Childhood Cancer Survivor Study
Concept Proposal

I. Title:

Physical activity as a predictor of neurocognitive outcomes in adult survivors of childhood cancers.

Working Groups: Psychology (Primary), Cancer Control (Secondary), Chronic Disease (Secondary)

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II. Background and Rationale:

Cancer occurs in 17 out of every 100,000 individuals in the United States under the age of 20 [1]. With advances in the treatment of pediatric cancers, survival rates have improved to approximately 80%, leading to a growing population of adult survivors of childhood cancer [1]. Notably, the majority of these cases require invasive treatments such as chemotherapy or irradiation, which put survivors at risk for late effects, such as second cancers, endocrinopathies, and cognitive deficits [2].

Cognitive dysfunction affects one third or more of childhood cancer survivors, and may continue to progress for years after the termination of treatment [3-7]. Although the severity of impairment has been strongly associated with exposure to specific chemotherapy agents and cranial irradiation, evidence also exists for direct effects of both CNS and non-CNS cancers on cognitive function in adults [8-12]. Moreover, cognitive difficulties may be exacerbated by comorbid chronic health conditions [13-14]. Dysfunction in childhood cancer survivors has been characterized by a decline in full scale intelligence quotient (FSIQ), and/or impairment in core functional domains, such as attention, working memory, executive function, processing speed, or visuomotor integration [15-19]. Survivors have reported neurocognitive problems in day-to-day living, and have demonstrated greater challenges in academic, vocational, social, and psychological aspects of their lives [20-23].

Survivors of childhood cancer have reported lower engagement in physical activity than healthy controls, as well as greater declines in activity over time [24]. These lower rates of activity have been associated with the receipt of a cancer diagnosis, reduced psychosocial well-being, greater somatic symptoms, and

an elevated risk for secondary chronic health conditions and mortality [25-28]. Notably, engagement in physical activity has been associated with hippocampal neurogenesis in rodents, as well as with neuroimaging indices of brain health and better cognitive function in a variety of healthy and clinical populations [29], suggesting that this is an important variable to consider in studying the cognitive sequelae of childhood cancer. These relationships may be mediated by changes to adiposity, with negative relationships observed between Body Mass Index (BMI) and cognitive performance in healthy children, adolescents and adults [30]. Meta-analyses have noted significant relationships between physical activity and measures of attention, memory, motor control, spatial cognition, and processing speed, with particularly strong associations observed for executive functions [29, 31]. Although the largest effect sizes have been observed for aerobic exercise [31-32], efficacy has been demonstrated for a range of interventions, leaving it unclear as to what intensity and quantity of physical activity is optimal for the prevention and/or treatment of cognitive deficits.

In the adult cancer literature, higher levels of physical activity have been associated with better neuropsychological outcomes in both cross-sectional and intervention studies [33]. Survivors of childhood cancer reporting higher levels of leisure-time physical activity have also endorsed more positive ratings of cognitive function, social function, and overall health-related quality of life [34]. Moreover, increased hippocampal volume and white matter fractional anisotropy, as well as improved reaction time have been observed in children treated with radiation for brain tumors following a 12-week aerobic exercise intervention [35]. However, no large-scale study has examined whether physical activity predicts late cognitive effects in childhood cancer survivors more broadly. In the current study, we aim to examine associations between physical activity and neurocognitive outcomes in a cohort of North American childhood cancer survivors who have taken part in the Childhood Cancer Survivor Study (CCSS), and to explore BMI and secondary chronic health conditions as factors influencing this relationship.

III. Objective/Specific aims/Research Hypotheses:

Aim 1. To examine associations between persistent physical activity (i.e. meeting CDC guidelines) and neurocognitive outcomes on the CCSS-NCQ at follow-up in survivors and siblings, after controlling for relevant covariates.

