Impact of Age at Exposure of Total Body Irradiation on Neurocognitive and Psychosocial Outcomes in Survivors of Pediatric Hematopoietic Cell Transplantation: A Report From The Childhood Cancer Survivor Study

Takuto Takahashi, MD, PhD
Assistant Professor, Pediatric Stem Cell Transplantation, Boston Children's Dana-Farber Cancer and Blood Disorders Center
Takuto.takahashi@childrens.harvard.edu

Working Groups

- **Primary: Psychology**
- **Secondary:** Cancer control/Chronic Disease

Investigators:

Name	Institute	Email
Takuto Takahashi	Dana-Farber Cancer Institute	takuto.takahashi@childrens.harvard.edu
Ellen van der Plas	Arkansas Children's Hospital/University of Arkansas for Medical Sciences	evanderplas@uams.edu
Tara Brinkman	St. Jude Children's Research Hospital	Tara.Brinkman@STJUDE.ORG
Paul Nathan	The Hospital for Sick Children	paul.nathan@sickkids.ca
Claire Snyder	Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University	csnyder@jhu.edu
Kevin Oeffinger	Duke University	kevin.oeffinger@duke.edu
Eric Chow	Fred Hutchinson Cancer Center	ericchow@uw.edu
Rebecca Howell	MD Anderson Cancer Center	rhowell@mdanderson.org
Kumar Srivastava	St. Jude Children's Research Hospital	kumar.srivastava@stjude.org
Greg Armstrong	St. Jude Children's Research Hospital	greg.armstrong@stjude.org
Scott Baker	Fred Hutchinson Cancer Center	ksbaker@fredhutch.org
Miki Nishitani	Dana-Farber Cancer Institute	miki_nishitani@dfci.harvard.edu
Elizabeth Weiskopf	Dana-Farber Cancer Institute	elizabeth_weiskopf@dfci.harvard.edu
Rohini Chakravarthy	University of Chicago	rohini.chakravarthy@bsd.uchicago.edu

Background

Allogeneic hematopoietic cell transplantation (HCT) is a well-established curative treatment for children with high-risk hematologic malignancies. Total Body Irradiation (TBI) has historically been utilized as an established HCT conditioning regimen in hematologic malignancies[1-3], including the recent FORUM randomized controlled study[4]. While effective in curing malignancies, TBI is associated with significant late effects[5-7]. These late effects appear to be more pronounced in survivors who were exposed to TBI at a younger age (e.g., neurocognitive impairment, growth restriction) relative to those who were older at exposure[7-9]. The concerns of late effects have often dissuaded the use of TBI in patients <4 years. At the same time, there is evidence to

suggest that TBI confers superior relapse-free survival even in this young age group with high-risk hematologic malignancy[10,11], posing the difficult challenge of balancing disease cure and long-term morbidity.

Understanding the long-term risks of TBI therapy in children aged <4 years is critical for guiding clinical decision-making and counseling families. Prior research highlights increased susceptibilities to radiation toxicities in young children. For example, Willard, et al. examined a longitudinal trend of neurocognitive functions over 5 years in 183 survivors of pediatric hematologic malignancy who received HCT (95 TBI and 88 non-TBI)[6]. Children <3 years demonstrated declines in cognitive functioning at the first year after HCT. While those who did not receive TBI showed cognitive function recovery by 5 years post HCT, those who received TBI did not. However, the study was limited to a 5-year follow up and evaluated a limited number of adolescents and young adults, with only 10 people being aged ≥16 years at the last evaluation.

In another study, Krull, et al. assessed very long-term neurocognitive effects of cranial radiation therapy (CRT) at 18 or 24 Gy using the data from the St. Jude Life Cohort[12]. Among 567 adult survivors of pediatric ALL who survived ≥10 years from diagnosis, those treated at younger ages experienced more pronounced impairments in intelligence, academic, and memory functions. However, the use of CRT was not associated with employment or education status. While the age-dependent late neurocognitive impairment by CRT is well-established, the effects of lower radiation exposures to whole body (i.e., TBI, typically delivered at 12-13 Gy) in HCT survivors remain understudied. Moreover, broader long-term psychosocial outcomes by TBI have not been comprehensively evaluated.

Leveraging the comprehensive neurocognitive and psychosocial assessments of adult survivors of pediatric hematologic malignancy in CCSS, the goal of this proposal is to analyze TBI-related late effects on neurocognitive outcomes, health-related quality of life, and psychosocial outcomes in relation to the age at therapy. The findings from this study will generate critical, practice-guiding data to inform conditioning regimen selection in HCT, support evidence-based counseling of patients and families, and individualized long-term follow-up care. As such, the overall aim of this proposal is to characterize TBI-related late effects on the longitudinal psychosocial outcomes in relation to the age at therapy.

Table 1: Overview of groups and comparisons proposed for each aim.

Group definition			Group	Outcome comparisons							
HM	HCT	TBI		Aim 1: Neurocognition			Aim 2: Social Attainment		Aim 3:Health and Well-being		
				1a	1b	1c	2a	2b	3a	3b	3c
Yes	Yes	Yes	**TBI-HCT (n=204)**	X	X	X	X	X	X	X	X
Yes	Yes	No	**Non-TBI-HCT (n=90)**	X	X	X	X	X	X	X	X
Yes	No	No	**HM-control (N=3,086)**	X		X	X		X		X
No	No	No	**Siblings (n=5,022)**	X		X	X		X		X

HM=hematologic malignancy; HCT=Hematopoietic cell transplantation; TBI=total body irradiation; Sample sizes based on inclusion/exclusion criteria described below.

