Published in final edited form as:

Pediatr Blood Cancer. 2019 March ; 66(3): e27506. doi:10.1002/pbc.27506.

Physical fitness in survivors of childhood Hodgkin Lymphoma: a report from the St. Jude Lifetime Cohort

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Abstract

Background: There are limited data describing fitness and associated health-related quality of life (HRQoL) in survivors of childhood Hodgkin Lymphoma (HL).

Procedure: Fitness was evaluated among 336 adult survivors of childhood onset HL, treated at St. Jude Children's Research Hospital and 327 controls who never had childhood cancer. The controls were frequency matched on age, sex, and race. Associations were examined between chronic disease and fitness and between fitness and HRQoL using a multivariable linear and logistic regression.

Results: Male survivors had lower endurance (six minute walk (6MW) distance: 604.4±7.9 vs. 637.0±7.5 meters (m), $p<.01$), and worse neuropathy (modified total neuropathy score (mTNS): 2.7±0.2 vs. 1.3±0.2, $p<.01$), compared to controls. Female survivors had lower endurance (6MW distance: 564.5±6.9 vs. 590.6±7.0 m, $p<.01$), quadriceps strength (145.7±4.0 vs. 163.4±4.0 newton meters per kilogram, $p<.01$), and worse neuropathy (mTNS 3.2±0.2 vs. 1.2±0.3, $p<.01$), compared to controls. Moderate, severe/disabling, or life-threatening (Grade 2–4) neurological conditions were associated with impaired quadriceps strength (Odds ratio (OR): 2.94, 99% confidence interval (CI): 1.24–6.96) and impaired endurance (OR: 2.96, 99% CI: 1.28–6.69). Cardiovascular (OR: 2.36, 99% CI: 1.00–5.61) and pulmonary (OR: 2.78, 99% CI: 1.30–5.94) conditions were associated with impaired endurance. Quadriceps strength (β : -6.44±2.01, $p<.01$), endurance (β : -4.63±1.54, $P<.01$), and neuropathy (β : -4.98±1.14, $p<.01$) were associated with a lower physical component summary on the HRQoL.

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This work was presented previously at the American College of Sports Medicine National Conference on May 2015.

Conflict of Interest Disclosure

The authors declare no competing financial interests. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Conclusion: Survivors of childhood HL, particularly those with neurological, cardiac and pulmonary chronic conditions, are at risk for impaired fitness and HRQoL.

Keywords

Pediatric Cancer; Late Effects; Physical Function; Quality of Life; Chronic Disease

Introduction

Five-year survival rates for those diagnosed with Hodgkin lymphoma (HL) before the age of 20 years exceed 96% in the United States. Many survivors of childhood/adolescent HL experience cancer- or treatment-related adverse health outcomes. These adverse outcomes are associated with lower health-related quality of life (HRQoL) among childhood cancer survivors.

Improving levels of physical fitness may help prevent or remediate poor health conditions experienced by survivors of childhood HL as well as improve HRQoL. In the general population, evidence supports the preventive role of physical fitness for chronic diseases such as cardiovascular disease, and stroke. Exercise has also been shown to benefit those with chronic disease, such as heart failure and fibromyalgia, as well as having a positive effect on HRQoL. Recent findings have shown a reduction in all-cause mortality in survivors of childhood cancer who exercise 15 to 18 MET-h per week. Findings also indicate a decreased risk of cardiovascular events (e.g. coronary artery disease, heart failure) among survivors who exercise regularly. Positive associations have been reported between HRQoL and fitness levels in childhood cancer survivors. Thus, improving levels of fitness and exercise in childhood survivors is important.

Previous studies have indicated that long-term survivors of childhood HL are less active than their peers. The reasons for these differences are not known, and objective measurements of physical fitness in survivors of childhood HL are scarce. It is possible that survivors of childhood HL are less active because they have fitness deficits related to overt or subtle organ system impairments, limiting participation in regular physical activity. It is known that deficits in physical fitness are responsive to intervention in other populations with chronic disease. Knowledge of specific fitness deficits among survivors of childhood HL, and particularly survivors with chronic disease, has the potential to provide a foundation for development of tailored interventions to promote health and well-being in this population. Thus, the aims of this study were to compare physical fitness in survivors of childhood HL to a control population without a history of childhood cancer, describe physical fitness among survivors with and without chronic conditions, and to evaluate associations between fitness measures and HRQoL.