> Hypothesis. Those who have consistently met CDC guidelines from baseline to follow-up will show fewer symptoms on the NCQ or lower rates of impairment than those who have been inconsistent, or have consistently not met guidelines. This relationship is anticipated to occur in both survivors and their siblings; however, we anticipate a stronger relationship in survivors.
>
> Although the literature provides a rationale for those engaging in higher levels of activity to demonstrate fewer symptoms across each of the NCQ domains (Emotional Regulation, Memory, Organization, and Task Efficiency), the Memory domain (which captures both working memory and long-term memory) and Organization domain are hypothesized to be most strongly associated with one's engagement in physical activity.

Aim 2. To explore associations between the intensity of physical activity, the quantity of physical activity (minutes per week) and neurocognitive outcomes on the CCSS-NCQ in survivors and siblings, after controlling for relevant covariates.

> Hypothesis. Those engaging in more intense and more frequent activity will demonstrate fewer symptoms on the NCQ scores or lower rates of impairment. This relationship is anticipated to occur in both survivors and their siblings; however, we anticipate a stronger relationship in

survivors. Similar to Aim 2, out of the neurocognitive domains measured, we anticipate that Memory will be most strongly associated with physical activity intensity and frequency.

Aim 3. To evaluate BMI as a mediator of the relation between persistence of physical activity and neurocognitive outcome on the CCSS-NCQ.

Hypothesis. BMI will partially mediate this relationship; however, physical activity is anticipated to predict NCQ symptomatology over and above BMI. A negative relationship is anticipated to occur between PA and BMI, as well as in the direct relationship between PA and NCQ symptomatology. The relationship between BMI and NCQ symptom reporting is anticipated to be positive.

Aim 4. To evaluate physical activity as a mediator of the association between chronic health conditions (e.g. cardiovascular, respiratory) and neurocognitive outcome on the CCSS-NCQ.

Hypothesis. Physical activity will account for a modest proportion of the relationship between chronic health conditions and symptoms on the NCQ. The presence of a chronic health condition is anticipated to be associated with lower PA, which in turn, is anticipated to have a negative association with NCQ symptomatology. Moreover, having a chronic health condition is expected to be positively associated with NCQ symptomatology.

Aim 5. To examine associations between patterns of PA and change in NCQ symptoms over time, using latent cluster analyses.

Hypothesis. We anticipate that survivors will cluster in the following pattern:

- Consistently high PA and healthy BMI
- Consistently high PA and high BMI
- Variable PA over time and healthy BMI
- Variable PA over time and high BMI
- Consistently low PA and high BMI
- Consistently low PA and healthy BMI

Moreover, we expect that clusters engaging in greater and more consistent PA, with healthy BMI scores, will be more likely to demonstrate stability or improvement in NCQ symptoms over time.

IV. Analysis Framework:

Population

We propose to conduct our analysis on the original and expanded CCSS survivor cohorts. We propose to also include siblings as a comparison group for the CCSS-NCQ.

Subject population

Survivors and siblings from the original and expanded cohorts who completed physical activity information at baseline and follow-up (FU), as well as the CCSS-NCQ at FU. To allow for greater consistency in the timespan between baseline and FU measurements between the original and expanded cohorts, FU will be defined as FU2 for the original cohort and as FU5 for the expanded cohort.

Measures

Independent variables:

