

Prevalence and Predictors of Neurocognitive Impairment in Long-term Survivors of Childhood Hodgkin Lymphoma

A report from the Childhood Cancer Survivor Study

[AnnaLynn M. Williams](#), Mengqi Xing, Nicholas Phillips, Yutaka Yasui, Matthew J. Ehrhardt, Rebecca Howell, Kevin Oeffinger, Todd Gibson, Eric J. Chow, Wendy Leisenring, Sedigheh Mirzaei Salehabadi, Deo Kumar Srivastava, Leslie L. Robison, Gregory T. Armstrong, Kevin R. Krull.

Childhood Hodgkin Lymphoma

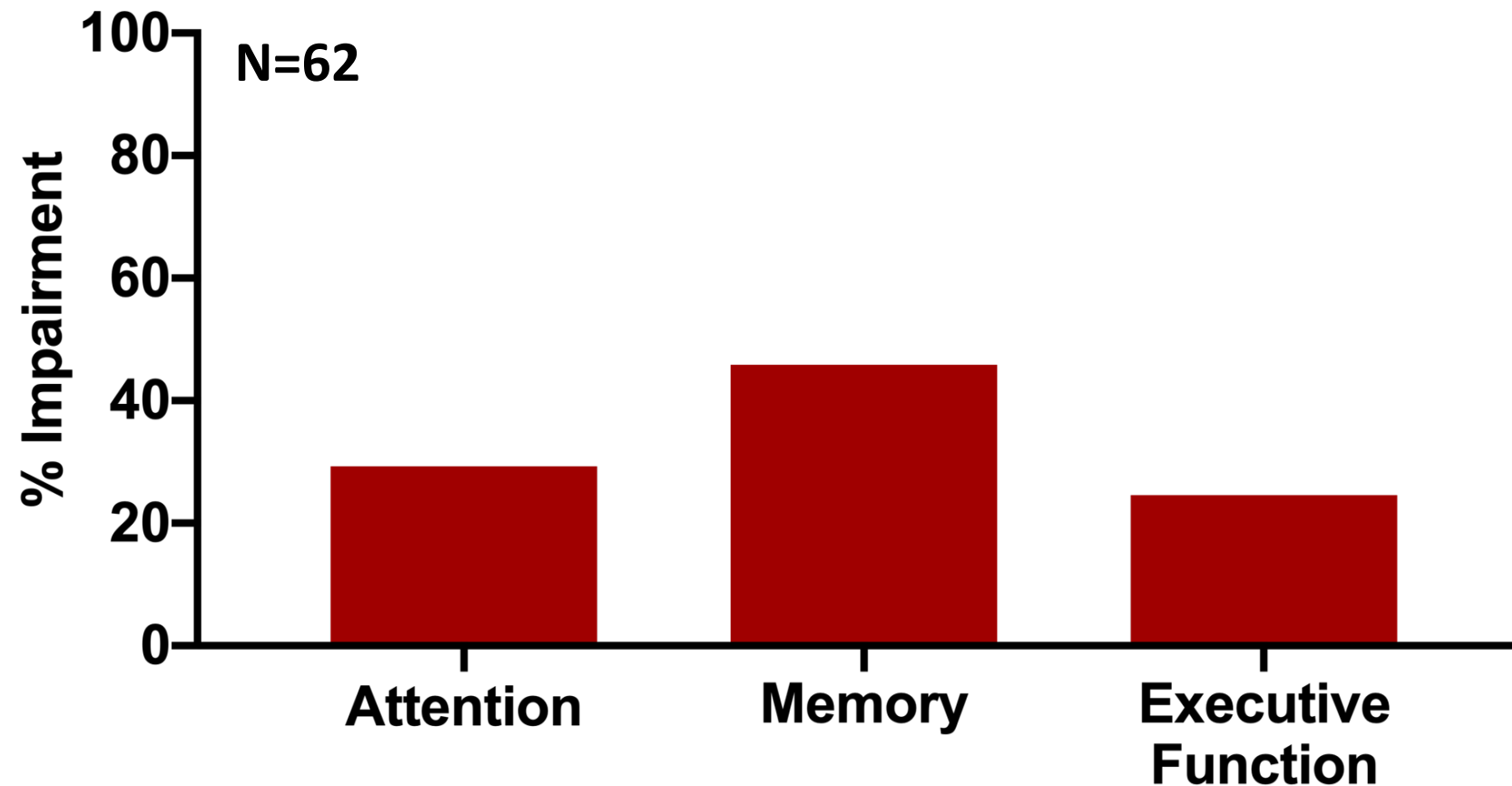
CCSS

- Most common cancer diagnosed in adolescence
- High five-year survival rates (~97%)
- High-risk of cardiovascular, respiratory, neurologic, and endocrine late morbidity
- Risk for neurocognitive dysfunction not comprehensively described

Neurocognitive Dysfunction in Hodgkin Lymphoma

ccss

- Do not receive direct neurotoxic therapies
- Pilot data suggest 29-45% impaired on attention, memory, executive function



Deficits associated with cardiac and pulmonary functioning

- Abnormal Diastolic Function 0.5 SD Worse
- Abnormal DLCO 1 SD Worse

- Aim 1: Describe the neurocognitive impairment in survivors of childhood Hodgkin lymphoma compared to sibling controls.
- Aim 2: Among survivors, identify individual demographic and treatment factors, as well as chronic health conditions associated with neurocognitive impairment.

