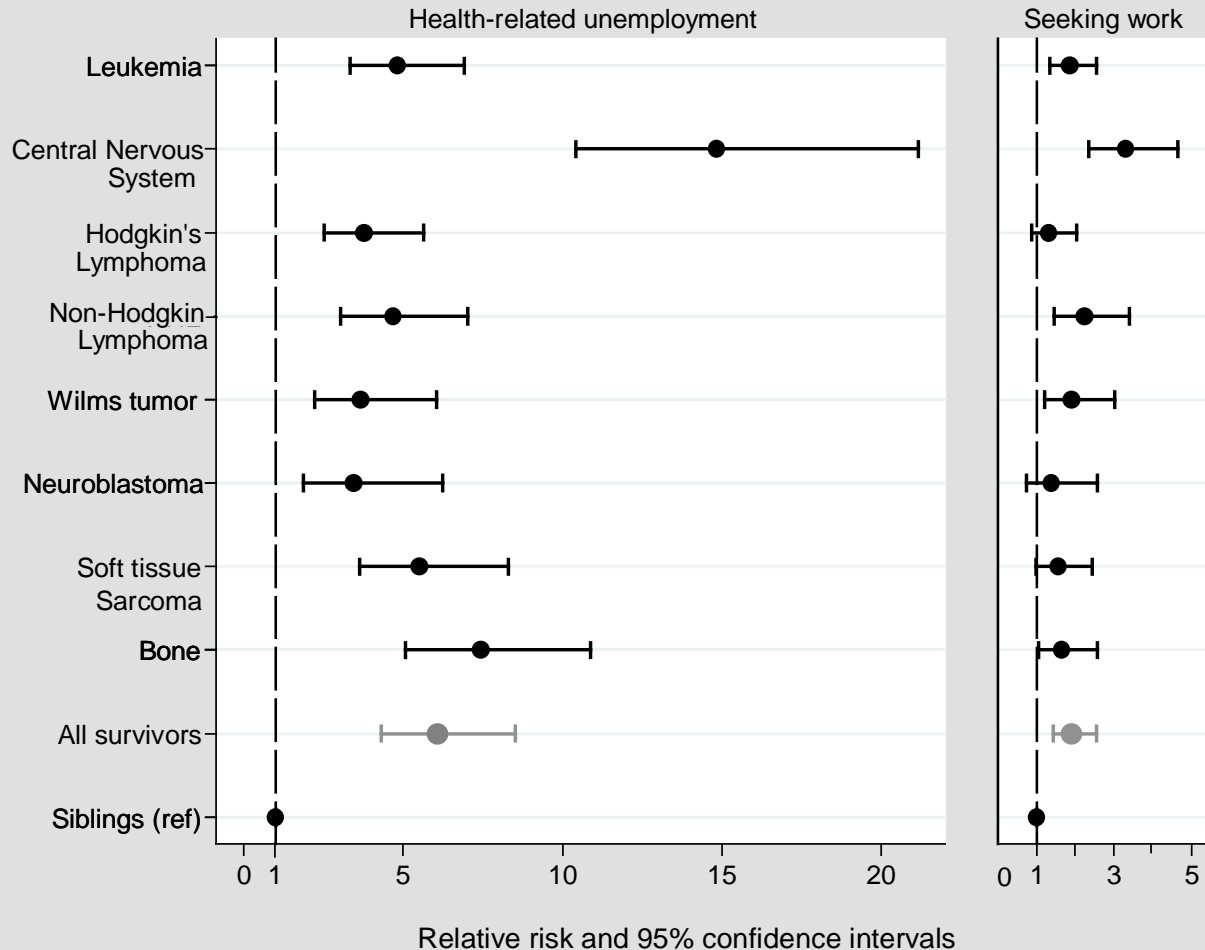


Kirchhoff AC, Leisenring W, Krull KR, Ness KK, Friedman DL, Armstrong GT, Stovall M, Park ER, Oeffinger KC, Hudson MM, Robison LL, Wickizer T. Unemployment among adult survivors of childhood cancer. *Medical Care*, in press.