Specific aims

Aim 1a: To compare neurocognitive impairment in survivors of TBI-HCT, non-TBI-HCT, hematologic malignancy (HM)-control, and siblings.

Hypothesis 1a: Relative to siblings, HM-controls and non-TBI-HCT, TBI-HCT survivors will be at increased risk of neurocognitive impairment.

Aim 1b: To determine the association of age at TBI exposure on neurocognitive impairment in TBI-HCT and non-TBI-HCT survivors.

Hypothesis 1b: Younger age at TBI exposure is expected to be associated with further increased risk of neurocognitive impairment vs. non-TBI-HCT, compared to the risk in TBI-HCT vs. non-TBI-HCT at an older age.

Aim 1c: To explore changes in neurocognitive impairment in TBI-HCT and non-TBI-HCT survivors.

Hypothesis 1c: TBI-HCT survivors are expected to experience declining neurocognitive functions over time relative to non-TBI-HCT.

Aim 2a: To compare social attainment outcomes (e.g., education, employment, income, financial hardship) in survivors of TBI-HCT, non-TBI-HCT, HM-control, and siblings.
Hypothesis 2a: Relative to siblings, HM-controls and non-TBI-HCT, TBI-HCT survivors will have inferior social attainment outcomes.

Aim 2b: To determine the association of age at TBI exposure and social attainment in TBI-HCT vs. non-TBI-HCT survivors.
Hypothesis 2b: Younger age at TBI exposure is associated with further increased risk of inferior social attainment outcomes vs. non-TBI-HCT, compared to the risk in TBI-HCT vs. non-TBI-HCT at an older age.

Aim 3a: To compare mental health, quality of life, frailty, physical performance limitation, and participation restrictions in survivors of TBI-HCT, non-TBI-HCT, HM-control, and siblings.
Hypothesis 3a: Relative to siblings, HM-controls and non-TBI-HCT, TBI-HCT survivors will be at increased risk of inferior mental health, quality of life, frailty, physical performance limitation, and participation restrictions.

Aim 3b: To examine if age at exposure (e.g., <4 years vs. ≥4 years) differentially affects mental health, quality of life, frailty, physical performance limitation, and participation restrictions in in TBI-HCT, non-TBI-HCT, and HM-control.
Hypothesis 3b: Younger age at TBI exposure is associated with further increased risk of inferior social attainment outcomes vs. non-TBI-HCT, compared to the risk in TBI-HCT vs. non-TBI-HCT at an older age.

Aim 3c: To explore longitudinal trajectories of mental health, quality of life, frailty and physical performance limitations in TBI-HCT and non-TBI-HCT survivors.
Hypothesis 3c: TBI-HCT survivors experience inferior mental health, quality of life, frailty, physical performance limitation, and participation restrictions over time relative to non-TBI-HCT.

Methods
Synopsis
The outcome data from individuals will be evaluated both cross-sectionally (using earliest impairment) and by survival analysis from FU2, FU4, FU5, FU6, and FU7. We will also assess longitudinal change of outcome status from FU5 to FU7.

In terms of survival analysis, event times were subject to interval censoring due to the periodic nature of the study collection. Following a discrete-time approach, the date of onset was recorded as the date of the first follow-up visit where the condition was observed, representing the right-endpoint of the censoring interval.

Study population
The survivor cohort includes individuals who survived at least 5 years from the diagnosis of hematologic malignancy, categorized into 3 mutually exclusive groups (see Table 1). This study will also utilize the previously linked HCT-specific data from the Center for Blood and Marrow Transplant Research as feasible[13].

To limit impact of potential confounders and lack of relevant data, individuals meeting any of the following criteria are excluded: 1) HCT at ≥5 years from diagnosis, 2) relapse of the primary disease at ≥5 years from diagnosis, 3) received more than one HCT, 4) cranial radiation ≥200 cGy for those who do not receive TBI, 5) cranial radiation ≥200 cGy at ≥6 months prior to HCT for those who receive TBI, or 6) neurological CTCAE events at grade ≥3 at any time.

Our preliminary estimates suggest that we will be able to include N=204 TBI-HCT survivors, N=90 Non-TBI-HCT survivors, 3,086 HM controls and 5,022 siblings in the analyses.

The analysis will be restricted to the CCSS dataset. External data sources will not be incorporated; specifically, we will not use the previously linked data from the Center for International Blood and Marrow Transplant

Research (CIBMTR). In preliminary analyses, only a subset of the cohort had linked CIBMTR data (120 of 204 in the TBI-HCT group and 45 of 90 in the non–TBI-HCT group), which would substantially reduce the effective sample size and statistical power in an already limited cohort.

Furthermore, the CCSS dataset contains the key variables necessary to address the study aims, including detailed information on radiation exposure. Additional variables available through CIBMTR, such as more granular HCT regimen data and acute post-HCT complications, are not essential for the current analysis.