Methods

Study Population

Participants included members of the St. Jude Lifetime Cohort (SJLIFE), assembled to assess health outcomes in aging survivors of childhood malignancies. For these analyses, we

included survivors of HL treated at St. Jude Children's Research Hospital (SJCRH) between 1962 and 2004, who were at least 10 years from their original diagnosis and who completed an on campus assessment (e.g., self-reported questionnaires and a functional assessment). A comparison group (community controls) was also recruited from parents/relatives of current pediatric patients, and adult friends of survivors. Controls were not first-degree relatives of SJLIFE participants and had no history of childhood cancer. Controls were frequency matched to survivors on age, sex, and race. The SJCRH Institutional Review Board approved all procedures. Written informed consent was obtained on all participants prior to testing.

Outcomes

The primary outcomes for these analyses were physical fitness, the presence of specific chronic health conditions and HRQoL. Fitness measures were chosen using the American College of Sports Medicine definition of the physical fitness components. They included, anthropometrics (body composition), muscular strength, muscular endurance, flexibility, cardiopulmonary endurance. Peripheral nervous system integrity, and balance were also chosen due to their potential effects on physical fitness.

Anthropometrics

Height in centimeters (cm) and weight in kilograms (kg) were measured using a wall mounted stadiometer and electronic scale (Model 5002, Scale-Tronix, Inc., Wheaton, IL). Body mass index (BMI) was calculated by dividing weight in kg by height in meters (m) squared. Waist and hip circumference were obtained with a Gulick® spring tape measure to the nearest tenth cm. Body fat percentage was calculated from Harpenden skinfold caliper (Baty, West Sussex, United Kingdom) measures using the three site technique (men: pectoral, abdominal, and thigh; women: triceps, suprailiac, and thigh).

Muscular Strength and Endurance

Isokinetic knee extension strength and endurance were measured in a seated position using a Biodex III dynamometer (Biodex Medical Systems, Shirley, NY). Strength was measured as peak torque (Newton meters per kilogram (N·m/kg)) from five repetitions at 60 degrees per second, and endurance was expressed as the difference between average peak torque from the first three and the last three of 15 repetitions at 300 degrees per second (expressed as work fatigue). Isometric handgrip strength was measured in a seated position with the shoulder in 0–10° of flexion, the elbow in flexion, and the forearm in neutral using a Baseline® handheld dynamometer (Fabrication Enterprises Inc., White Plains, NY). The maximum value (kg) was used for analysis.

Flexibility

Low back and hamstring flexibility was assessed using a Flex-Tester® sit and reach box (Novel Products Inc., Rockton, IL). Participants were instructed to sit with their legs fully extended in front of them and the bottoms of their feet in contact with the box. With their hands overlapped, participants were asked to reach forward (toward their feet) as far as possible, without bending the knees. The better of two trials (cm) was used for analysis.

Cardiopulmonary Fitness

Vital signs were measured after five minutes of quiet rest and prior to all physical fitness testing. Supine resting heart rate (HR) by standard 12-lead electrocardiogram was included in this study.

Aerobic endurance was assessed with a six minute walk test. Participants were instructed to walk as fast as possible in a level corridor for six minutes without running. Encouragement was given at defined intervals, and the distance recorded in meters. HR was recorded at 0, 2, 4, and 6 minutes and after one minute of recovery. The distance (m) walked in six minutes was used for analysis.

Sensory Organization Test

Balance was evaluated using the sensory organization test (SOT) composite score. Participants were asked to stand on a force plate in a visual surround under six conditions: 1) eyes open, 2) eyes closed, 3) eyes open - vision sway referenced (the visual surround moves in concert with participant anterior-posterior sway), 4) eyes open - proprioception sway referenced (the force plate moves in concert with participant anterior-posterior sway), 5) eyes closed – proprioception sway referenced, and 6) eyes open – vision and proprioception sway referenced. Each condition was evaluated for 20 seconds at least twice, and the percentage of time spent inside a normal 12.5 degree sway envelope recorded. Scores range from 0–100; higher scores are better. Participants with composite scores <70 were categorized with poor balance.