- Aims:
 - To estimate the prevalence of health-related unemployment in adult survivors of childhood cancer
 - To examine predictors of health-related unemployment
- Method:
 - 6339 survivors and 2280 siblings aged ≥ 25
 - 2003 Follow-up survey

- Results
 - Health-related unemployment higher in survivors (10.4%) than siblings (1.8%) (RR 6.07, 95% CI 4.32-8.53)
 - Survivors were unemployed but seeking work more often
 - Risk for health-related unemployment:
 - Females (OR 1.73, 95% CI 1.43-2.08).
 - CRT doses ≥ 25 Gy (OR 3.46, 95% CI 2.53-4.72)
 - Compared to employed survivors, unemployed survivors
 - reported poorer physical functioning
 - had lower education and income
 - were more likely to be publicly insured

Employment and Occupations...



Kirchhoff et al. Occupational outcomes of adult childhood cancer survivors

- Sample:
 - Mutually-exclusive occupational categories: Managerial/Professional, Non-Physical, and Physical occupations.
 - 5070 employed survivors and 1799 siblings ages ≥ 25 years
- Results:
 - Survivors were less often in Professional jobs (RR 0.92, 95% CI 0.87-0.96)
 - Survivors were more likely in non-physical jobs (RR 1.11, 95% CI 1.03-1.20)
 - Risk for non-professional employment:
 - High dose CRT
 - Race
 - Male sex

Kirchhoff et al. Psychosocial and neurocognitive predictors of employment

Kunin-Batson et al. Predictors of independent living status in adult survivors of childhood cancer

- Aims:
 - To estimate prevalence of dependent living in adult survivors of childhood cancer
 - To examine predictors of dependent living
- Method:
 - 6,047 survivors and 2,326 siblings ≥ 25 years of age
 - 2003 Follow-up survey
 - SF-36, BSI-18, CCSS-NCQ

Dependent Living....

Table 2. Multivariate analysis of patient characteristics, treatment factors, and late effects with dependent living status

Variable	Odds Ratio (95% CI)	p-value*
Cranial Radiation Therapy		
>0 to <2400 versus None	1.35 (1.11-1.65)	<.0001
>2400 versus None	3.63 (2.82-4.68)	<.0001
Task Efficiency Difficulty	1.91 (1.57-2.33)	<.0001
Depression	1.61 (1.23-2.10)	<.0001
Poor Physical Functioning	1.96 (1.53-2.50)	<.0001
Use Neuroleptic/Stimulant/Anticonvulsant Meds	3.05 (2.31-4.03)	<.0001
Ethnic/Racial Minority Status	2.60 (2.02-3.36)	<.0001
Current Age over 35	0.50 (0.40-0.62)	<.0001
Age at Diagnosis		
> 12 v <6	0.43 (0.33-0.55)	<.0001
≥6 and <12 v <6	0.71 (0.58-0.87)	<.0001
Chemo w/o Methotrexate/Steroid vs No Chemo	0.69 (0.53-0.89)	<.0001
Emotion Tolerance Difficulty	0.70 (0.54-0.92)	<.0001
Anxiety	0.68 (0.49-0.96)	.03