Table 2. Outcomes of interest:

Aim	Outcome	Measure	Levels
1	Neurocognitive Function	CCSS-NCQ	T-score<63 vs T-score ≥63
2	Social Attainment*	Education	≥college graduation vs. < college graduation
		Employment	Full-time vs. no full-time employment. Exclude those in school.
		Marital Status	Married or living as married vs. single/divorced/widowed/separated
3	Emotional Distress	BSI-18[14]	T-score<63 vs T-score ≥63
	HRQOL	SF-36[15,16]	T-score≤40 vs. T-score >40
	Frailty	Fried frailty criteria[17,18]	Pre-frail=endorsing 2/5 criteria; Frail=endorsing ≥3 criteria
	Physical performance limitations	Physical activity[19]	Score <10th percentile of siblings as the sum of responses to the 6 domains of activity limitations.
	Participation restrictions	Physical activity[19]	Confirmatory response to the 3 domains: 1) Limited personal care skills, 2) Limited routine activities, 3) Poor health preventing school or work attendance

*Participants aged ≥25 years; CCSS-NCQ=CCSS-Neurocognitive Questionnaire; BRFSS= Behavioral Risk Factor Surveillance System ETC, ETC. **Administered at Follow-up 6 only.

Longitudinal change of outcome status is defined as follows (change from FU5 to FU7).

- Remained impaired: Impaired at FU5-> Impaired at FU7
- Remained unimpaired: Unimpaired at FU5-> Unimpaired at FU7
- Became impaired: Unimpaired at FU5-> Impaired at FU7
- Became unimpaired: Impaired at FU5-> Unimpaired at FU7

Exploratory variables

- Chronic health conditions:
  - Status and severity of organ-based health conditions based existing CTCAE grade ≥3.
- Cumulative Illness Rating Scale for Geriatrics (CIRS-G):
  - The CIRS-G summarizes disease burden across 14 systems.

Treatment variables

- Radiotherapy
  - TBI (yes/no; cumulative dose [Gy]; single fraction vs. fractionated)
  - Brain (yes/no; cumulative dose [Gy])

- Chemotherapy
  - Alkylating agents (yes/no; cumulative exposure [mg/m2])
  - Anthracyclines (yes/no; cumulative exposure [mg/m2])
  - Antimetabolites (yes/no; cumulative exposure [mg/m2])

- Methotrexate (yes/no; cumulative exposure [mg/m2])
- Glucocorticoid (yes/no; cumulative exposure [mg/m2])

Statistical Framework
For all aims, descriptive statistics will be used to summarize outcomes, including t-scores and proportions of impairment. To ensure the inclusion of the most relevant treatment covariates (radiation, chemotherapy agents), we will employ Elastic Net regression. This approach is preferred over standard LASSO as it effectively handles potential multicollinearity among highly correlated treatment variables.

1. Cross-Sectional Analysis
   To compare outcomes across groups, we will analyze the earliest available event (e.g., first documented impairment) from the FU2, FU4, FU5, FU6 and FU7 assessments and adjust for length of follow-up.

   - Group comparisons (Aim 1a, 2a, 3a): Multiple logistic regression will be applied for binary outcomes (e.g., “Impaired” vs. “Not Impaired”), while multinomial logistic regression will be used for categorical outcomes (e.g., “Normal” vs. “Pre-frailty” vs. “Frailty”). Odds ratios (ORs) will be reported to quantify associations. For a fair comparison, our analyses should be restricted to survivors, with time since diagnosis serving as the time scale.

   - Age at Exposure Effects (Aim 1b, 2b, 3b): We will examine whether age at exposure (e.g.,0-3, 4-6, 7-10, 11-15, 16-19) impact outcomes in survivors who received HCT. Interaction term (Age category x Group) can be included to test if the effect of early exposure is more pronounced in the TBI-HCT cohort.

2. Survival Analysis
   Survival analysis can be used to model the longitudinal progression of neurocognitive, mental health, and physical decline. The “event” is defined as the first instance of an adverse outcome (e.g., neurocognitive impairment, pre-frailty, physical limitation). The time of onset will serve as the survival outcome, and participants who do not experience the event will be right-censored at the end of the study period (e.g., FU7).

   - Group comparisons (Aim 1a, 3a): Given alive study population, there are no competing risks (e.g., death). Kaplan-Meier (KM) curves will be used to visualize the ‘impairment-free survival’ over time across groups. Cox Proportional Hazards models will be used to estimate Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) to quantify the relative risk of decline. Because survivors who died before diagnosis or study entry are excluded, we will adjust for left truncation and use age at onset as the time scale.
   - Age at Exposure Effects (Aim 1b, 3b): Age at exposure (as a categorical predictor) will be evaluated within the Cox Proportional Hazard model.

3. Longitudinal analysis
   To assess the longitudinal changes (Aim 1c and 3c), the outcome trajectory status (maintain, improve, decline) was defined as changes from FU5 to FU7. Maintain was defined as no change; improve as impaired to non-impaired, and decline as non-impaired to impaired. Odds ratios (ORs) will be reported to quantify associations.

Scientific impact
TBI is effective for disease control in pediatric HCT, but its long-term neurocognitive and psychosocial effects, especially after early-age exposure, remain poorly understood. By leveraging the large, longitudinal CCSS data, this project will define age-related vulnerability to TBI and its lasting impact on cognition and quality of life. Findings will guide evidence-based conditioning choices, improve counseling for families, and inform targeted survivorship care to better balance cure with long-term well-being.