- Physical activity
  - Meeting CDC guidelines
    - Meeting CDC guidelines = >75 mins of vigorous; >150 mins moderate per week
    - Group participants based on persistence of PA from baseline to FU.
    - Consistently active (yes/yes); Inconsistently active (yes/no; no/yes); Consistently inactive (no/no)
    - For baseline – can only get a rough estimate of #minutes/per week engaged in vigorous exercise
      - **< 18 yrs Baseline: Original cohort N.5; Expanded cohort O1**
        - "On how many of the past 7 days did your child exercise or do sports for at least 20 minutes that made him/her sweat or breathe hard"
      - **> 18 yrs Baseline: Original cohort N.9; Expanded cohort O15**
        - "How many days (/7) did you exercise or do sports for at least 20 minutes that made you sweat or breathe hard"
      - If 4 or more days – yes, meeting guidelines
    - FU – Given # minutes of vigorous and moderate activity per week
      - Classify as meeting CDC guidelines if >75 vigorous, or >150 moderate per week (**FU2 D.2-7; FU5 N.16-21**)
        - If <75 vigorous and <150 moderate – count vigorous minutes toward moderate total
  - Intensity of physical activity = (#days per week vigorous * 9) + (#days per week moderate * 5)
    - **FU2 D.3, D.6; FU5 N.17, N.20**
  - Quantity = (#days per week * minutes per day vigorous) + (# days per week * minutes per day moderate)
    - **FU2 D.2-D.7; FU5 N.16-N.21**
- BMI = (weight in pounds / (height in inches * height in inches)) * 703
  - **FU2 7,8; FU5 A.1-2**
- Chronic condition (yes/no) at any time point
  - Yes = existing grade 3-4 "relevant" conditions

Relevant	"Not relevant"
Cardiovascular	Neurologic – Memory problems (redundant)
Respiratory	GI, Renal (not listed elsewhere)
Musculoskeletal	Speech
Neurological	Hearing
Hematologic	
Infectious/Immunologic	
Diabetes	
Renal – dialysis	
Endocrine	
Hepatitis	
Vision	
Secondary malignancy	

Dependent variable:

- CCSS-NCQ
  - Raw scores
    - Composite, task efficiency, emotion regulation, organization, memory)
    - **FU2 J.1-25; FU5 Q.1-33**
  - Impairment (yes/no)
    - Impaired = symptom level reported in ≤10% of the sibling normative sample Composite, task efficiency, emotion regulation, organization, memory
  - Change
    - (x2-x1) > SE of (x2-x1) for sibling sample
      - If YES (with increased symptoms) = cognitive decline
      - If YES (with decreased symptoms) or if NO = no decline
    - Composite, task efficiency, emotion regulation, organization, memory

Covariates:

- Health behaviours
  - Tobacco use – **FU2 L.2; FU5 N.9**
    - Do you smoke cigarettes now (yes/no)
- Demographics
  - Age – **FU Date – Baseline A.1 (DOB)**
  - Education – **FU2 Question 1; FU5 A.4**
    - What is the highest grade or level of schooling you have completed (ordinal scale)
  - Race – **Original cohort Baseline A.4; Expanded cohort Baseline A.5**
  - Sex – **Baseline A.2**
- Clinical variables
  - Age at diagnosis
  - Time since diagnosis
  - Diagnosis
  - Treatment
    - CNS radiation dose
    - Mediastinal radiation dose
    - Chemotherapy dose (antimetabolites, anthracyclines, alkylating agents, corticosteroids)
    - Bone marrow transplant
  - Psychiatric symptomatology – BSI composite (**FU2 G.1-18; FU5 L.1-18**)

Analyses

- Descriptive statistics and comparison of demographics across childhood cancer survivors and siblings. T-test or chi-square, as appropriate.
- Covariance matrix – Covariates vs. PA and NCQ
  - Include relevant covariates ($p < 0.05$) in subsequent analyses
- **Aim 1** (Tables 2-5)
  - Multivariable regression
    - Predictors: PA (persistence; baseline → FU), Group (survivors vs. siblings)
    - Interaction (PA & Group)
    - Outcome: NCQ-raw and NCQ-impairment at FU (composite, task efficiency, emotion regulation, organization, memory)
    - Covariates: age at NCQ (and others identified in covariance matrix)
  - This analysis will be run separately for CNS tumor and non-CNS tumor survivors because of possible collinearity between PA and NCQ in the CNS group.