*All analyses adjusted for age, sex, and race

Survivor and Treatment Moderators of Living Independently

Direct and Mediating Influences on Living Independently

Current Age

Race

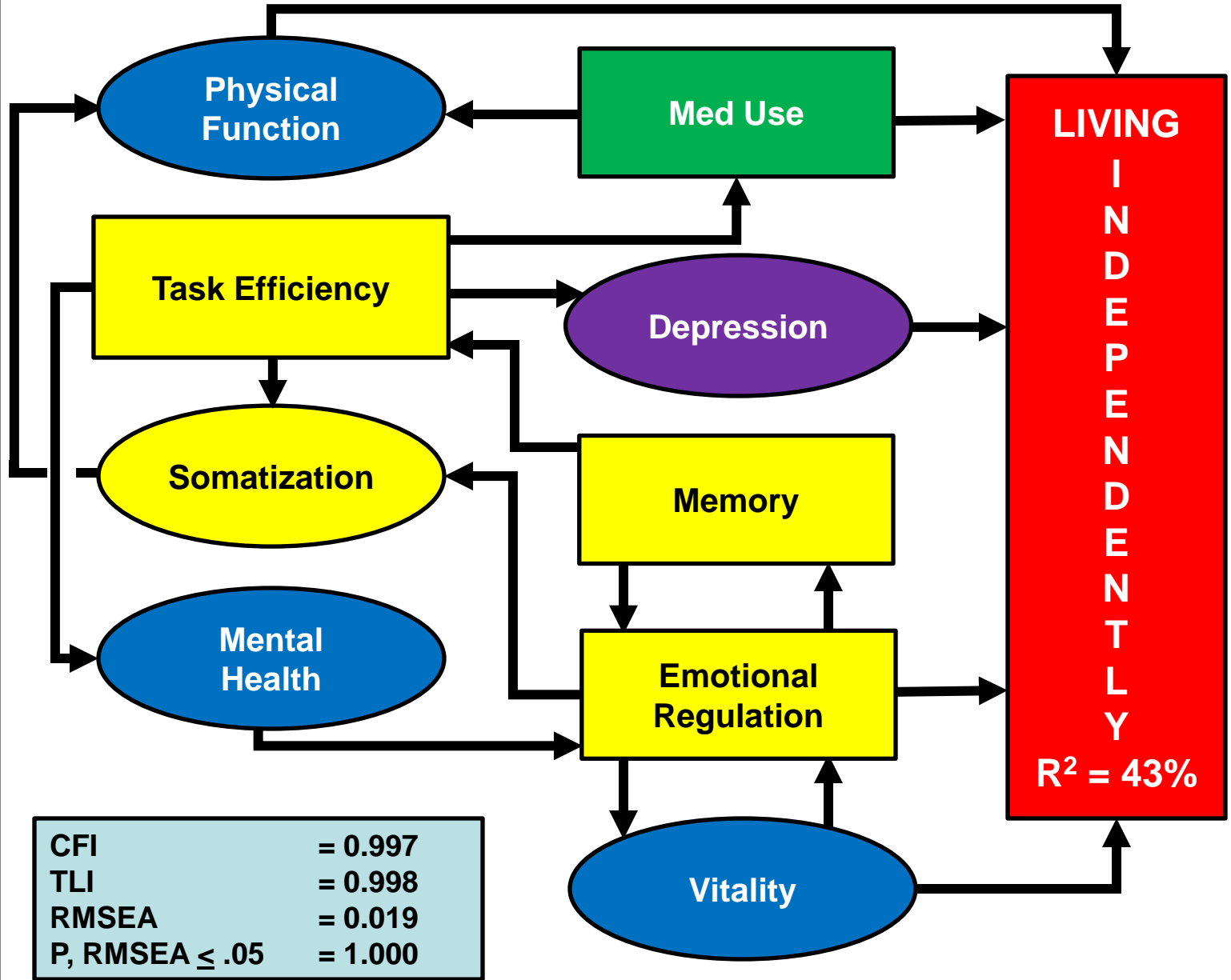
Age @ Diagnosis

Cranial Radiation Therapy

Growth Hormone Deficiency

Chemotherapy

Diagnosis



Recklitis CJ, Diller LR, Li X, Najita J, Robison LL, Zeltzer L. Suicide ideation in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *J Clin Oncol*, 2010; 28(4): 655-61.

- Aims:
 - To estimate prevalence of suicide ideation in adult survivors of childhood cancer
 - To examine predictors of suicide ideation
- Method:
 - Baseline survey
 - BSI-18

- Results:
 - 7.8% SI in survivors vs. 4.6% of siblings (OR 1.79, 95% CI, 1.4 - 2.4)
 - CNS cancer diagnosis (OR 1.5, 95% CI 1.1 – 1.9)
 - Poor physical health (OR 2.6, 95% CI 1.5 – 4.5)
 - SI unrelated to age, age at diagnosis, sex, cancer therapy, recurrence, time since diagnosis, or second malignancy

Stuber ML, Meeske KA, Krull KR, Leisenring W, Stratton K, Kazak AE, Huber M, Zebrack B, Uijtdehaage SH, Mertens AC, Robison LL, Zeltzer LK. Prevalence and predictors of posttraumatic stress disorder in adult survivors of childhood cancer. *Pediatrics*. 2010; 125(5): 1124-34.