Eligibility Criteria:

- Childhood Cancer Survivor Study (CCSS) participant
- Hodgkin lymphoma diagnosis
- Age ≥ 18 at time of assessment

Exclusion Criteria:

- Genetic disorder predisposing for mental or physical impairment not related to disease/treatment (e.g. trisomy 21)

Neurocognitive Questionnaire (NCQ)

- Developed and validated for use in cancer survivors
- Four domains:
 - **Task efficiency:** processing speed, attention, persistence
 - **Emotional regulation:** control and expression of emotions
 - **Organization:** organization of one's environment and plans
 - **Memory:** immediate, short, and long-term memory
- Impairment:
 - $\geq 90^{\text{th}}$ percentile of community controls from St. Jude Lifetime Cohort

Treatment History (abstracted from the medical record)

- Chemotherapy
- Chest radiation
- Relapse/subsequent malignant neoplasm

Demographic/Lifestyle Factors (self-reported)

- Age, sex, smoking status, & physical activity

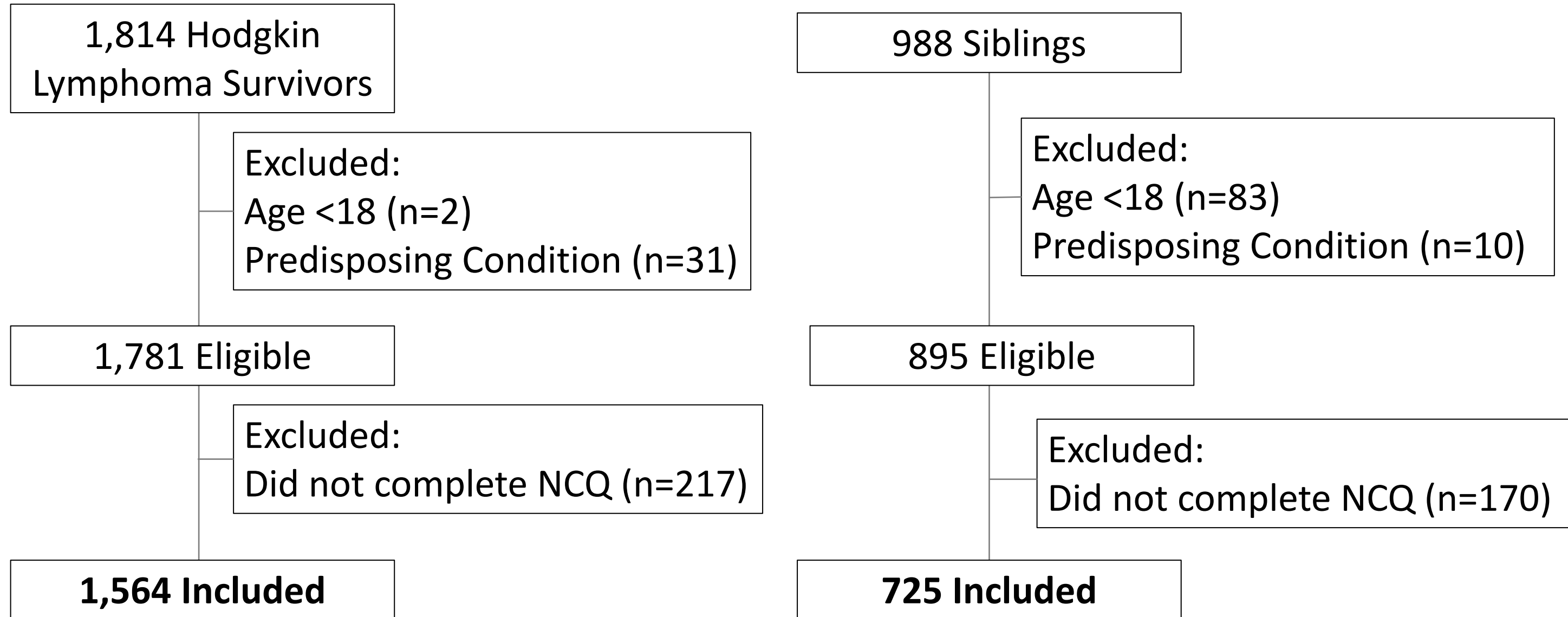
Chronic Health Conditions (self-reported)

- CTCAE grades 1: mild, grade 2: moderate, grade 3: severe/disabling, grade 4: life-threatening
- Cardiovascular, respiratory, endocrine, neurologic

- Generalize estimating equations estimated risk of impairment in survivors compared to siblings adjusted for age, sex, and race.
- Multivariable Poisson regression estimated the risk of impairment associated with:
 - Demographic, clinical, and treatment factors
 - Grade 2+ cardiovascular, endocrine, pulmonary, and neurologic conditions adjusting for age, sex, and race
- Structural equation models to examine if chronic health conditions mediate treatment effects.

