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Cardiorespiratory Fitness in Survivors of Pediatric Posterior Fossa Tumor

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Abstract

Advances in medical therapies have greatly improved survivorship rates in children diagnosed with brain tumor; as a result, morbidities associated with survivorship have become increasingly important to identify and address. In general, pediatric posterior fossa tumor survivors tend to be less physically active than peers. This may be related to late effects of diagnosis and treatment, including cardiovascular, endocrine, psychological, and neurocognitive difficulties. Exercise has been shown to be effective in improving physical functioning, mood, and even cognitive functioning. Consequently, the benefits of physical exercise need to be explored and incorporated into the daily lives of pediatric posterior fossa tumor survivors. The primary aim of the present study was to establish the feasibility and safety of cardiorespiratory fitness testing in pediatric posterior fossa tumor survivors who had received cranial radiation therapy. Additionally, comparing our cohort to previously published data, we found that pediatric posterior fossa tumor survivors tended to be less fit than children with pulmonary disease as well as healthy controls, and approximately as fit as children with chronic heart disease and survivors of other types of childhood cancer. The importance of cardiorespiratory fitness in pediatric posterior fossa tumor survivors is discussed along with implications for future directions.

Keywords

Pediatric posterior fossa tumor; Cardiorespiratory fitness; VO_2max testing; Pediatric brain tumor

Introduction

Childhood brain tumors, the second most common type of childhood cancer, account for approximately 20 percent of the pediatric oncology population.[1] Brain tumors vary widely according to location, size, and histological composition. In a recent epidemiological review, males comprised about 57% of the pediatric brain tumor population. The overall incidence of pediatric brain tumor is approximately 4.5 in 100,000;[2] however, various types of tumors peak in incidence at different points of development.

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Late Effects

Survivors of pediatric brain tumor tend to be less active than their same-age peers.[3] This is likely related to the myriad of late effects that survivors often experience related to the tumor and treatment, including physical complications. In a large, multi-center study, 18% of pediatric brain tumor survivors reported having one or more cardiovascular conditions, and 43% reported having one or more endocrine conditions.[4] These cardiovascular conditions (e.g., shortness of breath or angina-like symptoms) and endocrine conditions (specifically growth hormone deficiency) might negatively affect cardiorespiratory fitness in this population. While few late effects were observed for those survivors receiving only surgical resection, the risk level was elevated for those treated with cranial radiation therapy and adjuvant chemotherapy.

Multi-modal medical treatment has also been associated with increased late effects across several other domains of functioning. For example, studies of cognitive sequelae from pediatric brain tumor and its treatment consistently document that individuals treated with radiation and chemotherapy have poorer neurocognitive outcomes relative to youth treated with only surgical resection across domains of IQ, executive function, memory, and processing speed.[5,6,7] Additionally, a systematic literature review of studies assessing psychological outcomes in pediatric brain tumor survivors noted that receipt of radiation therapy was associated with internalizing (e.g., anxiety, depression) and externalizing (e.g., acting out, aggression) disorders across several studies.[8]

Tumors arising in the posterior fossa are the most common type of childhood brain tumor.[9] Cerebellar tumors may lead to a number of additional difficulties because of their location within the brain, including poor balance[10] as well as difficulty regulating thoughts and emotions secondary to cerebellar cognitive affective syndrome (CCAS).[11] Additionally, standard treatment for medulloblastoma and ependymoma, two of the most common cerebellar tumors in children, typically involves radiation therapy and sometimes adjuvant chemotherapy.[9,12] Thus, survivors of pediatric medulloblastoma and ependymoma are at increased risk for late effects across domains of functioning given the tumor location and treatment received.