- Aims:
 - To estimate prevalence of PTSD in adult survivors of childhood cancer
 - To examine predictors of PTSD
- Method:
 - 6542 survivors and 368 siblings
 - 2003 Follow-up survey

- Results:
 - 589 survivors (9%) and 8 siblings (2%) with PTSD (OR: 4.14, 95% CI: 2.08–8.25)
 - Increased risk associated with:
 - Treatment intensity (OR: 1.36, 95% CI: 1.06 –1.74)
 - Educational of high school or less (OR: 1.51, 95% CI: 1.16 –1.98)
 - Being unmarried (OR: 1.99, 95% CI: 1.58 –2.50)
 - Annual income below \$20 000 (OR: 1.63, 95% CI: 1.21–2.20)
 - Being unemployed (OR: 2.01, 95% CI: 1.62–2.51)
 - NS: Sex, Race, Chemo agents, SMN's, Recurrence

- Stuber et al. PTSD symptom pattern and severity
 - Symptom categories
 - Impact of symptoms
- Stuber et al. PTSD symptoms maintenance
 - Chronic illness
 - Quality of life
- Phipps et al. PTSD-PTGI associations

Lu Q, Krull KR, Owen JE, Kawashima T, Leisenring W, Tsao JCI, Zebrack B, Mertens A, Armstrong GT, Stovall M, Robison LL, Zeltzer LK. Pain in Survivors of Childhood and Adolescent Cancer.

- Aims:
 - To characterize pain outcomes among long-term survivors of childhood cancer.
 - To examine predictors of pain
- Method:
 - 10,397 survivors and 3,034 sibling controls
 - Baseline survey
 - Pain symptom categories of pain/abnormal sensation, migraines, and other headaches.

- Results:
 - Risk higher among survivors than siblings, adjusting for gender, ethnicity, annual household income, marital status, and education.
 - Risk factors:
 - Younger age at diagnosis, female gender, lower education
 - Hodgkin lymphoma, Wilms tumor, neuroblastoma, and soft tissue sarcoma (vs. leukemia)

Sibling Psychological Health

Buchbinder D, Casillas J, Leisenring W, Goodman P, Recklitis C, Armstrong GT, Alderfer M, Kunin-Batson A, Stuber M, Krull KR, Robison LL, Zeltzer LK. Psychological outcomes of siblings of cancer survivors. Submitted to Psycho-Oncology

- Aims:
 - To estimate psychological long-term outcomes in siblings of survivors of childhood cancer
- Method:
 - 3,083 siblings (mean age 29 years, range 18-56 years)
 - Baseline survey
 - Brief Symptom Inventory-18 (BSI-18)

Sibling Psychological Health

- Results:
 - Psychological distress reported by 3.8% of the siblings
 - Less than 1.5% of siblings elevated on two or more of the subscales of the BSI-18.
 - Risk for sibling depression:
 - Having a brother survivor (OR 2.22, 95% CI 1.42-3.55)
 - Having a survivor with impaired health (OR 2.15, 95% CI 1.18-3.78)
 - Risk for sibling distress:
 - Having an older survivor (OR 1.81, 95% CI 1.05-3.12)

Post-traumatic Growth

Zebrack BJ, Stuber ML, Meeske KA, Yasui Y, Liu Q, Krull KK, Phipps S, Robison LL, Zeltzer LK. Prevalence and predictors of posttraumatic growth in adult survivors of childhood cancer. Submitted to J Pediatr Psychol.

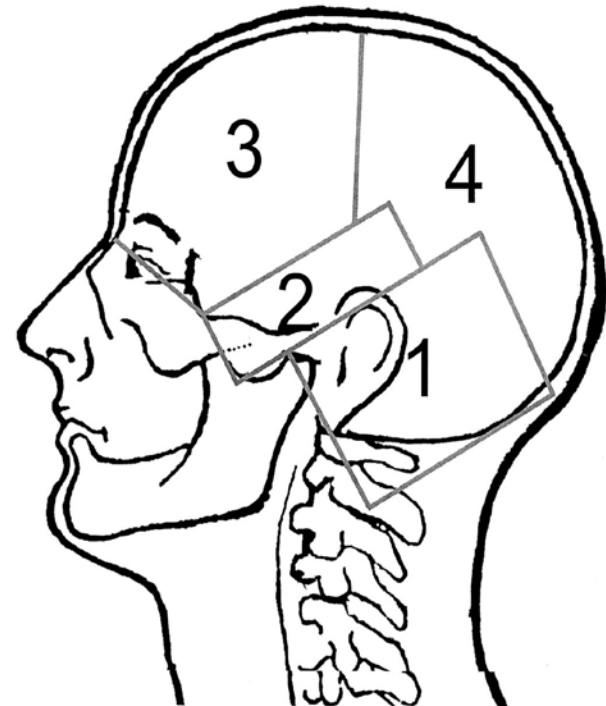
Neurocognitive Function

Kadan-Lottick NS, Zeltzer LK, Liu Q, Yasui Y, Ellenberg L, Gioia G, Robison LL, Krull KR. Neurocognitive functioning in adult survivors of childhood non-central nervous system cancers. *J Natl Cancer Inst*, 2010. Epub ahead of print.