Participants

CCSS



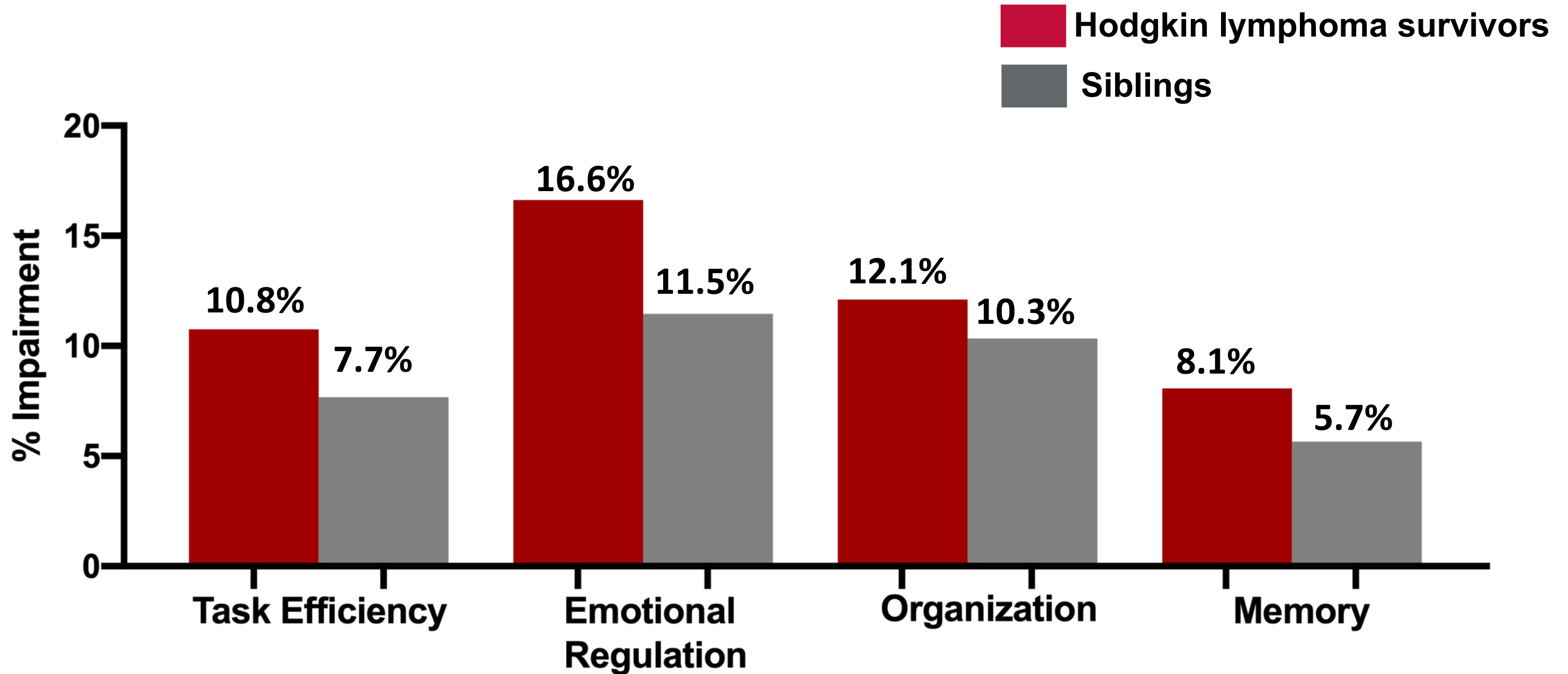
Participant Characteristics

CCSS

	Hodgkin Lymphoma Survivors	Siblings	
	Median (min, max)	Median (min, max)	P-value
Age at follow-up	37 (21, 54)	32 (18, 58)	<0.001
Age at diagnosis	14 (2, 20)	-	
Time since diagnosis	23 (15, 34)	-	
	N(%)	N(%)	
Male	717 (45.8)	317 (43.7)	0.343
White	1439 (92.0)	666 (91.9)	0.904
Smoking status			
Never	1070 (68.4)	500 (68.0)	0.942
Former	310 (19.8)	125 (17.2)	
Current	184 (11.8)	100 (13.8)	
Meet CDC exercise criteria	983 (62.9)	495 (68.3)	0.009

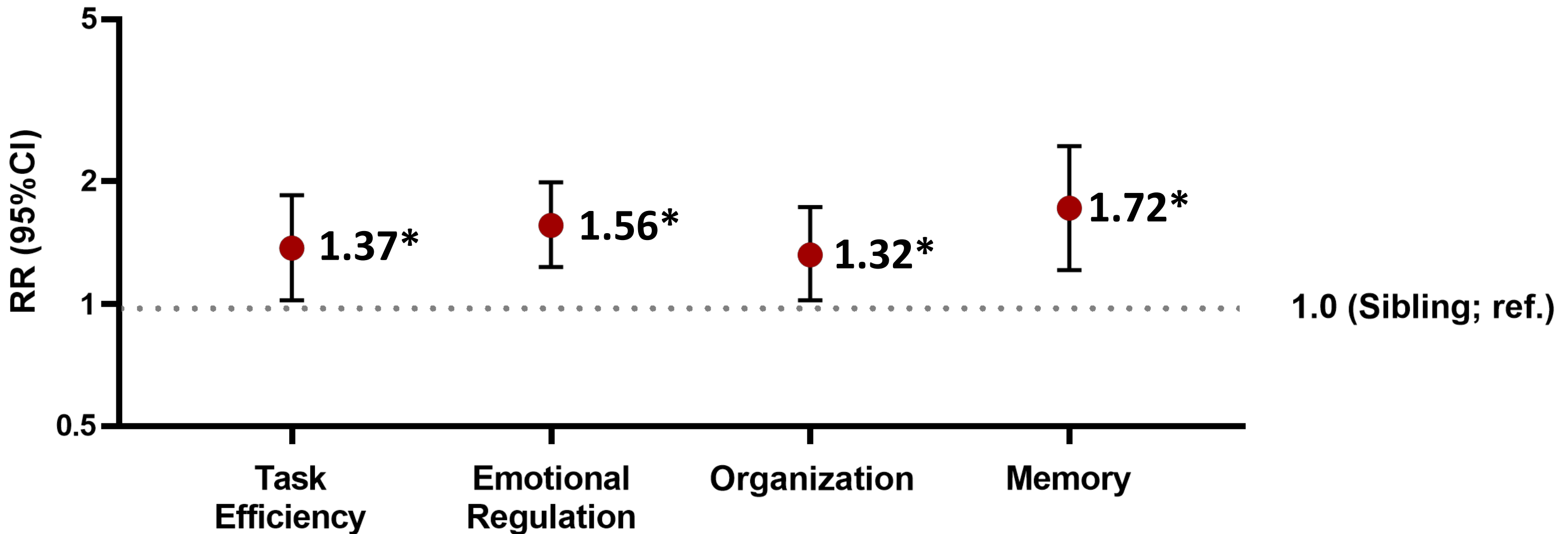
Neurocognitive Impairment

CCSS



Risk of Neurocognitive Impairment in Survivors Compared with Siblings

CCSS



* p<0.05

Model adjusted for age, sex, and race

Risk Factors for Neurocognitive Impairment Among Survivors

Relative Risk of Impairment (95%CI)