References:

1. Rehman MEU, Chattaraj A, Mahboob A, et al. Total Body Irradiation Versus Chemotherapy Conditioning in Pediatric Acute Lymphoblastic Leukemia Patients Undergoing Hematopoietic Stem Cell Transplant: A Systematic Review and Meta-Analysis. *Clin Lymphoma Myeloma Leuk*. Apr 2023;23(4):249–258. doi:10.1016/j.clml.2023.01.004
2. Gupta T, Kannan S, Dantkale V, Laskar S. Cyclophosphamide plus total body irradiation compared with busulfan plus cyclophosphamide as a conditioning regimen prior to hematopoietic stem cell transplantation in patients with leukemia: a systematic review and meta-analysis. *Hematol Oncol Stem Cell Ther*. 2011;4(1):17–29. doi:10.5144/1658-3876.2011.17
3. Cusatis R LC, Feng Z, Allbee-Johnson M, Shaw BE. Current Uses and Outcomes of Cellular Therapies: CIBMTR Summary Slides, 2023. Accessed 6/14/20024, https://cibmtr.org/CIBMTR/Resources/Summary-Slides-Reports
4. Peters C, Dalle J-H, Locatelli F, et al. Total Body Irradiation or Chemotherapy Conditioning in Childhood ALL: A Multinational, Randomized, Noninferiority Phase III Study. *Journal of Clinical Oncology*. 2021;39(4):295–307. doi:10.1200/jco.20.02529
5. Pearlman R, Hanna R, Burmeister J, Abrams J, Dominello M. Adverse Effects of Total Body Irradiation: A Two-Decade, Single Institution Analysis. *Advances in Radiation Oncology*. 2021;6(4)doi:10.1016/j.adro.2021.100723
6. Willard VW, Leung W, Huang Q, Zhang H, Phipps S. Cognitive outcome after pediatric stem-cell transplantation: impact of age and total-body irradiation. *J Clin Oncol*. Dec 10 2014;32(35):3982–8. doi:10.1200/jco.2014.56.2223
7. Mulcahy Levy JM, Tello T, Giller R, et al. Late effects of total body irradiation and hematopoietic stem cell transplant in children under 3 years of age. *Pediatr Blood Cancer*. Apr 2013;60(4):700–4. doi:10.1002/pbc.24252
8. Bresters D, Lawitschka A, Cugno C, et al. Incidence and severity of crucial late effects after allogeneic HSCT for malignancy under the age of 3 years: TBI is what really matters. *Bone Marrow Transplant*. Nov 2016;51(11):1482–1489. doi:10.1038/bmt.2016.139
9. Lee CJ, Kim S, Tecca HR, et al. Late effects after ablative allogeneic stem cell transplantation for adolescent and young adult acute myeloid leukemia. *Blood advances*. Mar 24 2020;4(6):983–992. doi:10.1182/bloodadvances.2019001126
10. Bader P, Pötschger U, Dalle J-H, et al. Low rate of nonrelapse mortality in under-4-year-olds with ALL given chemotherapeutic conditioning for HSCT: a phase 3 FORUM study. *Blood advances*. 2024;8(2):416–428. doi:10.1182/bloodadvances.2023010591
11. Balduzzi A, Buechner J, Ifversen M, Dalle JH, Colita AM, Bierings M. Acute Lymphoblastic Leukaemia in the Youngest: Haematopoietic Stem Cell Transplantation and Beyond. *Front Pediatr*. 2022;10:807992. doi:10.3389/fped.2022.807992
12. Krull KR, Brinkman TM, Li C, et al. Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: a report from the St Jude lifetime cohort study. *J Clin Oncol*. Dec 10 2013;31(35):4407–15. doi:10.1200/jco.2012.48.2315
13. Turcotte LM, Whitton JA, Leisenring WM, et al. Chronic conditions, late mortality, and health status after childhood AML: a Childhood Cancer Survivor Study report. *Blood*. Jan 5 2023;141(1):90–101. doi:10.1182/blood.2022016487
14. Zabora J, Brintzenhofeszoc K, Jacobsen P, et al. A new psychosocial screening instrument for use with cancer patients. *Psychosomatics*. 2001;42(3):241–246.
15. Hays RD, Sherbourne CD, Mazel RM. The rand 36-item health survey 1.0. *Health Economics*. 1993;2(3):217–227. doi:https://doi.org/10.1002/hec.4730020305

16. Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36): I. Conceptual Framework and Item Selection. *Medical Care*. 1992;30(6):473–483.
17. Hayek S, Gibson TM, Leisenring WM, et al. Prevalence and Predictors of Frailty in Childhood Cancer Survivors and Siblings: A Report From the Childhood Cancer Survivor Study. *J Clin Oncol*. Jan 20 2020;38(3):232–247. doi:10.1200/JCO.19.01226
18. Daniel LC, Lubas MM, Wang H, et al. Frailty and Sleep in Adult Survivors of Childhood Cancer: A Childhood Cancer Survivor Study Report. *Psychooncology*. Feb 2025;34(2):e70098. doi:10.1002/pon.70098
19. Wilson CL, Bjornard KL, Partin RE, et al. Trends in physical functioning in acute lymphoblastic leukemia and non-Hodgkin lymphoma survivors across three decades. *J Cancer Surviv*. Apr 2025;19(2):496–506. doi:10.1007/s11764-023-01483-1