Peripheral Nervous System Integrity

Peripheral nervous system integrity was evaluated with the modified Total Neuropathy Scale (mTNS). This instrument includes patient reported sensory and motor symptoms, and quantitative testing. Protective sensation was evaluated with a 4.17 log force Semmes Weinstein Monofilament and vibration was measured using a Bioesthesiometer with a threshold of 9.0 volts (Bio-Medical Instrument Company, Newbury, Ohio). Manual muscle testing was performed on the fingers, ankles, and wrists. Reflex testing was performed in the ankles, knees, brachioradialis, biceps and triceps tendons. A total score of 24 was possible; having fewer or no symptoms or measured deficits equated to having lower scores.

Quality of Life

To assess HRQoL, participants completed the Medical Outcomes Survey Short-Form 36 (SF-36), previously validated in adult survivors of childhood cancer. The SF-36 contains eight subscales and two summary scales. For these analyses, we used the physical component summary (PCS) and the mental component summary (MCS) scores. These two composite scores represent the physical and mental components to quality of life. Raw scores were calculated and converted into T-scores where the general population mean is 50 and the standard deviation 10. Higher scores indicate better mental and physical HRQoL.

Chronic Health Conditions

Chronic cardiovascular, pulmonary, endocrine, and musculoskeletal conditions were classified using the Common Terminology Criteria for Adverse Events version 4.03 modified specifically for childhood cancer survivors (Supplementary Table S1). Chronic conditions were ascertained retrospectively using medical records, using a standardized SJLIFE questionnaire, or discovered clinically as part of their SJLIFE campus visit. Each chronic condition was categorized by organ system (Supplementary Table S2). Moderate (grade 2), severe/disabling (grade 3), and life-threatening (grade 4) chronic conditions were retained for subsequent analyses.

Other measures

Diagnosis and treatment information were obtained from medical records by trained abstractors, and included type and cumulative doses of chemotherapy, site and dose of radiation therapy, and surgical procedures. Demographic information was obtained from questionnaires. Information on physical activity levels were obtained using six items from the National Health and Nutrition Examination Survey. The questions asked if the participant spent at least ten minutes doing vigorous physical activity, on how many days per week they did these activities, and for how many minutes total time per day they spent doing these activities. Identical questions were asked for moderate physical activities. Weekly minutes of vigorous activity were multiplied by six, weekly minutes of moderate activities were multiplied by three, and then summed to get metabolic equivalent minutes per week. For analysis, physical activity was dichotomized into meeting (450 metabolic equivalent minutes per week) or not meeting the 2008 Center for Disease Control and Prevention guidelines.

Statistical Analysis

Descriptive statistics of participants and non-participants were calculated and compared using chi-squared tests for categorical variables, and two sample t-test or Wilcoxon Rank-Sum tests for continuous variables. Physical fitness measures were compared between survivors and controls using a multivariable linear regression (stratified by sex and adjusted for age, race smoking status, and meeting physical activity recommendations, with additional adjustments for height and weight for six-minute walk distance). To characterize the proportion of survivors with significant fitness impairments, Z-scores were created for each survivor from controls' fitness data. Those with Z-scores <-1.5 (or >1.5 for BMI, waist circumference, body fat percentage, resting heart rate) were considered impaired. Missing data from survivors and controls were reviewed and participants who were missing outcomes because a medical condition precluded testing were categorized as "impaired". If a participant was missing due to reasons that were not medical, they were not included in the analysis. Multivariable logistic regression was used to evaluate associations between chronic health conditions and impaired fitness (adjusted for age and sex) among survivors. Multivariable linear regression was also used to evaluate associations between fitness measures and HRQoL (adjusted for age and sex). To reduce errors from multiple tests, statistical significance was set *a priori* at $p < 0.01$. Data were analyzed with SAS version 9.4 (SAS Institute, Cary NC).

Results

Among 544 potentially eligible survivors of childhood HL, 347 agreed to participate and 336 (61.7%) completed an on-campus functional assessment within one year of their survey visit and were included in the analysis. The 186 non-participants either declined participation, were lost to follow-up, completed the survey portion only, or were interested but had not complete their campus visit yet (Supplementary Figure S1). The characteristics of the study population are shown in Table 1. Participants were a median of 36.7 (range: 19.1–60.6) years of age at assessment; 53.6% were male and 14.9% non-white. Participants did not differ from non-participants by sex, race, or radiation and chemotherapy exposures, with the exception of a higher median dose of vincristine among participants.