Treatment Exposures	Task Efficiency	Emotional Regulation	Organization	Memory
Relapsed/Subsequent Malignancy (yes vs. no)	1.59 (1.13, 2.24)*	1.14 (0.86, 1.51)	1.38 (0.98, 1.95)	1.13 (0.75, 1.71)
Anthracycline (yes vs. no)	1.10 (0.71, 1.70)	0.56 (0.38, 0.82)*	0.69 (0.44, 1.08)	1.34 (0.75, 2.36)
Alkylating Agents (yes vs. no)	1.27 (0.83, 1.94)	1.30 (0.93, 1.81)	0.59 (0.39, 0.90)*	0.90 (0.53, 1.53)
Bleomycin (yes vs. no)	0.78 (0.51, 1.19)	0.96 (0.66, 1.40)	1.30 (0.86, 1.96)	1.03 (0.60, 1.75)
Corticosteroids (yes vs. no)	1.05 (0.69, 1.58)	1.03 (0.74, 1.42)	1.63 (1.06, 2.51)*	0.95 (0.56, 1.61)
Chest Radiation (yes vs. no)	1.02 (0.69, 1.49)	1.07 (0.79, 1.46)	0.96 (0.67, 1.36)	1.13 (0.73, 1.75)

* **p<0.05** Model mutually adjusted for the factors above in addition to age, sex, race, time since diagnosis, smoking status, and physical activity.