Proposed tables

Table 1. Participant characteristics

	TBI-HCT	Non-TBI-HCT	HM-control	Siblings
	(n = ___)	(n = ___)	(n = ___)	(n = ___)
Age at diagnosis, median (range)				.
Age at diagnosis, by group, N (%)				.
≥0 & <4 years				.
≥4 & <8 years				.
≥8 & <12 years				.
≥12 & <16 years				.
≥16 & <20 years				.
Age at HCT, median (range)			.	.
Age at HCT, by group, N (%)			.	.
≥0 & <4 years			.	.
≥4 & <8 years			.	.
≥8 & <12 years			.	.
≥12 & <16 years			.	.
≥16 & <20 years			.	.
Age at last follow-up, median (range)				
Age at last follow-up, by group, N (%)				
≥18 & <29 years				
≥30 & <39 years				
≥40 years				
Time since treatment, median (range)				.
Time since treatment, by group, N (%)				.
≥0 & <5 years				.
≥5 & <10 years				.
≥10 & <20 years				.
≥20 & <30 years				.
≥30 years				.
Sex, N (%)				
Female				
Male				
Ever smoking, N (%)				
BMI, N (%)				
Diagnosis, N (%)				.
TBI dose (Gy)				.
Total, median (range)				.
Cranial radiation (Gy), median (range)				.
Relapse, N (%)				.
Second cancer, N (%)				.
Chemotherapy (mg/m2), median (range)				.
Methotrexate IV				.
Methotrexate IT				.
Vincristine				.

Table 2a. Multivariable analysis for neurocognitive function (t score)
(Tables for health and well-being will be similarly formatted; 2b, 2c, etc)

	Task Efficiency	Emotional Regulation	Planning/ Organization	Memory
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Group				
HM-control	Ref	Ref	Ref	Ref
TBI-HCT				
Non-TBI-HCT				
Age at Diagnosis				
Age at Follow-Up				
Sex				
Males	Ref	Ref	Ref	Ref
Females				

Table 3a. Multivariable analysis for neurocognitive impairment
(Tables for social attainment outcomes and health and well-being will be similarly formatted. 3a, 3b, etc)

	Task Efficiency	Emotional Regulation	Planning/ Organization	Memory	Any 1 impairment	Any 2 impairment
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Group						
HM-control	Ref	Ref	Ref	Ref	Ref	Ref
TBI-HCT						
Non-TBI-HCT						
Age at Diagnosis						
Age at Follow-Up						
Sex						
Males	Ref	Ref	Ref	Ref	Ref	Ref
Females						

Outcomes are T scores of each domain with reference to the sibling control.

Table 4a. Longitudinal trend of neurocognitive impairment
(Tables for health and well-being will be similarly formatted; 4b, 4c, etc)

	FU5		FU7		Interval change		
	Mean, SD	%impaired	Mean, SD	%impaired	Maintain (%)	Improve (%)	Decline (%)
Memory impairment							
TBI-HCT							
Non-TBI-HCT							
HM-control							
Siblings							
Organization							
TBI-HCT							
Non-TBI-HCT							
HM-control							
Siblings							

Emotional regulation							
TBI-HCT							
Non-TBI-HCT							
HM-control							
Siblings							
Task efficiency							
TBI-HCT							
Non-TBI-HCT							
HM-control							
Siblings							

Table 5a. Multivariable analysis: Changes in neurocognitive function (T score)
(Tables for health and well-being will be similarly formatted; 5b, 5c, etc)