Survivors are Less Physically Active

These physical, cognitive, and psychological late effects may be related to the decreased functional performance abilities noted in pediatric brain tumor survivors, who report more difficulties with completing routine activities and attending work or school relative to survivors of any other type of cancer.[13] Pediatric brain tumor survivors are also more likely to be underweight and less overweight than population norms. Being underweight has been associated with lower social competence, lower verbal IQ, and higher internalizing behaviors in this population.[3] In addition to the multi-domain late effects, children diagnosed with a brain tumor are often not physically active while on treatment due to fatigue, pain, and general malaise. Thus, they are likely at greater risk to develop sedentary habits than healthy peers, a pattern which may continue into survivorship and manifest as lower rates of exercise and thus lower cardiorespiratory fitness. Neurological late effects such as poorer balance due to cerebellar injury may also contribute to lower rates of exercise in pediatric posterior fossa tumor survivors. It is likely that these late effects interact with one another across domains. For example, cognitive difficulties might include low initiation, which could contribute to depression, both of which might result in less frequent physical activity. Overall, survivors of pediatric brain tumor experience more barriers to physical activity than survivors of other types of childhood cancer and typically developing peers.[13]

Physical exercise has shown benefits across various areas of health, improving emotional, physical, and cognitive functioning.[14,15] Thus, it follows that exercise would be of great importance for survivors of pediatric posterior fossa tumor, given their documented difficulties across these domains. However, feasibility and safety of vigorous physical exercise has yet to be shown for this population, and is of particular concern given the aforementioned physical complications that may present. Survivors of pediatric posterior fossa tumor might not be as capable of reaching peak aerobic capacity due to the late effects of the tumor and treatment. Principal concerns with aerobic exercise with this population would include the possibility of adverse cardiac events (e.g., shortness of breath, angina-like symptoms), lightheadedness, or general malaise. Thus, the purpose of the present pilot study was to determine the preliminary feasibility and safety of cardiorespiratory fitness testing in survivors of pediatric posterior fossa tumor who had undergone surgical resection and radiation therapy, with or without adjuvant chemotherapy. A secondary aim was to compare the body composition variables from youth in this sample with normative means, and the physical fitness variables with those previously reported in healthy and other childhood chronic illness samples. We hypothesized that cardiorespiratory fitness testing would be feasible and safe with this population. Additionally, we expected that our cohort of pediatric brain tumor survivors would have lower cardiorespiratory fitness compared with typically developing youth, and comparable fitness with other childhood chronic illness samples, because of the various cognitive, emotional, and physical late effects associated with the tumor and its treatment.

Materials and Methods

Participants

Participants were consecutively recruited from the Neuro-Oncology clinic at an urban children's hospital in the southern United States. Inclusion criteria were youth ages 11–18 years, who had survived a posterior fossa tumor, received cranial radiation therapy as part of their medical treatment regimen, were at least 2-years post completion of therapy, and had a Modified Lansky score of ≥ 70. The Lansky score is a play performance scale in children who have or have been treated for cancer, indicating their functional abilities (e.g., to sit down on the floor, walk independently, etc.).[16] Exclusion criteria included child residence outside of primary caregiver's home, disabilities that prohibited child or primary caregiver from completing measures, and the child or caregiver not being English-speaking. The final sample included 14 posterior fossa tumor survivors, who were grossly similar to the national pediatric posterior fossa survivor population in terms of male gender predominance, younger ages at diagnosis, and that they were treated with standardized Children's Oncology Group protocols. No eligible participants that were approached to take part in this study declined participation.

Procedures

Eligible survivors were identified through patient databases of children and adolescents treated in the UAB Division of Pediatric Hematology and Oncology Neuro-oncology clinic at Children's Hospital of Alabama since 1993. Medical records were reviewed to determine eligibility. Eligible participants were recruited during regular clinic follow-up visits or by phone. Informed consent and assent were obtained when the participant came for the study in accordance with the approval of the UAB Institutional Review Board. The parent/caregiver completed a demographics questionnaire, and the survivor completed a self-report seven day recall of physical activity and the cardiorespiratory fitness testing. Following completion of fitness testing, the caregiver was given a $10 incentive, and the survivor a $50 incentive.