Risk Factors for Neurocognitive Impairment Among Survivors

CCSS

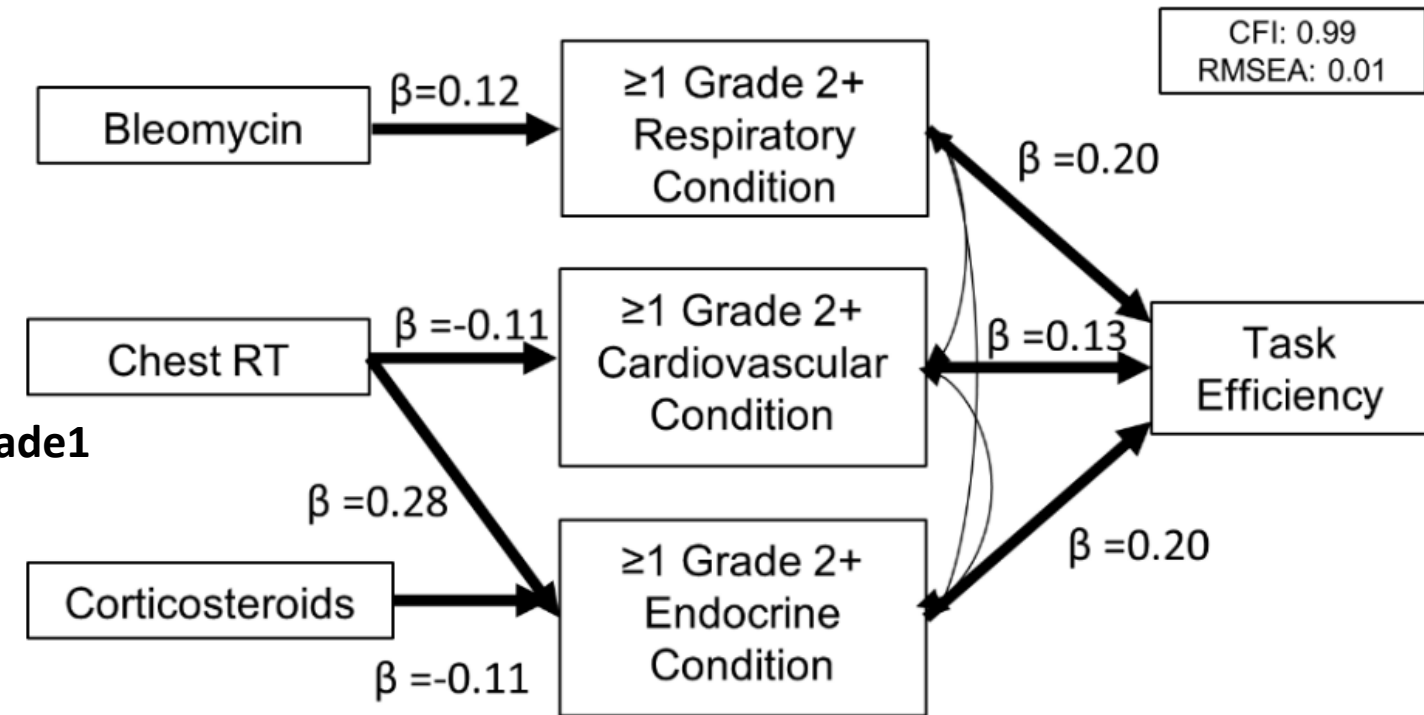
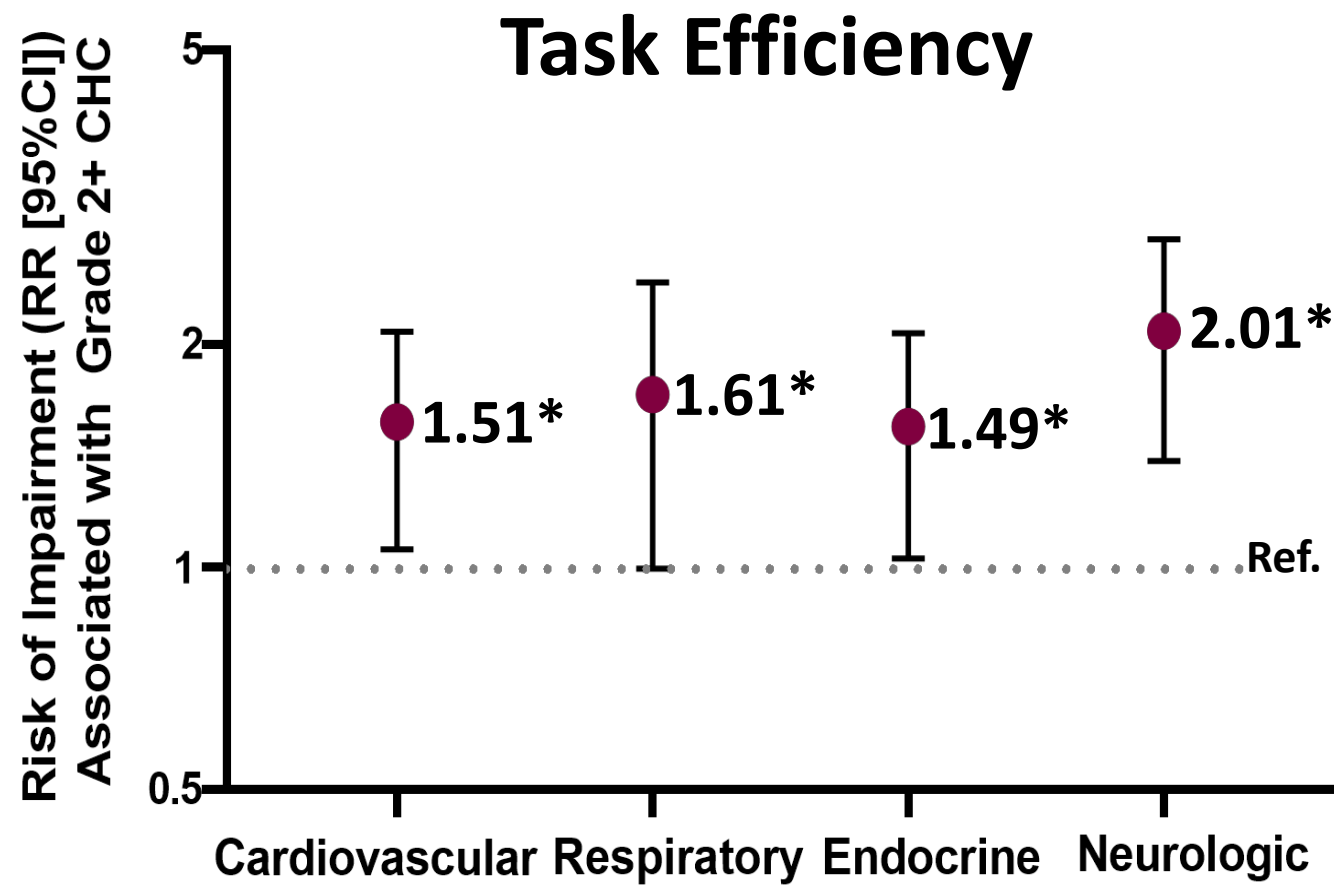
Relative Risk of Impairment (95%CI)