Physical fitness comparing HL survivors to controls

The proportions of survivors and controls in meeting physical activity guidelines (Odds ratio: 0.78, 99% confidence interval: 0.56, 1.09) did not differ. Mean ($\pm$ standard error) values for physical fitness outcomes are shown in Table 2. After excluding survivors (13%) whose health prevented them from completing testing (see table footnotes), survivors had lower values than controls for flexibility, resting heart rate and six minute walk distance. Female survivors had lower quadriceps strength than controls. Mean resting heart rate and peripheral nervous system integrity scores were higher among HL survivors compared to controls.

The percentages of survivors of childhood HL with impaired fitness are presented in Figure 1. Both male and female childhood survivors had excess impairment in muscular strength, flexibility, resting HR, distance walked in six minutes, balance, and peripheral nervous system integrity. Male survivors also had excess impairment in body composition and muscular fatigue.

Associations between chronic disease and fitness

Associations between chronic disease and physical fitness among childhood HL survivors are shown in Table 3. After adjusting for age and sex, survivors with cardiovascular chronic conditions had greater odds of having impaired aerobic endurance than those without a cardiovascular condition. Survivors with a neurologic chronic condition had greater odds of having impaired aerobic endurance, impaired muscular strength, impaired balance, and impaired peripheral nervous system integrity compared to survivors without a neurologic chronic condition. Survivors with pulmonary chronic conditions had greater odds of impaired aerobic endurance compared to survivors without pulmonary chronic conditions.

Associations between quality of life and fitness

Survivors of childhood HL had a mean (SD) PCS score of 48.1 (11.2) and a mean MCS score of 46.8 (11.8). Results of multivariable linear regression examining associations between impaired fitness and HRQoL for survivors of childhood HL are presented in Table 4. After adjusting for age and sex, impaired quadriceps strength, balance, aerobic endurance, and peripheral nervous system integrity were associated with lower physical composite

scores. Impaired nervous system integrity was associated with lower mental composite scores.

Discussion

Adult survivors of childhood HL have lower mean muscular strength, flexibility, and cardiopulmonary fitness than age-, sex-, and race- matched otherwise healthy peers. The rates of fitness impairment (z-scores -1.5) in the survivors exceeded 10% for muscular strength, peripheral nervous system integrity, and endurance. Expected rates of impairment in the general population are 6.7%. Values in this range are predictive of increased 30 year risk of cardiovascular disease mortality. Importantly, in our cohort, cardiovascular, neurological, and pulmonary conditions were associated with impaired fitness and impaired fitness was associated with lower HRQoL. Our data support the need for the development of fitness interventions for survivors of childhood HL that take into account chronic disease status.

Muscular strength and cardiopulmonary fitness are hallmarks of health and are associated with increased morbidity in adult populations. For example, lower extremity strength among women, demonstrated in our study, is significantly associated with self-reported functional limitations (ability to complete daily tasks). In addition, a shorter six minute walk distance (20–25 m), like we found in this study, is associated with diminished scores on self-reported measures of quality of life. Studies also suggest that walking <400 m in six minutes increases risk for cardiovascular morbidity and mortality. Fortunately, only ten survivors in our cohort walked <400 meters. Nevertheless the mean distance walked by survivors in our cohort places them below the 50th percentile for their age group. As walk distances decrease with age, these values suggest that survivors of childhood HL may be at increased risk for cardiovascular morbidity and mortality compared to their cancer-free counterparts.

The prevalence of impairments among survivors of childhood HL reported in this study are similar to those reported by our group among survivors of childhood acute lymphoblastic leukemia (ALL). Rates of impairment in muscular strength, flexibility, and peripheral nervous system integrity exceed 10% for both diagnoses. However, the rates of impaired cardiopulmonary fitness measures are much higher in survivors of childhood HL than among survivors of childhood ALL (impaired resting heart rate: 28.4%, 8.9% respectively; aerobic endurance: 23.0%, 10.5% respectively). This likely because survivors of childhood HL in these analyses are older (median age: 36.7 yr. vs. 28.5 yr.), and more likely to have received cardiotoxic exposures during cancer therapy. Clinicians caring for survivors of childhood HL are usually aware of their increased risk for adverse cardiac outcomes, but may be less familiar with the potential for reduced muscular strength and flexibility, and for neuropathy. Traditional fitness counseling or cardiac rehabilitation programs may not be adequate to improve fitness in members of this population. Our data indicate that deconditioning is not solely responsible for poor fitness in survivors of childhood HL. Underlying chronic disease and physical limitations may make it difficult for them to simply exercise on their own. Interventions need to be developed to accommodate underlying organ system impairments.