- **Aim 2** (Tables 5-9)
    - Multivariable regression
        - Predictors: PA (quantity at FU), Group (survivors vs. siblings)
        - Interaction (PA & Group)
        - Outcome: NCQ-raw and NCQ-impairment at FU (composite, task efficiency, emotion regulation, organization, memory)
        - Covariates: age at NCQ (and others identified in covariance matrix)
    - Multivariable regression
        - Predictors: PA (intensity at FU), Group (survivors vs. siblings)
        - Interaction (PA & Group)
        - Outcome: NCQ-raw and NCQ-impairment at FU (composite, task efficiency, emotion regulation, organization, memory)
        - Covariates: age at NCQ (and others identified in covariance matrix)
- **Aim 3** (Table 10)
    - Mediation analysis
        - Predictor: PA (as defined in Aim 1),
        - Mediator: BMI at FU
        - Outcomes: NCQ-raw at FU (composite, task efficiency, emotion regulation, organization, memory)
        - Covariates: age at NCQ (and others identified in covariance matrix)
- **Aim 4** (Table 11)
    - Mediation analysis
        - Predictor: Presence of chronic condition [yes/no]
        - Mediator: PA (as defined in Aim 1)
        - Outcome: NCQ-raw at FU (composite, task efficiency, emotion regulation, organization, memory)
        - Covariates: age at NCQ (and others identified in covariance matrix)
- **Aim 5***original cohort, survivors only (Table 12-14)
    - Latent profile analysis in a random sample of half the original cohort. The remainder of the cohort will be used as a validation sample. We will subsequently explore demographic, disease, and treatment predictors of cluster membership, as well as how effectively cluster membership predicts meaningful change on the NCQ.
        - Variables: PA intensity (baseline, FU2, FU5), BMI (FU5)
        - Run validation analysis with remaining 50% of sample
    - Multinomial regression analysis
        - Predictors
            - Demographic: sex, age at FU5, educational attainment
            - Disease: diagnosis, age at diagnosis
            - Treatment: chemotherapy exposure ([yes/no], antimetabolites, anthracyclines, alkylating agents, corticosteroids), radiation (cranial [yes/no], non-cranial [yes/no]), cranial radiation dose
            - Presence of chronic health condition [yes/no]
            - Clinically significant psychiatric symptomatology [yes/no]
        - Outcome: cluster membership
    - Regression
        - Predictor: cluster membership
        - Outcome: change in NCQ [decline/no decline]

Table 1. Characteristics of participants who completed the NCQ at follow-up in the original and expanded cohorts, (i.e. study sample) and survivors excluded from analyses due to missing NCQ and/or PA data.

Characteristics	Survivors		Survivors excluded		p	Siblings		p
	N	%	N	%		N	%	
Sex								
Male								
Female								
Race								
White								
Black								
Other								
Ethnicity								
Hispanic								
Non-Hispanic								
Age at baseline								
18-29 yrs								
30-39 yrs								
40-54 yrs								
Education								
< 12 yrs								
High school graduate								
Some college								
College graduate								
Household income								
< $19,999								
$20,000-39,999								
$40,000-59,999								
Over $60,000								
Physical activity (meeting CDC guidelines)								
Consistently active								
Inconsistently active								
Consistently inactive								
Body Mass Index								
Normal/underweight								
Overweight								
Obese								
Current tobacco use								
Yes								
No								
Age at diagnosis								
< 1 yr								
1-3 yrs								
4-7 yrs								
8-10 yrs								
11-14 yrs								
15-20 yrs								

Cancer diagnosis								
Leukemia								
CNS malignancy								
Hodgkin lymphoma								
Non-Hodgkin lymphoma								
Kidney tumors								
Neuroblastomas								
Soft tissue sarcoma								
Bone tumors								
Treatment era								
1970-1979								
1980-1989								
1990-1999								
Chemotherapy								
Antimetabolites								
Anthracyclines								
Alkylating agents								
Corticosteroids								
Radiation								
None								
Non-cranial								
Cranial								
Cranial radiation dose								
None								
0.1-19 Gy								
20-39 Gy								
40-59 Gy								
≥ 60 Gy								
Mediastinal radiation dose								
None								
< 20 Gy								
≥ 20 Gy								
Grade 3+ health condition								
Yes								
No								
Clinically significant psychiatric symptomatology (BSI > 63)								
Yes								
No								

Table 2. Multivariate regression exploring persistence in PA as a predictor of NCQ symptomatology in CNS cancer survivors.