Demographic/Lifestyle Exposures	Task Efficiency	Emotional Regulation	Organization	Memory
Female (vs. Male)	1.09 (0.81, 1.48)	1.40 (1.10, 1.79)*	0.84 (0.63, 1.12)	1.91 (1.31, 2.80)*
Non-White (vs. White)	1.70 (1.07, 2.68)*	1.40 (0.93, 2.10)	1.17 (0.71, 1.92)	1.40 (0.79, 2.48)
Former Smoker (vs. Never)	1.51 (1.06, 2.16)*	1.36 (1.03, 1.81)*	1.01 (0.70, 1.45)	1.87 (1.24, 2.81)*
Current Smoker (vs. Never)	1.63 (1.06, 2.50)*	1.90 (1.40, 2.58)*	1.07 (0.69, 1.66)	1.53 (0.90, 2.58)
Meet CDC Exercise Criteria (vs. No)	0.69 (0.51, 0.93)*	0.89 (0.71, 1.13)	0.59 (0.44, 0.78)*	0.86 (0.60, 1.23)

* **p<0.05**

Model mutually adjusted for factors above in addition to age, time since diagnosis, and treatment exposures.

Task Efficiency: Impact of Chronic Health Conditions

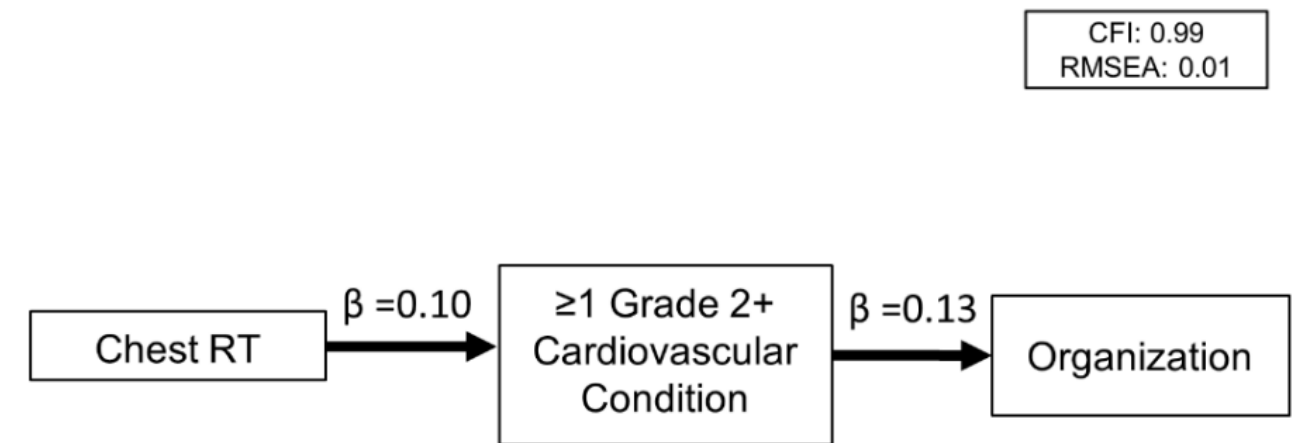
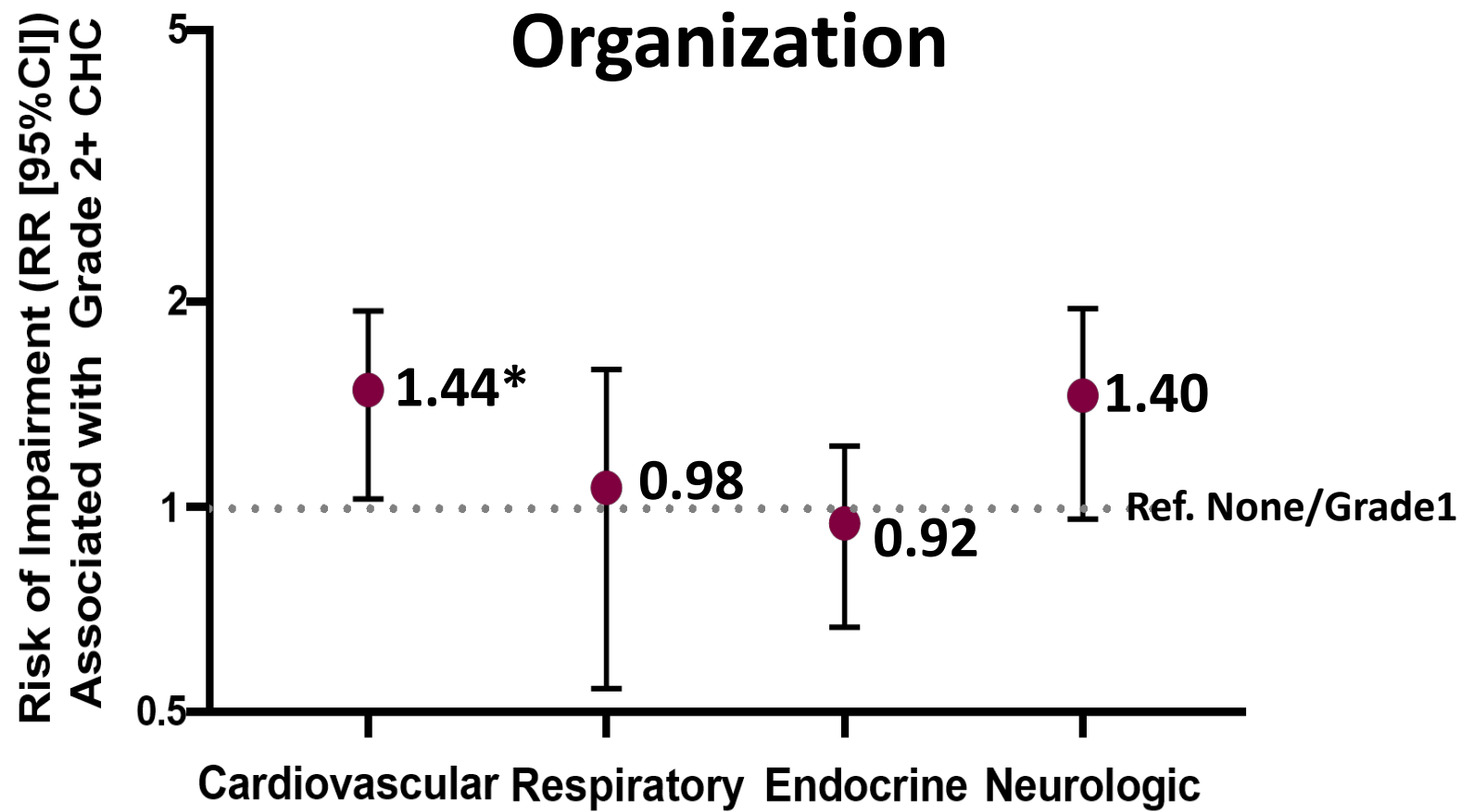