Neurocognitive Specificity

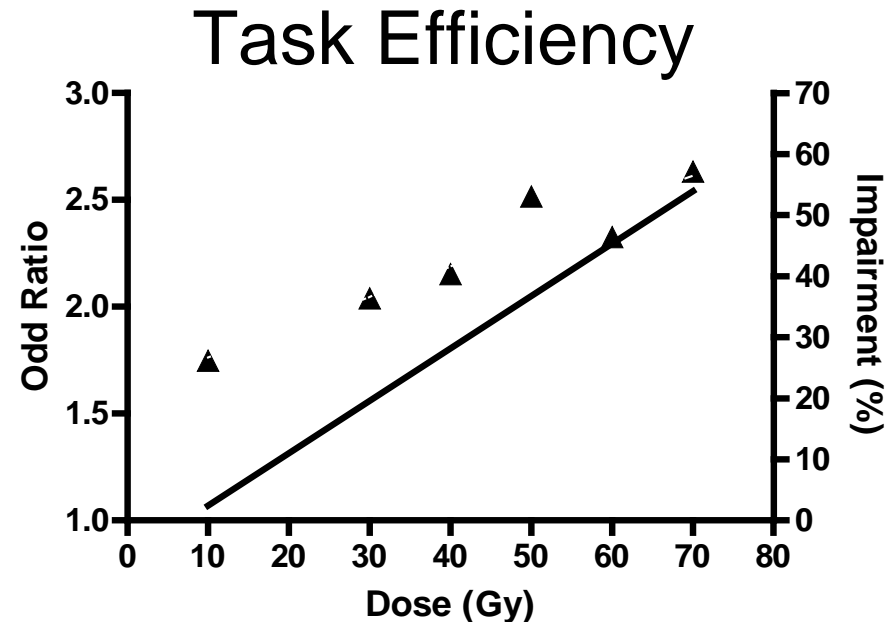
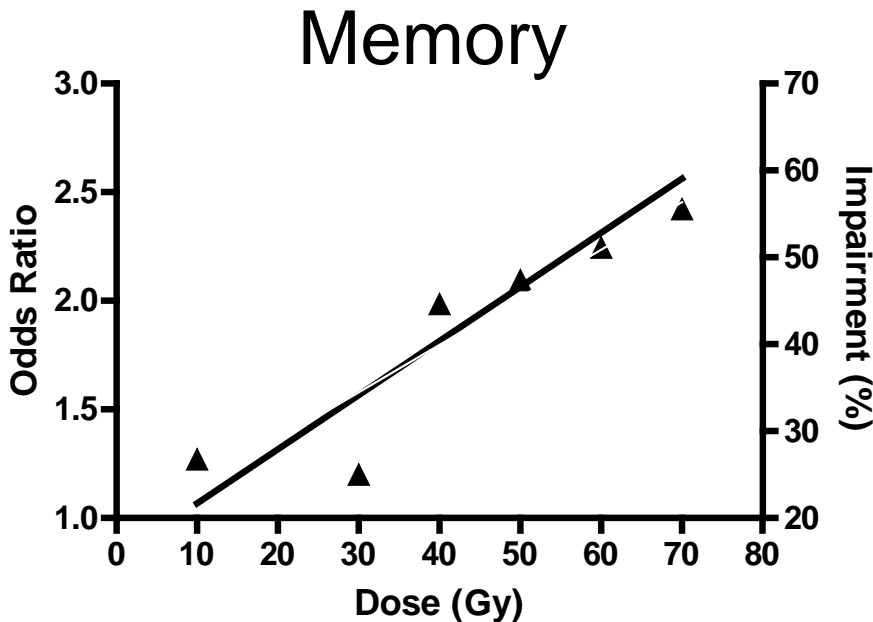
Armstrong GT, Jain N, Liu W, Merchant TE, Stovall M, Srivastava DK, Gurney JG, Packer RJ, Robison LL, Krull KR. Region-Specific Radiotherapy and Neuropsychological Outcomes in Adult Survivors of Childhood CNS Malignancies. *Neuro-Oncology* (Conditionally accepted).