Variable	β	p-value	sr^2
NCQ Composite			
Group			
PA			
Group*PA			
Task Efficiency			
Group			
PA			
Group*PA			
Emotion Regulation			
Group			
PA			
Group*PA			
Organization			
Group			
PA			
Group*PA			
Memory			
Group			
PA			
Group*PA			

Table 3. Logistic regression exploring persistence in PA as a predictor of impairment on the NCQ in CNS cancer survivors.

Variable	OR	95% CI	p-value
NCQ Composite			
Group			
PA			
Group*PA			
Task Efficiency			
Group			
PA			
Group*PA			
Emotion Regulation			
Group			
PA			
Group*PA			
Organization			
Group			
PA			
Group*PA			
Memory			
Group			
PA			
Group*PA			

Table 4. Multivariate regression exploring persistence in PA as a predictor of NCQ symptomatology in non-CNS cancer survivors.

Variable	β	p-value	sr^2
NCQ Composite			
Group			
PA			
Group*PA			
Task Efficiency			
Group			
PA			
Group*PA			
Emotion Regulation			
Group			
PA			
Group*PA			
Organization			
Group			
PA			
Group*PA			
Memory			
Group			
PA			
Group*PA			

Table 5. Logistic regression exploring persistence in PA as a predictor of impairment on the NCQ in non-CNS cancer survivors.

Variable	OR	95% CI	p-value
NCQ Composite			
Group			
PA			
Group*PA			
Task Efficiency			
Group			
PA			
Group*PA			
Emotion Regulation			
Group			
PA			
Group*PA			
Organization			
Group			
PA			
Group*PA			
Memory			
Group			
PA			
Group*PA			

Table 6. Multivariate regression exploring PA intensity at follow-up as a predictor of NCQ symptomatology.

Variable	β	p-value	sr^2
NCQ Composite			
Group			
PA			
Group*PA			
Task Efficiency			
Group			
PA			
Group*PA			
Emotion Regulation			
Group			
PA			
Group*PA			
Organization			
Group			
PA			
Group*PA			
Memory			
Group			
PA			
Group*PA			

Table 7. Logistic regression exploring PA intensity at follow-up as a predictor of impairment on the NCQ.

Variable	OR	95% CI	p-value
NCQ Composite			
Group			
PA			
Group*PA			
Task Efficiency			
Group			
PA			
Group*PA			
Emotion Regulation			
Group			
PA			
Group*PA			
Organization			
Group			
PA			
Group*PA			
Memory			
Group			
PA			
Group*PA			

Table 8. Multivariate regression exploring PA quantity at follow-up as a predictor of NCQ symptomatology.

Variable	β	p-value	sr^2
NCQ Composite			
Group			
PA			
Group*PA			
Task Efficiency			
Group			
PA			
Group*PA			
Emotion Regulation			
Group			
PA			
Group*PA			
Organization			
Group			
PA			
Group*PA			
Memory			
Group			
PA			
Group*PA			

Table 9. Logistic regression exploring PA quantity at follow-up as a predictor of impairment on the NCQ.

Variable	OR	95% CI	p-value
NCQ Composite			
Group			
PA			
Group*PA			
Task Efficiency			
Group			
PA			
Group*PA			
Emotion Regulation			
Group			
PA			
Group*PA			
Organization			
Group			
PA			
Group*PA			
Memory			
Group			
PA			
Group*PA			

Table 10. Analysis of BMI as mediator of persistence of PA and NCQ symptomatology at follow-up.

	Path a PA → BMI	Path b BMI → NCQ	Path c' PA → NCQ	Mediation path a*b
NCQ Composite				
β				
p-value				
Task Efficiency				
β				
p-value				
Emotion Regulation				
β				
p-value				
Organization				
β				
p-value				
Memory				
β				
p-value				

Table 11. Analysis of PA as a mediator between presence of a chronic health condition (CHC) and NCQ at follow-up.