* P<0.05

Model mutually adjusted for chronic health condition groups, age, sex, and race

Organization: Impact of Chronic Health Conditions

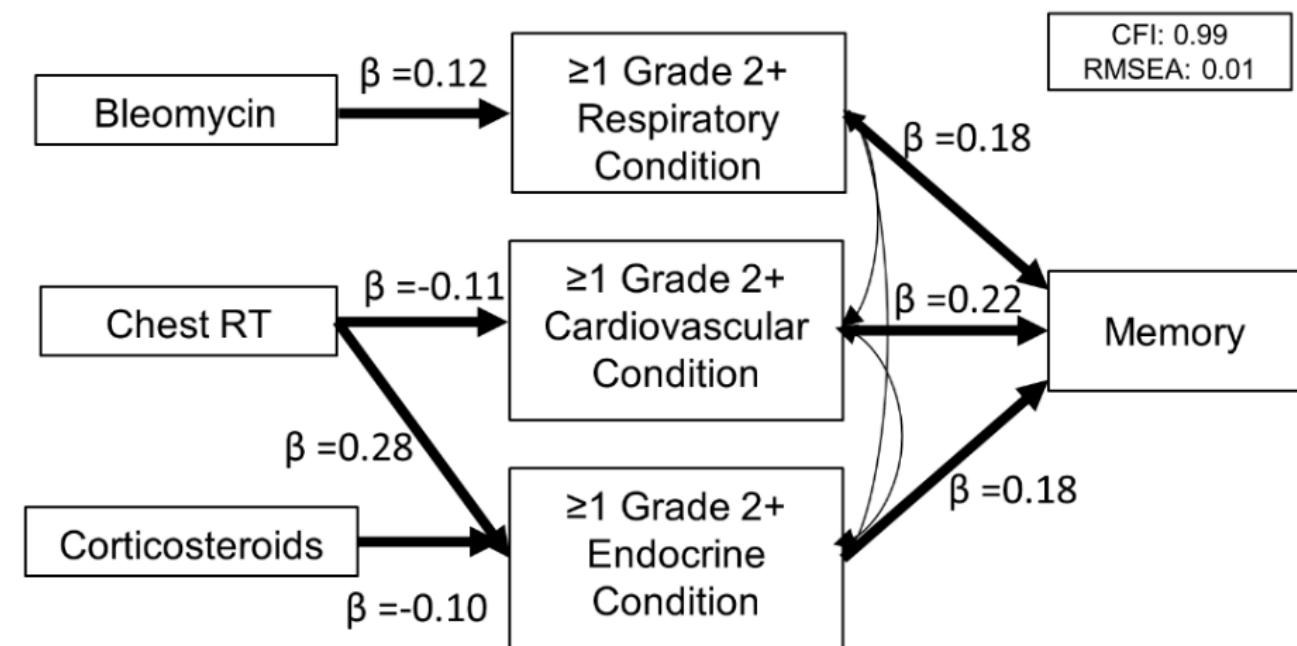
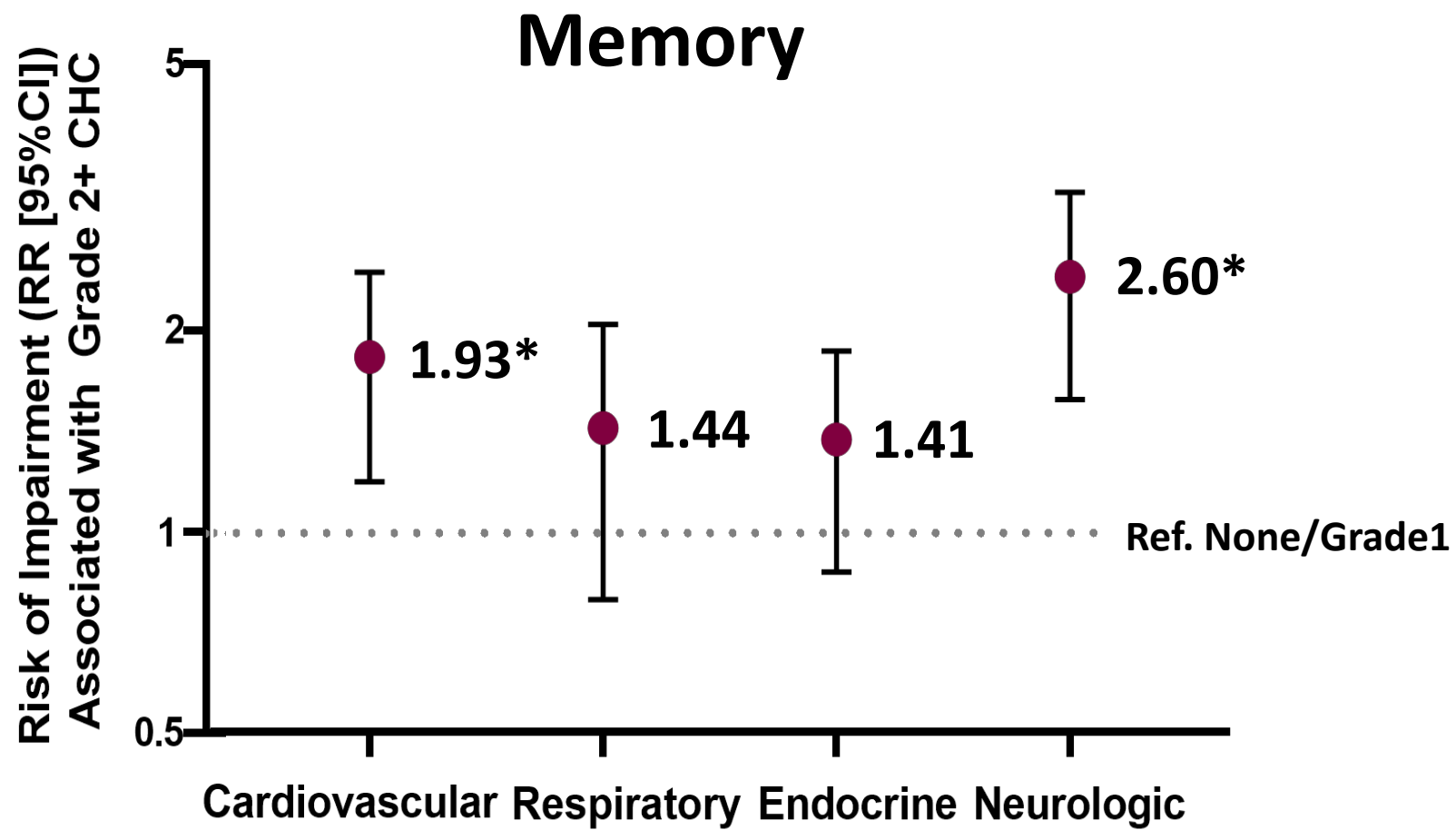
ccss