- Aim:
 - To examine associations between regional dosimetry and neurocognitive outcome
- Methods
 - 818 survivors
 - 2003 Follow-up survey
 - Cumulative radiation dose for four specific brain regions
 - CCSS-NCQ, SF-36



Neurocognitive Specificity...

- Results:
 - HD CRT to temporal regions associated with memory impairment
 - doses ≥ 30 to < 50 Gy OR 1.95, 95% CI 1.01–3.78
 - dose ≥ 50 Gy: OR 2.34, 95% CI 1.25-4.39



Sleep and Fatigue

Clanton NR, Klosky JL, Li C, Jain N, Morris EB, Srivastava DK, Mulrooney D, Zeltzer L, Stovall M, Robison LL, Krull KR. Fatigue, vitality, sleep and neurocognitive functioning in adult survivors of childhood cancer.

- Aims:
 - To examine the association between fatigue and sleep disturbance and neurocognitive function in adult survivors of childhood cancer.
- Method:
 - 1,426 participants from Childhood Cancer Survivor Study (CCSS)
 - 2003 Follow-up and sleep survey
 - Short Form-36 (Vitality), FACIT-Fatigue, Pittsburgh Sleep Quality, Epworth Sleepiness
 - CCSS-NCQ, BSI-18

Sleep and Fatigue

	Task Efficiency		Memory		Organization		Emotional Reg	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
↓ Low Vitality	1.71	1.30-2.25	2.01	1.42-2.86	1.68	1.22- 2.32	3.10	2.00- 4.82
↑ Fatigue	1.38	1.23-1.56	---	---	---	---	1.78	1.23- 2.56
↑ Sleepiness	1.66	1.52-1.81	2.05	1.62-2.56	1.57	1.15- 2.12	1.40	1.16- 1.70
↓ Sleep Quality	1.20	1.03-1.41	1.44	1.21-1.73	---	---	---	---
↑ Depression	---	---	---	---	1.55	1.10- 2.19	1.80	1.24- 2.63
↑ Anxiety	---	---	---	---			1.67	1.21- 2.30
↑ Somatization	1.20	1.03-1.40	1.44	1.21-1.71	1.39	1.01- 1.93	---	---
Antidepressant Use	1.64	1.37-1.96	1.70	1.37-2.11	---	---	---	---
CRT >18Gy	1.40	1.08-1.82	2.14	1.46-3.13	---	---	1.86	1.20- 2.89
Sex (Female)	0.84	0.73-0.98	---	---	---	---	1.41	1.16- 1.70
HH Income >\$20K	0.72	0.65-0.81	---	---	0.54	0.40- 0.73	---	---

Brackett J, Krull KR, Scheurer M, Liu W, Srivastava DK, Stovall M, Merchant T, Packer R, Robison LL, Okcu MF. Free radical scavenging enzyme polymorphism and neurocognitive impairment in medulloblastoma survivors.

- Aim:
 - To investigate the role of antioxidant enzyme polymorphisms in prediction of neurocognitive impairment and psychological distress in survivors treated with CRT.
- Methods:
 - 109 medulloblastoma survivors
 - CCSS-NCQ, BSI-18
 - PCR for SOD2, GPx1, GSTP1, and GSTM1 and T1 gene deletions.

Genetic moderators

- Results:
 - Age at diagnosis < 7 years more problems with task efficiency ($p < 0.00001$) and less somatic complaints ($p = 0.004$)
 - Females more organization problems ($p = 0.02$)
 - Controlling for age at diagnosis, sex, and CRT dose:
 - GSTM1 gene deletion related to higher anxiety ($p = 0.04$), more depression ($p = 0.03$), and more global distress ($p = 0.01$)