	Path a CHC → PA	Path b PA → NCQ	Path c' CHC → NCQ	Mediation path a*b
NCQ Composite				
β				
p-value				
Task Efficiency				
β				
p-value				
Emotion Regulation				
β				
p-value				
Organization				
β				
p-value				
Memory				
β				
p-value				

Table 12a. Latent clusters for PA intensity and BMI in the original cohort.

	Cluster 1		Cluster 2		Cluster X	
	M	SD	M	SD	M	SD
PA baseline						
PA FU2						
PA FU5						
BMI FU5						

Table 12b. Proportion (%) of original cohort by latent cluster.

	Cluster 1	Cluster 2	Cluster X
Original cohort			

Table 13. Logistic regression exploring cluster membership as a predictor of NCQ decline.

	OR	95% CI	p-value
Cluster 1			
Cluster 2			
Cluster X			

Table 14. Multinomial logistic regression model exploring demographic and clinical predictors of cluster membership.

Variable	Cluster 1		Cluster 2		Cluster X	
	OR	95% CI	OR	95% CI	OR	95% CI
Sex						
Male						
Female						
Age at follow-up						
18-29 yrs						
30-39 yrs						
40-59 yrs						
50-69 yrs						
Education						
<12 years						
High school graduate						
Some college						
College graduate						
Age at diagnosis						
0-2						
3-5						
6-10						
11-15						
16-20						
Cancer diagnosis						
Leukemia						
CNS malignancy						
Hodgkin lymphoma						
Non-Hodgkin lymphoma						
Kidney tumors						
Neuroblastomas						
Soft tissue sarcoma						
Bone tumors						
Chemotherapy						
Antimetabolites						
Anthracyclines						
Alkylating agents						

Corticosteroids						
Radiation						
None						
Non-cranial						
Cranial						
Cranial radiation dose						
None						
0.1-19 Gy						
20-39 Gy						
40-59 Gy						
≥ 60 Gy						
Grade 3+ health condition						
Yes						
No						
Clinically significant psychiatric symptomatology (BSI ≥ 63)						
Yes						
No						

References

1. Howlader, N., Noone, A. M., Krapcho, M., Miller, D., Bishop, K., Altekruse, S. F., … & Cronin, K. A. (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016.

2. Armenian, S. H., & Robison, L. L. (2013). Childhood Cancer Survivorship: An Update on Evolving Paradigms for Understanding Pathogenesis and Screening for Therapy-Related Late Effects. *Current Opinion in Pediatrics*, *25*(1), 16–22.

3. Butler, R. W., & Haser, J. K. (2006). Neurocognitive effects of treatment for childhood cancer. *Ment Retard Dev Disabil Res Rev*, *12*(3), 184–91.

4. Campbell, L. K., Scaduto, M., Sharp, W., Dufton, L., Van Slyke, D., Whitlock, J. A., & Compas, B. (2007). A meta-analysis of the neurocognitive sequelae of treatment for childhood acute lymphocytic leukemia. *Pediatr Blood Cancer*, *49*(1), 65–73.

5. Mulhern, R. K., & Butler, R. W. (2004). Review Neurocognitive sequelae of childhood cancers and their treatment. *Pediatric rehabilitation*, *7*(1), 1-14.

6. Mulhern, R.K., Fairclough, D., & Ochs, J. (1991). A prospective comparison of neuropsychologic performance of children surviving leukemia who received 18-Gy, 24-Gy, or no cranial irradiation. *J Clin Oncol*, *9* (8),1348–56.

7. Moleski, M. (2000). Neuropsychological, neuroanatomical, and neurophysiological consequences of CNS chemotherapy for acute lymphoblastic leukemia. *Arch Clin Neuropsychol*, *15*(7):603–30.

8. Anderson, F. S., & Kunin-Batson, A. S. (2009). Neurocognitive late effects of chemotherapy in children: the past 10 years of research on brain structure and function. *Pediatric blood & cancer*, *52*(2), 159-164.