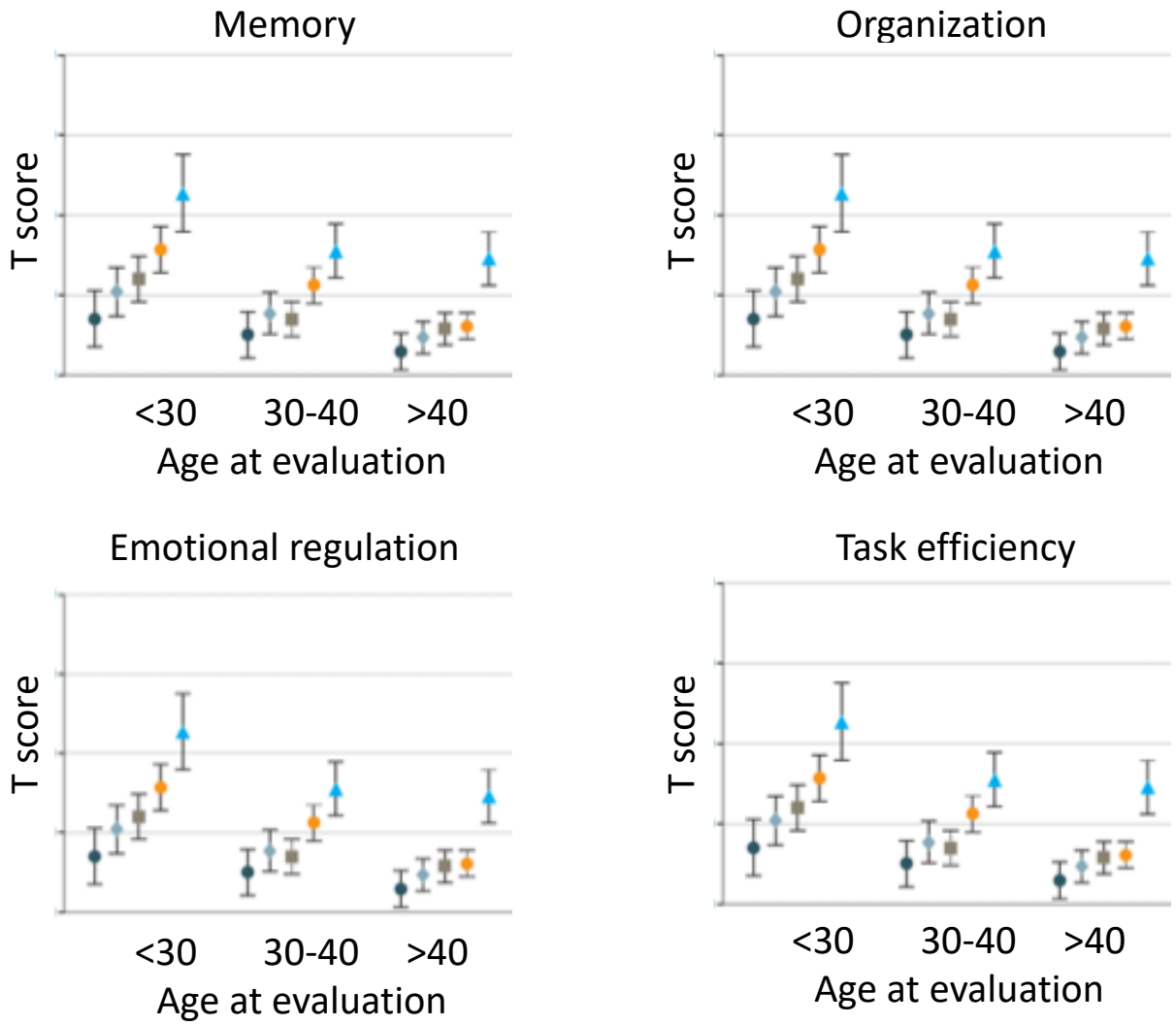
Effect	**Memory**	**Organization**	**Emotional regulation**	**Task efficiency**
	Estimate (SE)	**Estimate (SE)**	**Estimate (SE)**	**Estimate (SE)**
Group				
Sibling	**Ref**	**Ref**	**Ref**	**Ref**
TBI-HCT (age of HCT <__)				
TBI-HCT (age of HCT ≥__)				
Non-TBI-HCT (age of HCT <__)				
Non-TBI-HCT (age of HCT <__)				
HM-control				
(other variable A)				
(other variable B)				
(other variable C)				

Table 6a. Multivariable analysis: Decline in neurocognitive function
(Tables for health and well-being will be similarly formatted; 6b, 6c, etc)

Effect	**Memory**	**Organization**	**Emotional regulation**	**Task efficiency**
	RR (95%CI)	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**
Group				
Sibling	**Ref**	**Ref**	**Ref**	**Ref**
TBI-HCT (age of HCT <__)				
TBI-HCT (age of HCT ≥__)				
Non-TBI-HCT (age of HCT <__)				
Non-TBI-HCT (age of HCT <__)				

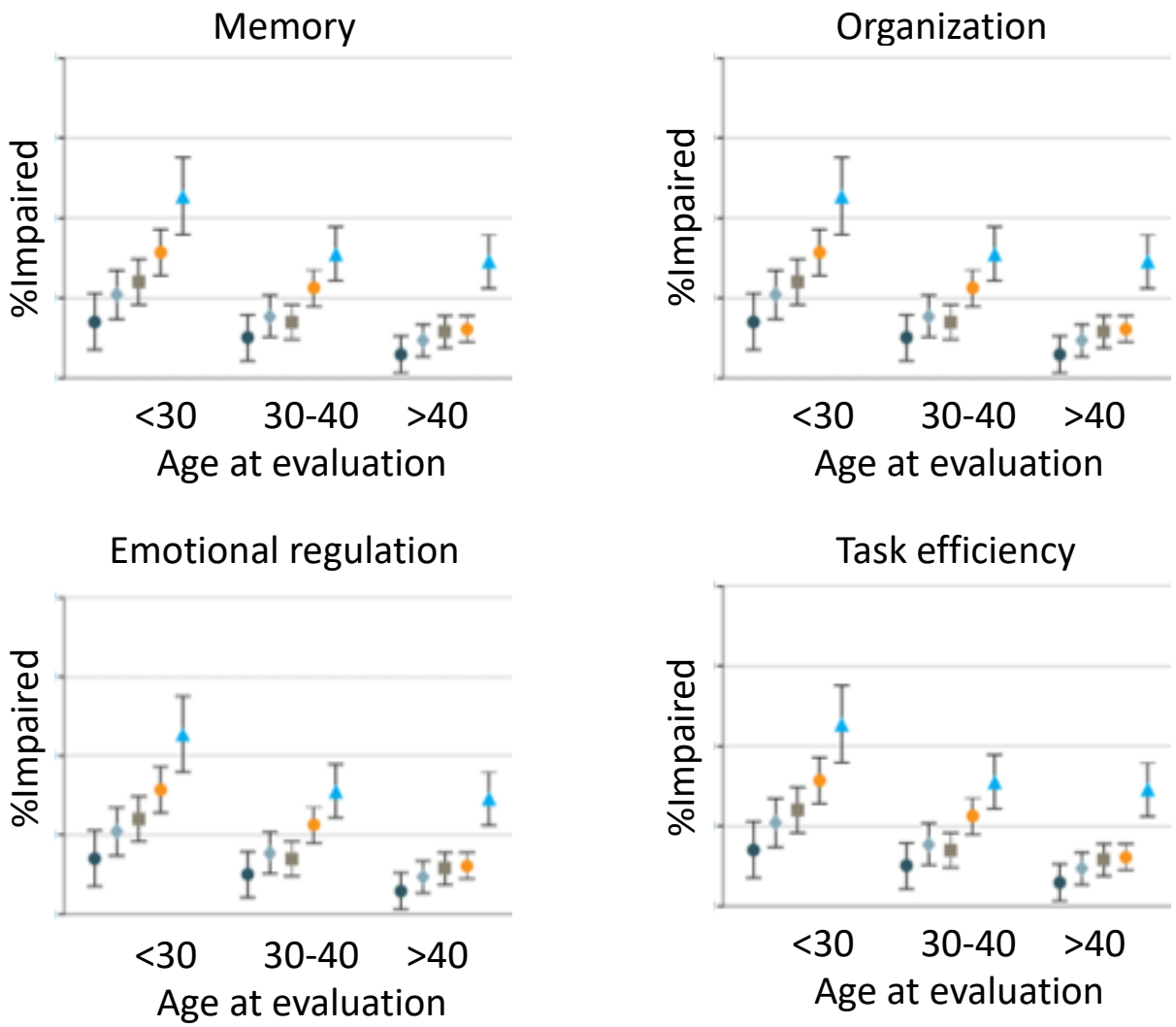
HM-control				
(other variable A)				
(other variable B)				
(other variable C)				