Measures

VO_2max Testing—Maximum oxygen uptake, or VO_2max, testing was completed on a Monark stationary cycle ergometer using a standardized protocol. We chose to use the cycle ergometer instead of the more traditional treadmill test because of the problems in balance often experienced by pediatric posterior fossa tumor survivors. Heart rate (HR) data was captured using a POLAR Vantage XL HR monitor (Gays Mills, WI, USA). Subjects warmed up by cycling at 25 Watts for 4 minutes. Those subjects with a heart rate of greater than 110 beats/minute after 4 the minute warm-up increased workload 12.5 Watts/minute throughout the rest of the test. Those subjects with a HR of less than 110 beats/minute after the 4 minute warm-up increased workload 25 Watts/minute throughout the rest of the test. Oxygen uptake and carbon dioxide production were measured continuously using a Physiodyne Instrument Corporation, MAX-II Cart (Quogue, NY, USA). Gas analyzers were calibrated with certified gases of known concentrations. Subjects were encouraged to maintain work output for as long as they could and the test was terminated when subjects could no longer maintain the prescribed work level. Standard criteria for HR, respiratory exchange ratio (RER), and plateauing were used to assess achievement of VO_2max[17]. Specifically, two of the following three criteria had to be met in order for the subject to have achieved a true VO_2max: (1) HR > 85th percentile of age-predicted maximum; (2) RER > 1.0; and (3) Observable plateau of VO_2 uptake.

Physical Activity Questionnaire—Participants also completed the age-appropriate version of the Physical Activity Questionnaire (PAQ), a self-report 7-day recall of physical activity in the past week. The psychometric properties of the two versions of this measure (i.e. the PAQ-C for older children and the PAQ-A for adolescents) have been well established.[18,19] The means and standard deviations of published normative data for the PAQ-A[20] and PAQ-C[21] were used to convert participants' data into z-scores standardized by age and gender.

Body Mass Index—The body mass index (BMI) of each participant was calculated from his or her weight and height (kg/m^2). Body composition indices (i.e. percent body fat and percent fat free mass) were calculated by measuring skin folds at the tricep, chest, abdomen, suprailium, and thigh. These skin folds were then used to estimate body density[22,23] and percent body fat was calculated from body density.[24]

Late Effects Severity Score (LESS)—We utilized Benesch and colleagues'[25] system for quantifying physical late effects in pediatric medulloblastoma survivors entitled the Late Effects Severity Score (LESS). This involved rating the late effects experienced by each survivor in the domains of neurology, endocrinology, visual/auditory, and other symptoms. In each domain, survivors received 0 points for no late effects, 1 point for one late effect in that area that did not require medical intervention (e.g., hearing loss not requiring correction with hearing aids), or 2 points for one or more late effects in that area requiring intervention (e.g., growth hormone replacement therapy). Thus, the maximum overall score would be 8, with a maximum score of 2 for each domain. All information for LESS ratings was found in the survivor's medical chart.

Data Analysis

BMI values were examined with regards to cutoffs from the CDC for underweight, overweight, and obese.[26] Relationships between physical fitness variables, treatment variables, LESS scores, and demographic variables were examined using correlational analyses. In order to put our cohort's VO_2max scores in broad context compared with other chronic illnesses or healthy controls, brain tumor survivors' VO_2max scores were compared to those reported in a previous study by Groen and colleagues,[27] who used a very similar

cycle ergometry protocol to obtain VO_2max scores from cohorts of older children and adolescents with cystic fibrosis (CF), with chronic heart disease (CHD), and a healthy control cohort. These comparisons were done using one sample two-tailed *t*-tests.

Studies assessing VO_2max with other pediatric oncology survivor populations have been published; however, they have used treadmill testing which consistently produces VO_2max scores that are consistently about 11% higher than those obtained through cycle ergometry protocols.[28] Therefore, in order to broadly compare the scores from our brain tumor survivor cohort with those of childhood cancer survivors (excluding brain tumor survivors), we multiplied the obtained VO_2max scores of our sample by 1.11 to obtain the estimated VO_2max scores for a treadmill protocol. We then compared these scores to the mean VO_2max scores reported by De Caro and colleagues[29] for childhood cancer survivors using one sample two-tailed *t*-tests. Significance was set at less than 0.05 for all analyses. While this was a somewhat less exact comparison due to the different measurement methods utilized, we felt it important to compare the aerobic fitness of our brain tumor survivors with survivors of other types of childhood cancer, because the two groups often experience quite different late effects

Results

The main results of this study are as follows: 1) VO_2 max testing was shown to be feasible and safe for a small cohort of survivors of pediatric posterior fossa tumor; 2) Survivors' self-reported physical fitness and objectively recorded VO_2max scores were lower than published norms for typically-developing children; 3) More severe neurological late effects were related to lower levels of cardiorespiratory fitness; and 4) Survivors' VO_2max scores were lower than those published for children with cystic fibrosis, but no different from the published VO_2 max scores of children with chronic heart disease or other types of childhood cancer.