9. Cleeland, C. S., Bennett, G. J., Dantzer, R., Dougherty, P. M., Dunn, A. J., Meyers, C. A., … & Lee, B. (2003). Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? *Cancer*, *97*(11), 2919-2925.

10. Kao, G. D., Goldwein, J. W., Schultz, D. J., Radcliffe, J., Sutton, L., & Lange, B. (1994). The impact of perioperative factors on subsequent intelligence quotient deficits in children treated for medulloblastoma/posterior fossa primitive neuroectodermal tumors. *Cancer*, *74*(3), 965-971.

11. Meyers, C. A., Albitar, M., & Estey, E. (2005). Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. *Cancer, 104* (4), 788-793.

12. Rodgers, S. P., Trevino, M., Zawaski, J. A., Gaber, M. W., & Leasure, J. L. (2013). Neurogenesis, exercise, and cognitive late effects of pediatric radiotherapy. *Neural Plasticity, 2013*, 1-12.

13. Champaloux, S. W., & Young, D. R. (2015). Childhood chronic health conditions and educational attainment: A social ecological approach. *Journal of Adolescent Health, 56*, 98-105.

14. Vassilaki, M., Aakre, J. A., Cha, R. H., Kremers, W. K., St. Sauver, J. L., Mielke, M. M., … & Roberts, R. O. (2015). Multimorbidity and risk for mild cognitive impairment. *J AM Geriatr Soc, 63*(9), 1783-1790.

15. Butler, R. W., & Mulhern, R. K. (2005). Neurocognitive interventions for children and adolescents surviving cancer. *Journal of Pediatric Psychology*, *30*(1), 65-78.

16. Janzen, L. A., & Spiegler, B. J. (2008). Neurodevelopmental sequelae of pediatric acute lymphoblastic leukemia and its treatment. *Developmental disabilities research reviews*, *14*(3), 185-195.

17. Meadows, A., Massari, D., Fergusson, J., Gordon, J., Littman, P., & Moss, K. (1981). Declines in IQ scores and cognitive dysfunctions in children with acute lymphocytic leukaemia treated with cranial irradiation. *The lancet*, *318*(8254), 1015-1018.

18. Nathan, P. C., Patel, S. K., Dilley, K., Goldsby, R., Harvey, J., Jacobsen, C., ... & Okcu, M. F. (2007). Guidelines for identification of, advocacy for, and intervention in neurocognitive problems in survivors of childhood cancer: a report from the Children's Oncology Group. *Archives of pediatrics & adolescent medicine*, *161*(8), 798-806.

19. Nazemi, K. J., & Butler, R. W. (2011). Neuropsychological rehabilitation for survivors of childhood and adolescent brain tumors: a view of the past and a vision for a promising future. *Journal of pediatric rehabilitation medicine*, *4*(1), 37-46.

20. Barrera, M., Shaw, A. K., Speechley, K. N., Maunsell, E., & Pogany, L. (2005). Educational and social late effects of childhood cancer and related clinical, personal, and familial characteristics. *Cancer*, *104*(8), 1751-1760.

21. Ellenberg, L., Liu, Q., Gioia, G., Yasui, Y., Packer, R. J., Mertens, A., ... & Robison, L. L. (2009). Neurocognitive status in long-term survivors of childhood CNS malignancies: a report from the Childhood Cancer Survivor Study. *Neuropsychology*, *23*(6), 705.

22. Kadan-Lottick, N. S., Zeltzer, L. K., Liu, Q., Yasui, Y., Ellenberg, L., Gioia, G., ... & Krull, K. R. (2010). Neurocognitive functioning in adult survivors of childhood non-central nervous system cancers. *Journal of the National Cancer Institute*, *102*(12), 881-893.

23. Mitby, P. A., Robison, L. L., Whitton, J. A., Zevon, M. A., Gibbs, I. C., Tersak, J. M., ... & Mertens, A. C. (2003). Utilization of special education services and educational attainment among long-term survivors of childhood cancer. *Cancer*, *97*(4), 1115-1126.