Associations between fitness and chronic disease are cyclical,, therefore, preventing the onset of chronic disease is an important goal. Interventions designed to optimize physical activity levels proximal to the end of therapy seem likely to be effective. Observational work from the Childhood Cancer Survivor Study suggests that adverse cardiac outcomes in survivors of childhood HL are preventable with participation in vigorous physical activity. Other data indicate that survivors do not reap the same physiologic benefits that their peers do when participating in recreational activity, suggesting that intensity may be key. Therefore, early interventions designed to increase physical activity should be tailored to the individual child/adolescent where the effects of neuromusculoskeletal impairments on mobility and the ability of the cardiopulmonary system to respond to exercise are incorporated into an overall fitness plan.

In the current study, we observed that impaired quadriceps strength, impaired cardiopulmonary fitness, decreased balance, and impaired peripheral nervous system integrity were associated with lower scores on the SF-36 summary scales. This finding is concordant with previous reports among childhood cancer survivors where self-reported function and/or symptoms influence HRQoL, and similar to studies in other cancer survivor populations (adult and pediatric) where reduced aerobic capacity, muscular weakness, inadequate postural control, and neuropathy influence perceived health. To our knowledge, this is the first study that has evaluated a link between fitness, peripheral nervous system integrity, and HRQoL among survivors of childhood HL. This is an important finding as poor fitness is modifiable, even among cancer survivors previously exposed to cardio toxic therapies. Interventions designed to prevent chronic disease or remediate poor fitness may have the additional benefit of improving HRQoL.

The results of our analysis should be considered in the context of potential study limitations. First, these data are cross-sectional. The temporal associations between lifestyle, chronic disease, HRQoL and fitness cannot be definitively determined. Second, although participants and non-participants did not differ by treatment exposures other than vincristine dose, if those who participated were more impaired or healthier than those who did not participate, our estimates may be somewhat inflated or conservative. Also, due to the significantly higher vincristine dosage in participants compared to non-participants, the impaired peripheral nervous system integrity data should be interpreted carefully. The higher median dose in our participants could indicate a non-representative sample, which may have inflated our prevalence estimate. Finally, some of our participants could not complete some of the physical performance testing because they had medical contra-indications that precluded measurement. Although we assigned these participants to the impaired group in subsequent analysis, our mean estimates are likely biased toward the null, as our analytic sample included less impaired survivors. Finally, we did not have comprehensive data on lifetime participation in physical activity, which is an important predictor of overall fitness.

Survivors of childhood HL are at greater risk for impaired cardiopulmonary, muscular strength, flexibility, and peripheral nervous system integrity outcomes. These outcomes, combined with the presence of chronic health conditions, may put survivors at greater risk for lower HRQoL. Current exercise interventions may be inadequate to address the fitness impairments and chronic disease challenges faced by survivors of childhood HL. Additional

work is needed to evaluate the feasibility and efficacy of tailored fitness interventions in survivors of childhood HL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors acknowledge Tracie Gatewood for her assistance preparing the manuscript. Grant support for this study was provided by the St. Jude Lifetime Cohort Study (U01 CA195547 (Hudson)), Cancer Center Support (CORE) grant (CA 21765 (Roberts)), National Cancer Institute grant (CA 132901 (Ness)), and American Lebanese Syrian Associated Charities.

Abbreviation

ALL	Acute Lymphoblastic Leukemia
β	Beta
BMI	Body mass index
bpm	beats per minute
CI	Confidence interval
cm	Centimeter
HL	Hodgkin Lymphoma
HR	Heart rate
HRQoL	Health related quality of life
6MW	Six minute walk distance
kg	Kilogram
m	Meter
MCS	Mental component summary
mTNS	Modified total neuropathy score
N·m	Newton meters
OR	Odds ratio
PCS	Physical component summary
SF-36	Medical Outcomes Survey Short-Form 36
SJCRH	St. Jude Children's Research Hospital
SJLIFE	St. Jude Life

SOT	Sensory organization test
vs	versus
yr	year

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Figure 1.