Approved Concepts in Progress

Adolescent Risk Factors

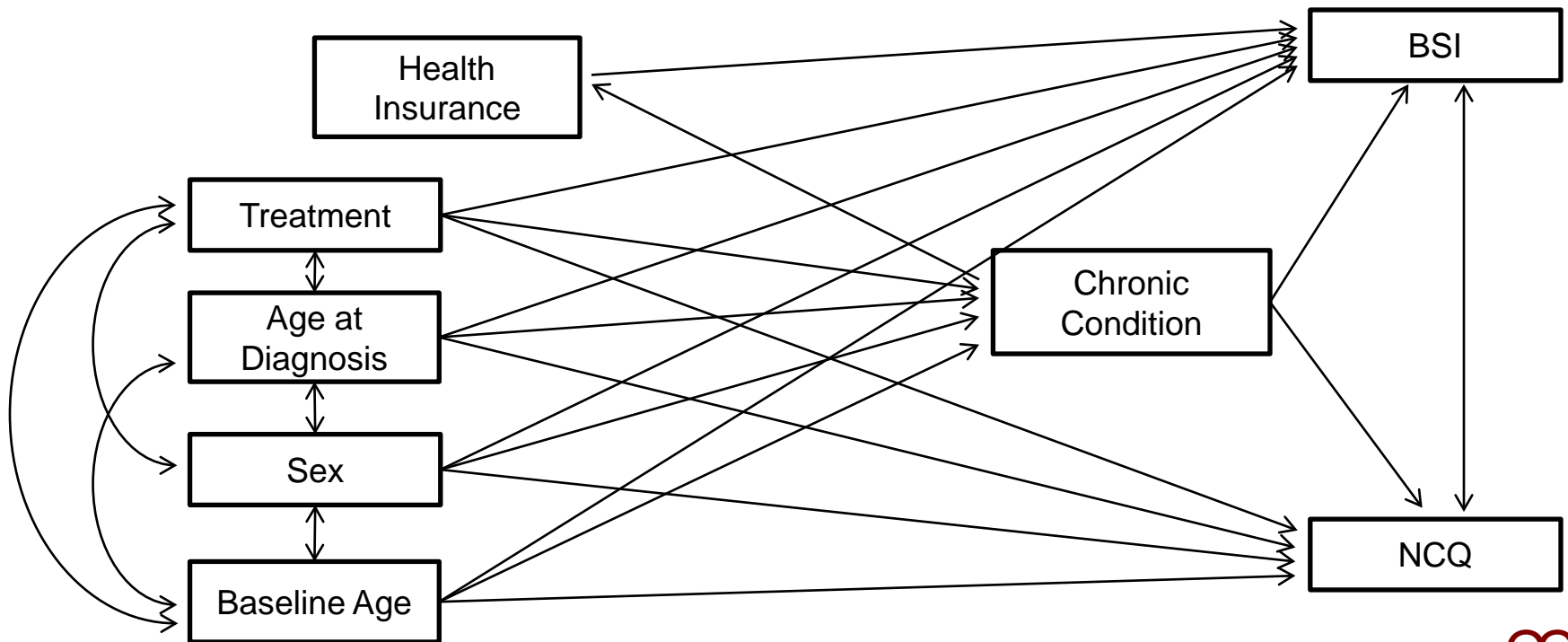
Vikki Nolan, et al. Predictors of Future Quality of Life in Adolescent Survivors of Childhood Cancer.

- **Aims:**
 - To develop predictive models that identify recently diagnosed adolescent cancer patients that are at risk for poor mental and/or physical HRQOL.
 - When validated, predictive models will be used to develop a screening questionnaire.
- **Method:**
 - Survivors diagnosed when 10 to 18 years of age, who participated in the psychosocial portion of the 2003 Follow-Up survey
 - ~ 2,203 participants completed both sections of the SF-36 on the 2003 Follow-Up survey
 - 424 (19%) report poor mental HRQOL
 - 451 (20%) report poor physical HRQOL

Neelam Jain, et al. Impact of Chronic Disease on Neurocognitive and Psychosocial Functions

- Aim:

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



Heather Fullerton et al. First and Recurrent Stroke in Long-term Survivors of Childhood Cancer

- Aims:
 - To reassess the incidence and predictors of self-reported first-stroke in childhood cancer survivors.
 - To determine whether cancer survivors with stroke have worse quality of life.
 - To determine rates and predictors of stroke recurrence.
- Method:
 - 2003 and 2007 Follow-up surveys
 - SF-36 HRQOL
 - Stroke-specific telephone follow-up and questionnaire to those with positive reports.

Scarring and Disfigurement

Karen Kinahan, et al. Treatment related scarring and disfigurement and health related quality of life in adult survivors of childhood cancer.