Thirteen participants were able to participate in the VO_2max testing with no adverse incidents such as a cardiovascular event, lightheadedness, or general malaise. The one participant that did not complete the test had a very strong gag reflex, and thus we were unable to adequately insert the mouthpiece in order to measure intake and expiration of gases. Self-report physical activity was collected for this participant, so he is included in those analyses.

Participant characteristics are presented in Table 1. BMIs ranged widely, from the 1st to the 87th percentiles. Although none of our participants had a BMI that met CDC criteria for the obese range y (>95th percentile), 3 were in the overweight range (>85th percentile), and 3 were classified as being underweight (<5th percentile). All participants received very similar doses of cranial radiation therapy (54.0–55.8 Gy), and none received any radiation to the heart.

Fitness variables including VO_2max, RER, ventilation (VE), maximum HR (HRmax) and self-report physical activity are presented in Table 2. Twelve of 13 participants reached VO_2max according to the aforementioned criteria. On average, participants reported almost a standard deviation less physical activity than their same age peers, though this ranged widely. LESS domain and overall scores are also presented in Table 2.

As would be anticipated, VO_2max was found to be related to percent body fat. Therefore, we calculated VO_2max using only fat-free body mass (VO_2max/FFM) to investigate its relationship with other demographic variables. Using two-tailed partial correlations, z-scores of self-report physical activity were related to VO_2max/FFM after accounting for age (Table 3; $p<0.05$). VO_2max/FFM was not related to gender, which is unusual but likely relates to

the unequal numbers of males and females in our cohort. VO_2max/FFM was also not related to receipt of chemotherapy, age at diagnosis, or race. In examining the relationship between fitness and late effects, greater neurological late effects were related to lower VO_2max/FFM scores. Cardiorespiratory fitness was not related to any other LESS domain scores or the overall LESS score.

In single sample two-tailed *t*-test comparisons to Groen et al.'s reported values[27] (Table 4), in order to grossly estimate a comparison between the cardiorespiratory fitness of pediatric brain tumor survivors compared to typically developing peers and other chronic illness control groups, brain tumor survivors' VO_2max scores were lower than those of healthy controls ($p<0.001$) as well as children with CF ($p<0.001$). No differences were found between brain tumor survivors and children with CHD on VO_2max. Brain tumor survivors had higher HRmax values than children with CHD. No differences among RER were found.

After adjusting our sample's VO_2max levels up by 11% to obtain estimated treadmill VO_2max scores, no differences were noted in VO_2max or HRmax between brain tumor survivors and other types of childhood cancer survivors using single sample two-tailed *t*-tests (Table 5). The brain tumor survivor cohort also had higher RER values than the childhood cancer cohort.

Discussion

Our preliminary findings suggest that VO_2max testing is feasible and safe to perform with survivors of pediatric brain tumor. Although 1 participant was unable to complete the testing due to a sensitive gag reflex, this is unlikely to be related to his tumor or treatment. In fact, posterior fossa syndrome, which can occur after resection of a posterior fossa tumor, may be associated with bulbar palsy, which includes loss of gag reflex[30]. Of the 13 participants who did complete VO_2 testing, 12 were able to reach a true VO_2max. This percentage of over 92% achieving a true VO_2max compares quite favorably with the 82% reported for healthy children in prior studies.[31,32] Though this was essentially a pilot study with a small sample size, our findings suggest that most pediatric brain tumor survivors are able to exercise to the point of maximum respiratory capacity as well as most healthy children.

Pediatric brain tumor survivors reported levels of exercise that were almost one standard deviation lower than normative means. This is consistent with previous studies reporting low levels of physical activity in this population[33]. The validity of self-report levels of exercise in this population was supported by the fact that lower self-reported physical activity was related to lower objective cardiorespiratory fitness scores. Additionally, greater neurological late effects were related to lower fitness scores in our cohort. The main specific neurological late effects included cranial nerve palsies and balance difficulties. While each of our participants was able to ride a stationary bicycle with little difficulty, it is likely that these neurological impairments contribute to lower rates of exercise in daily life.