* $P < 0.05$

Model mutually adjusted for chronic health condition groups, age, sex, and race

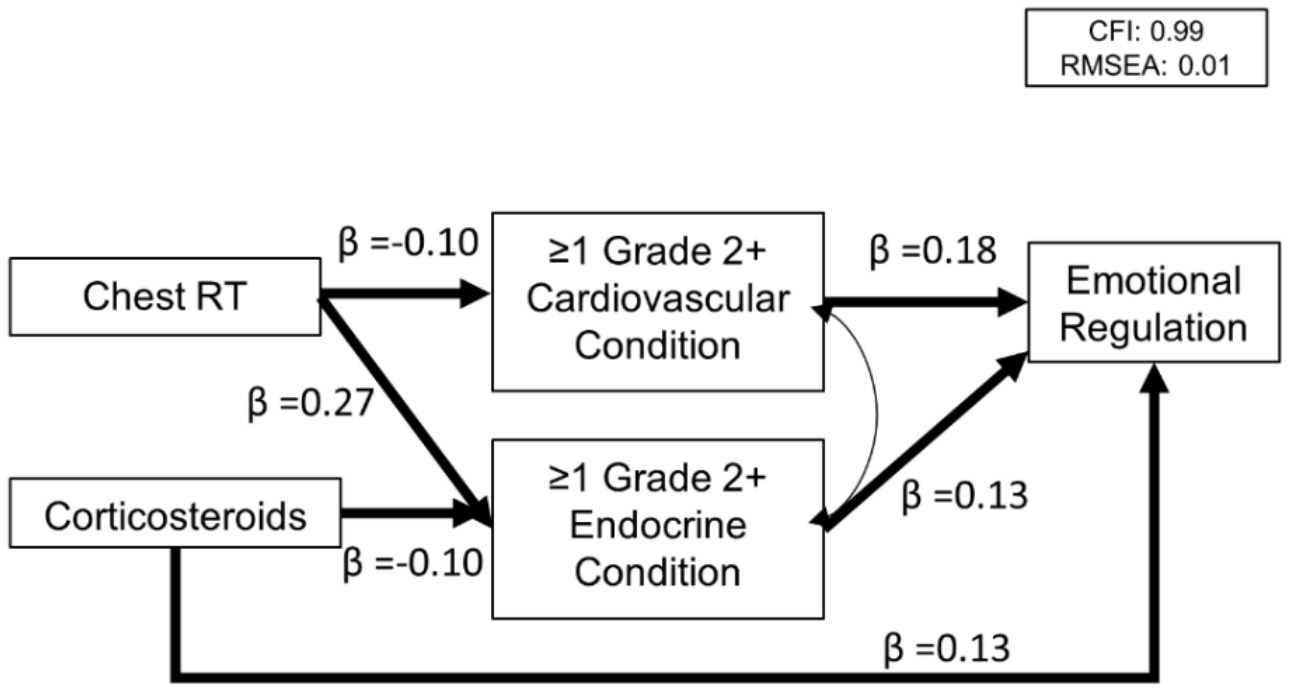
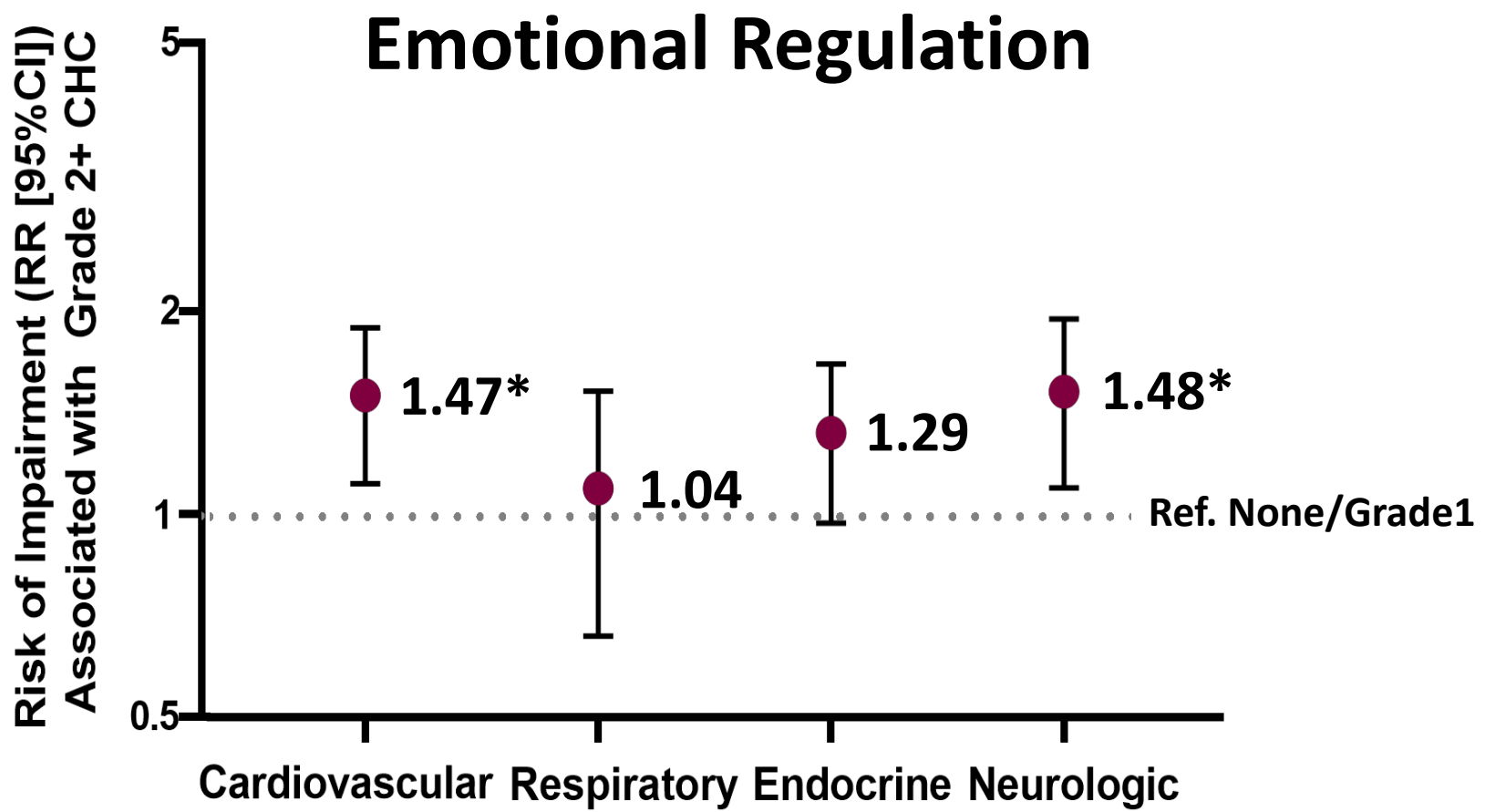
Memory: Impact of Chronic Health Conditions



* P<0.05

Model mutually adjusted for chronic health condition groups, age, sex, and race

Emotional Regulation: Impact of Chronic Health Conditions



* P<0.05

Model mutually adjusted for chronic health condition groups, age, sex, and race

- Long-term survivors of childhood Hodgkin lymphoma are at increased risk for neurocognitive impairment compared to sibling controls.
- Potentially modifiable factors, such as smoking and physical activity, as well as chronic health conditions were associated with neurocognitive impairment.
- Prevention or improvement of such factors may mitigate or prevent neurocognitive impairment.

Acknowledgements

CCSS

Collaborators:

Kevin R. Krull
Mengqi Xing
Sedigheh Mirzaei Salehabadi
Deo Kumar Srivastava
Nicholas Phillips
Yutaka Yasui
Matthew J. Ehrhardt
Rebecca Howell
Kevin Oeffinger
Todd Gibson
Eric J. Chow
Wendy Leisenring
Leslie L. Robison
Gregory T. Armstrong

Funding:

National Cancer Institute U24CA55727(to G.T.A)
and K00CA222742 (to A.M.W.).

All the Childhood Cancer Survivor Study Participants

- The Childhood Cancer Survivor Study is an NCI-funded resource to promote and facilitate research among long-term survivors of cancer diagnosed during childhood and adolescence.
- Investigators interested in potential uses of this resource are encouraged to visit:

www.stjude.org/ccss