- Aims:
 - To describe the prevalence and types of scarring and disfigurement experienced in long-term survivors of childhood cancer.
 - To examine the association between disease and treatment related factors and the risk for scarring and disfigurement.
 - To examine the association between scarring and disfigurement and health related quality of life and emotional distress among long-term survivors of childhood cancer and sibling controls.
- Method:
 - Baseline and 2003 Follow-up survey
 - SF-36 HRQoL and BSI-18

Marc Bornstein et al. Mental Retardation and Learning Disability in Survivors of Childhood Cancer Diagnosed in Infancy

- Aims:
 - To examine cancer in infancy as a risk factor for cognitive development
 - To examine the pattern of specific cognitive risk including “hardwired cognition” (i.e., mental retardation) and “wide-spectrum effects” (i.e. learning and academic achievement problems)
- Method:
 - Baseline and 2003 Follow-up survey
 - CCSS-NCQ

Ancillary Studies

Doug Ris et al. Adult Neurobehavioral Late Effects of Pediatric Low Grade Brain Tumors.

- Aims:
 - To ascertain the presence, degree and nature of neuropsychological dysfunction in adults treated as children for low grade brain tumors
 - To investigate accelerated cognitive aging
- Method:
 - Neurocognitive assessment at regional centers
- Status:
 - Funded R01 - NCI

Whitney Witt et al. Impact of Childhood Cancer on Family Burden and Parental Outcomes

- **Aims:** (R01 submitted to NCI, June 2010)
 - To examine psychosocial, health, and aging outcomes for parents of survivors
 - To estimate and identify determinants of family burden, stress, and poor QOL
 - To explore the impact of survivor clinical history on parental outcomes
 - To examine the association between parental stress/burden and cellular aging
- **Method:**
 - Expanded cohort
 - Ancillary survey of parents of survivors < 18 yrs of age
 - EMSI service for blood collection from participating parents
- **Status:**
 - R01 submitted to NCI

Concepts in development

Psychoactive Medication Use

Neelam Jain, et al . Prevalence and Predictors of Psychoactive Medication Use.

- **Aims:**
 - To estimate the prevalence of psychoactive medication use among CCSS survivors and the sibling control group
 - To identify predictors of psychoactive medication use among CCSS survivors
 - To evaluate HRQOL outcomes among survivors as a function of recent psychoactive medication use while controlling for cancer diagnosis and cancer therapy.
 - To examine the association between psychological distress and the initiation of psychoactive medication use
- **Methods:**
 - Baseline, 2000 Follow-up, 2003 Follow-up, and 2007 Follow-up surveys
 - SF-36 HRQOL 2003 Follow-up
 - BSI-18 Baseline survey

Claudia Kernan, et al. Causal Associations Between Psychological and Quality of Life Outcomes in CCSS

- Aims:
 - To determine causal associations among psychological and quality of life outcomes in CCSS
 - To examine latent variables associated with psychological and quality of life outcomes in adult survivors of childhood cancer.
- Methods:
 - 2003 Follow-up survey
 - CCSS-NCQ, BSI-18, PTSD, PTGI, SF-36
 - Structural Equation Modeling

Outcomes in AYA

Pinki Prasad, et al. Psychological and Neurocognitive outcomes in those diagnosed with cancer as adolescent and young adults in the CCSS

- **Aims:**
 - To describe patterns of psychological and neurocognitive outcomes among adolescents and young adult survivors who were diagnosed between the ages of 10 and 21 years to those survivors diagnosed before the 10 years of age
 - To examine the impact of age on psychological and neurocognitive outcomes among adolescents and young adult survivors
 - To determine changes in risk by age at diagnosis from prepubertal (age 10) to young adult status (age 18) by building a model that uses age at diagnosis as a predictor variable
 - To examine pathways to psychosocial and neurocognitive outcomes for each age group (10-12 yrs, 13-15yrs, 16-18 yrs and 19-21 yrs) risk cohort identified in aim 1
- **Methods:**
 - 2003 Follow-up survey

Stefan Essig, et al. Health Related Quality of Life in Adult Survivors of Relapsed ALL.

- Aims:
 - To examine quality of life in adult long-term survivors of childhood ALL with and without a history of relapse
 - To examine associations between quality of life and treatment exposures/toxicity in ALL survivors with and without history of relapse
- Methods:
 - 2003 Follow-up survey

Psychology Group Priorities

- Aging and progression of symptoms over time
 - Psychosocial aspects of cumulative burden
 - Accelerated cognitive decline
- Interventions
 - Promotion of psychological health
 - Cognitive and social stimulation
- Genetic mediators of outcomes
- Psychological outcomes of newer therapies