Proposed Figures



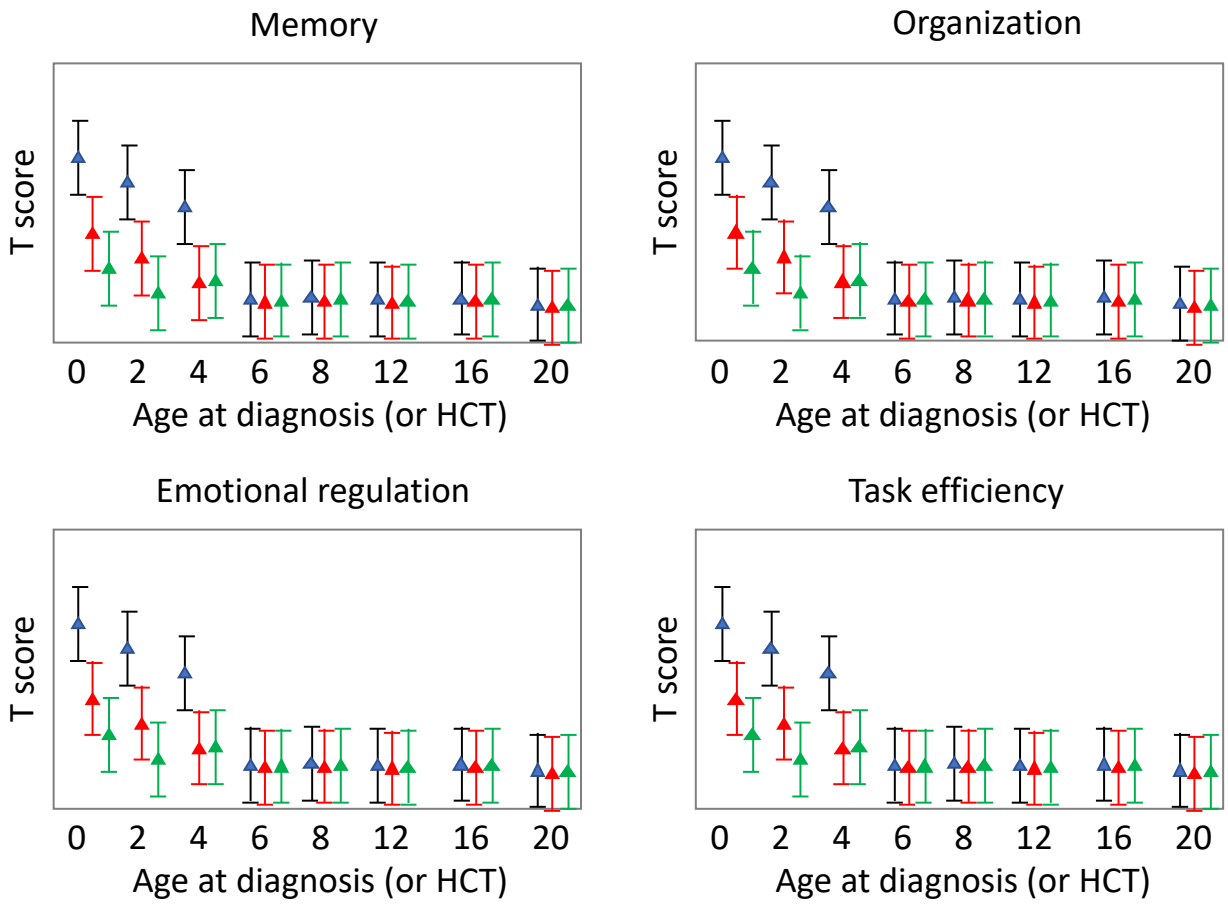
Groups (colors): 1. TBI-HCT, 2. Non-TBI-HCT, 3. HM-control, 4. Siblings