Comparison with control subjects reported elsewhere[27] indicated that cardiorespiratory fitness in pediatric brain tumor survivors is lower than that in healthy peers. Of note, the peak oxygen uptake scores of Groen and colleagues' cohort on the cycle ergometer may be somewhat elevated as this study was conducted in the Netherlands, where bicycle riding is more prevalent than in the United States[34]. However, pediatric brain tumor survivors' cardiorespiratory fitness was also poorer compared to that of children with pulmonary disease (Cystic Fibrosis), and was comparable to that of children with chronic heart disease in the Netherlands. The causes of reduced cardiorespiratory fitness in pediatric brain tumor survivors are not clear; it is likely due to a combination of tumor and treatment sequelae (including cardiovascular, endocrine, and functional problems) as well as lower rates of

physical exercise. The reduced cardiorespiratory fitness in our sample was not due to fat mass, as none of our participants were labeled obese and in fact almost one-fourth were classified as being underweight. Additionally, female adolescents tend to have lower cardiorespiratory fitness scores than males[35], and as our sample only contained 2 females, it might actually represent a slight overestimation of the cardiorespiratory fitness of the brain tumor survivor population as a whole.

Finally, our pediatric brain tumor survivor cohort's cardiorespiratory fitness, adjusted to estimate values obtained using a treadmill protocol, was not significantly different from that of survivors of other types of childhood cancer.[29] Notable, however, is that the childhood cancer survivor cohort tended to be obese (31% had BMIs > 95th percentile), which certainly reduced their cardiorespiratory fitness. Despite our pediatric brain tumor survivor cohort not being obese, their values were still comparable to that of the childhood cancer survivor cohort, indicating that other limiting factors are present for the brain tumor cohort. These might include growth hormone deficiency, depression, or balance problems that limit or inhibit participation in physical activity. Nonetheless, the brain tumor survivors in our study were able to push themselves to their respiratory capacities, as their RER values were equal to or greater than those reported in other studies, with no adverse events occurring.

The principal weakness of this study is the small sample size, which makes it difficult to draw definitive conclusions regarding the safety and feasibility of maximum capacity aerobic exercise for all survivors of pediatric posterior fossa tumor. Additionally, our statistical analyses comparing findings across published studies provide broad estimates of the fitness of our cohort compared to other pediatric healthy and chronic illness cohorts, not exact comparisons. Although we used a small cohort and compared findings across published studies, our data reports on the feasibility and safety of cardiorespiratory fitness testing on a novel population, which encourages further research in this area. Future studies should examine the cardiorespiratory fitness of survivors of other types of pediatric brain tumor, since we only included posterior fossa tumor survivors, to compare the effects of tumor location and treatment regimen across cohorts. Future studies should use larger sample sizes to more definitively establish the safety of vigorous exercise in this population, in addition to examining other factors that might contribute to reduced rates of exercise, including psychological and cognitive factors.

Regular exercise is important for various domains of health, including physical, emotional, and cognitive development. Pediatric posterior fossa tumor survivors are known to often have difficulties in all three of those areas. The pediatric posterior fossa tumor survivors in our study reported exercising less often than their peers, and had lower cardiorespiratory fitness scores than healthy and chronic illness samples from other published studies. However, the majority of our cohort demonstrated no impairments in the ability to reach peak respiratory capacity during exercise, indicating that physical exertion is likely a safe and feasible activity to include in their daily lives. This study lays groundwork for exercise interventions with pediatric brain tumor survivors, many of whom are in need of increased physical activity in their daily lives.

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Table 1

Participant characteristics

Demographic	M (SD)	Min	Max
Age	14.41 (1.86)	11.5	17.25
Age at brain tumor diagnosis	5.59 (2.89)	1.16	9.00
Male/Female	12/2	--	--
Caucasian/African-American	12/2	--	--
Medulloblastoma/ependymoma	10/4	--	--
Received radiation therapy; Average dose in Gy[§]	14 54.8 (9.1)	54.0	55.8
Received adjuvant chemotherapy	11	--	--
Received surgical resection	14	--	--
Weight (kg)	44.28 (10.51)	28.34	65.31
Fat free mass (kg)	39.70 (9.33)	26.22	55.43
Height (in)	59.54 (3.08)	54.00	63.00
BMI	19.20 (3.38)	14.50	25.50
BMI Percentile	40.84 (33.83)	1.00	87.00

[§]Radiation dose reported is total dose including boost to posterior fossa.