24. Wilson, C. L., Stratton, K., Leisenring, W. L., Oeffinger, K. C., Nathan, P. C., Wasilewski-Masker, K., ... & Brinkman, T. M. (2014). Decline in physical activity level in the childhood cancer survivor study cohort. *Cancer Epidemiology Biomarkers & Prevention*, *23*(8), 1619-1627.

25. Cox, C. L., Nolan, V. G., Leisenring, W., Yasui, Y., Ogg, S. W., Mertens, A. C., … & Robison, L. L. (2014). Non-cancer related mortality risks in adult survivors of pediatric malignancies: The Childhood Cancer Survivor Study. *J Cancer Surviv, 8*(3), 460-471.

26. Jones, L. W., Liu, Q., Armstrong, G. T., Ness, K. K., Yasui, Y., Devine, K., … & Oeffinger, K.C. (2014). Exercise and risk for major cardiovascular events in adults survivors of childhood Hodgkin Lymphoma: A report from the Childhood Cancer Survivor Study. *Journal of Clinical Oncology, 32*(32), 3643-3650.

27. Keats, M. R., Culos-Reed, S. N., Courneya, K. S., & McBride, M. (2006). An examination of physical activity behaviors in a sample of adolescent cancer survivors. *Journal of pediatric oncology nursing, 23*(3), 135-142.

28. Ness, K. K., Leisenring, W. M., Huang, S., Hudson, M. M., Gurney, J. G., Whelan, K., ... & Oeffinger, K. C. (2009). Predictors of inactive lifestyle among adult survivors of childhood cancer. *Cancer, 115*(9), 1984-1994.

29. Hotting, K., & Roder, B. (2013). Beneficial effects of physical exercise on neuroplasticity and cognition. *Neurosci Biobehav Rev, 37*(9 Pt B), 2243-2257.

30. Smith, E., Hay, P., Campbell, L., & Trollor, J. N. (2011). A review of the association between obesity and cognitive function across the lifespan: Implications for novel approaches to prevention and treatment. *Obesity reviews, 12*(9), 740-755.

31. Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci, 14*(2), 125-130.

32. Chaddock, L., Erickson, K. I., Prakash, R. S., Voss, M. W., VanPatter, M., Pontifex, M. B., . . . Kramer, A. F. (2012). A functional MRI investigation of the association between childhood aerobic fitness and neurocognitive control. *Biol Psychol, 89*(1), 260-268.

33. Zimmer, P., Baumann, F. T., Oberste, M., Wright, P., Garthe, A., Schenk, A., ... & Wolf, F. (2016). Effects of exercise interventions and physical activity behavior on cancer related cognitive impairments: A systematic review. *BioMed research international, 2016*, 1-13.

34. Paxton, R. J., Jones, L. W., Rosoff, P. M., Bonner, M., Ater, J. L., & Demark-Wahnefried, W. (2010). Associations between leisure-time physical activity and health-related quality of life among adolescent and adult survivors of childhood cancers. *Psycho-Oncology, 19*(9), 997-1003.

35. Riggs, L., Piscione, J., Laughlin, S., Cunningham, T., Timmons, B. W., Courneya, K. S., ... & Persadie, N. (2016). Exercise training for neural recovery in a restricted sample of pediatric brain tumor survivors: a controlled clinical trial with crossover of training versus no training. *Neuro-Oncology, 19*(3), 440-450.

36. van Praag, H. Kempermann, G. & Gage, F. H. (2000). Neuronal consequences of environmental enrichment. *Nat Rev Neurosci, 1*, 191-198.

37. Ainsworth, B. E., Haskell, W. L., Herrman, S. D., Meckes, N., Bassett, D. R. Jr., Tudor-Locke, C., … & Leon, A. S. (2011). 2011 Compendium of physical activities: A second update of codes and MET values. *Medicine and Science in Sports and Exercise, 43*(8), 1575-1581.