Figure 1a. Neurocognitive outcomes (T score)
(Figures for health and well-being will be similarly formatted; 1b, 1c, etc)



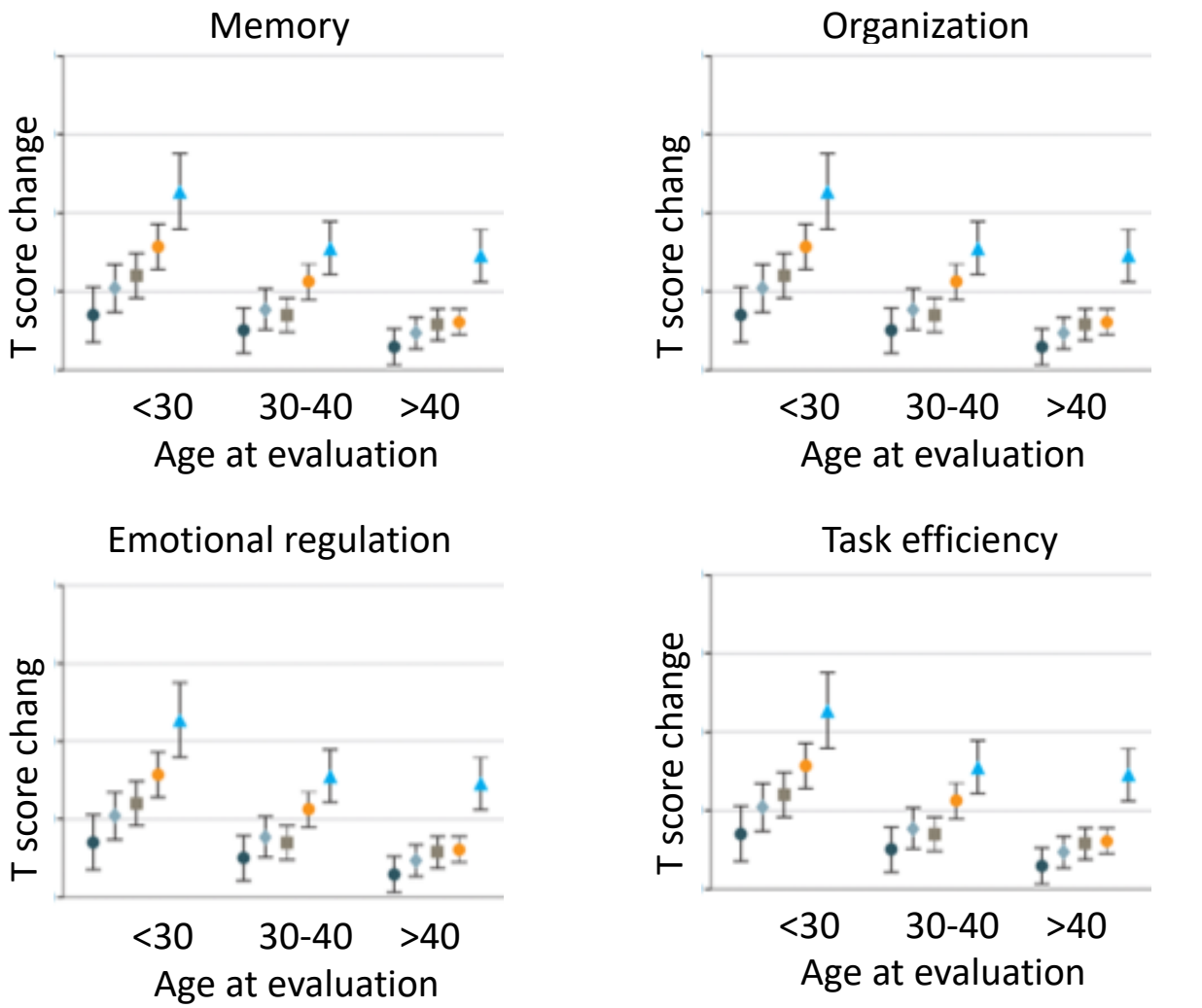
Groups (colors): 1. TBI-HCT, 2. Non-TBI-HCT, 3. HM-control, 4. Siblings

Figure 2a. Neurocognitive impairment (%)
(Figures for social attainment outcomes and health and well-being will be similarly formatted. 2a, 2b, etc)



Groups (colors): 1. TBI-HCT, 2. Non-TBI-HCT, 3. HM-control

Figure 3a. Neurocognitive function (T score) and age at diagnosis (or HCT)
(Figures for health and well-being will be similarly formatted; 3b, 3c, etc)



Groups (colors): 1. TBI-HCT <_ years, 2. TBI-HCT ≥_ years,
3. Non-TBI-HCT <_years, 4. Non-TBI-HCT ≥_years, 5. HM-control, 6. Siblings

Figure 4a. Longitudinal trend of neurocognitive impairment (%) in non-TBI-HCT cohort
(Figures for health and well-being will be similarly formatted; 4b, 4c, etc)