M = mean, SD = standard deviation, Gy = Gray, BMI = body mass index.

Table 2

Fitness test and self-report physical activity results

Fitness Measure	N	M (SD)	Min	Max
VO_2max (ml·kg^{-1}·min^{-1})	12	31.8 (7.2)	22.6	44.0
VO_2max /FFM (ml·kg FFM^{-1}·min^{-1})	12	35.3 (5.8)	28.6	45.8
HRmax(beats·min^{-1})	13	187.0 (11.2)	164.0	205.0
RER	13	1.2 (0.1)	0.9	1.4
VEmax	13	50.8 (18.0)	18.4	75.3
PAQ z-score	14	−0.8 (0.9)	−2.3	1.1
LESS Overall Score	14	3.8 (1.8)	0	7
LESS Neurology Score	14	0.5 (0.5)	0	1
LESS Endocrinology Score	14	1.6 (0.7)	0	2
LESS Visual/Auditory Score	14	0.9 (0.9)	0	2
LESS Other Score	14	0.7 (0.9)	0	2

VO_2max = peak oxygen uptake; VO_2/FFM = peak oxygen uptake relative to fat-free mass; HRmax = maximum heart rate; RER = respiratory exchange ratio; VEmax = maximum ventilatory threshold; PAQ = physical activity questionnaire (age-appropriate version). LESS = Late Effects Severity Score.

Table 3

Partial correlations between VO_2max (ml·kg FFM^{-1}·min^{-1}) and descriptive demographic/self report variables after accounting for age at evaluation

Descriptive Variable	VO_2max Partial Correlation	
	df	Partial *r*
PAQ z-score[1]	9	0.70*
Received chemotherapy[2]	9	0.03
Age at diagnosis[1]	9	−0.20
Gender[2]	9	−0.50
Race[2]	9	−0.39
LESS[3] Total	9	−0.24
LESS Neurology	9	−0.69*
LESS Endocrinology	9	0.03
LESS Visual/Auditory	9	0.29
LESS Other	9	−0.42

VO_2max = peak oxygen uptake calculated using only fat-free body mass; PAQ = physical activity questionnaire (age-appropriate version); LESS = Late Effects Severity Score

* $p<0.05$

[1] Pearson correlation coefficient reported. Higher scores on the PAQ indicate more reported exercise.

[2] Point-biserial correlation coefficient reported. Received chemotherapy: 0 = no, 1 = yes. Gender: 0 = male, 1 = female. Race: 0 = Caucasian, 1 = African-American.

[3] Pearson correlation coefficient reported. Higher LESS scores indicate more severe late effects.

Table 4

Comparison of our cohort of brain tumor survivors with healthy controls and other chronic illness groups from Groen and colleagues[25]

Fitness Variable	BTS	Healthy	CF	CHD
VO_2max (ml·kg^{-1}·min^{-1})	31.8 (7.2)	49.3 (7.9) ***	42.5 (6.8) ***	33.7 (8.9)
HRmax (beats·min^{-1})	187 (11)	193 (7)	188 (10)	164 (28) ***
RER	1.2 (0.1)	1.16 (.07)	1.19 (.06)	1.19 (.15)

VO_2max = peak oxygen uptake; HRmax = maximum heart rate; RER = respiratory exchange ratio; BTS= brain tumor survivors; CF=cystic fibrosis; CHD = chronic heart disease.

All values are mean (SD).

Single sample *T*-test comparisons with the BTS cohort:

*** $p<0.001$

Table 5

Comparison with other childhood cancer survivors from De Caro and colleagues[27]

Fitness Variable	BTS	CCS
VO_2max (ml·kg $^{-1}$·min^{-1})	35.3 (7.9)[§]	38.1 (8.4)
HRmax (beats·min^{-1})	187 (11)	191 (14)
RER	1.2 (0.1)	1.1 (0.1)*

[§]Estimated treadmill test value (equal to the cycle ergometer value multiplied by 1.11). VO_2max = peak oxygen uptake; HRmax = maximum heart rate; RER = respiratory exchange ratio; BTS = brain tumor survivors; CCS= childhood cancer survivors (excluded brain tumor survivors).

All values are mean (SD).

Single sample *T*-test comparisons with the BT cohort:

*$p<0.05$