Percentages of childhood HL survivors whose performance on fitness measures is 1.5 SD below (or above*) age-, sex-, and race-specific comparison group values (n=336). Ten survivors were removed from quadriceps strength, and quadriceps fatigue due to acute cardiopulmonary issues (7), uncontrolled diabetes (1), or size limitations (2). Four survivors were removed from handgrip strength due to the need for immediate medical attention (3), or high uncontrolled blood pressure (1). Three survivors were removed from sit and reach due to the need of immediate medical attention. Three survivors were removed from the six minute walk test due to musculoskeletal injuries (2), or cognitive impairment (1). Eleven survivors were removed for the sensory organization test due to size limitations (5), or need for immediate medical attention (6). Three survivors were removed from sit and reach due to the need of immediate medical attention. N·m = newton meters, kg = kilograms.

TABLE 1

Characteristics of childhood Hodgkin lymphoma participant and nonparticipant survivors

	Participant (n=336)	Non Participant (n=186)	p
Sex, n (%)			0.05
Male	180 (53.6)	116 (62.4)	
Female	156 (46.4)	70 (37.6)	
Race, n (%)			0.39 ^a
White	286 (85.1)	163 (87.6)	
Black	46 (13.7)	23 (12.4)	
Other	4 (1.2)	0 (0.0)	
Met physical activity guidelines, n (%)			
Yes	180 (53.6)	N/A	
No	149 (44.4)	N/A	
Unknown	7 (2.0)	N/A	
Smoker, n (%)			
Current	74 (22.0)	N/A	
Past	64 (19.0)	N/A	
Never	198 (59.0)	N/A	
Age at diagnosis, mean (SD)	13.8 (13.4)	13.7 (13.1)	0.81
Time off therapy, mean (SD)	28.1 (9.2)	26.6 (9.7)	0.08
Underwent transplant, n (%)	8 (2.3)	8 (4.3)	0.22
Any Radiation, n (%)	328 (97.6)	177 (95.2)	0.13
Any Radiation Dose, n (%)			0.32
None	8 (2.4)	9 (4.8)	
< 25 Gy	21 (6.3)	11 (5.9)	
25 Gy	307 (91.3)	166 (89.3)	
Lung RT			0.18
None	41 (12.2)	30 (16.1)	
< 25 Gy	80 (23.8)	33 (17.8)	
25 Gy	215 (64.0)	123 (66.1)	
Chest/Heart Radiation, n (%)			0.09
None	27 (8.0)	24 (12.9)	
< 25 Gy	20 (6.0)	6 (3.2)	
25 Gy	289 (86.0)	156 (83.9)	
Bleomycin, n (%)	84 (25.0)	51 (27.4)	0.54
Median (range) (mg/m ²)	58.0 (5.1, 112.3)	53.7 (9.8, 113.3)	0.51 ^b
Alkylating agent ^c , n (%)	230 (68.5)	129 (69.3)	0.83
Median (range) (mg/m ²)	7848.8 (1016.9, 51323.5)	7287.8 (1643.5, 46581.7)	0.07 ^b
Doxorubicin, n (%)	216 (64.3)	126 (67.7)	0.43
Median (range) (mg/m ²)	192.7 (68.6, 553.0)	172.5 (49.4, 312.4)	0.26 ^b
Dexamethasone	9 (2.7)	9 (4.9)	0.20

	Participant (n=336)	Non Participant (n=186)	p
Median (range) (mg/m ²)	307.2 (24.4, 528.0)	240.3 (159.7, 624.8)	0.59 ^b
Prednisone, n (%)	187 (55.7)	107 (57.5)	0.68
Median (range) (mg/m ²)	2240.0 (560.0, 3360.0)	2240.0 (560.0, 3714.3)	0.81 ^b
Vinblastine, n (%)	226 (67.3)	131 (70.4)	0.46
Median (range) (mg/m ²)	45.4 (4.0, 183.0)	41.3 (11.7, 178.6)	0.96 ^b
Vincristine, n (%)	224 (66.7)	126 (68.3)	0.71
Median (range) (mg/m ²)	17.1 (3.0, 118.1)	9.4 (2.9, 87.8)	0.01 ^b

Chi-square or t-test unless otherwise noted, physical activity guidelines based off of the Center for Disease Control's 2008 recommendations of 450 metabolic equivalent hours per week

Gy = gray units, N/A = not applicable, m = meters, mg = milligrams

^a: Fischer's exact test

^b: Wilcoxon test

^c: cyclophosphamide equivalent dose

Adjusted mean scores and beta coefficients (99% confidence interval) on fitness and function measures for childhood Hodgkin lymphoma survivors and age- sex- race-matched comparison group members by sex

TABLE 2

	Males				Females			
	Survivors (n=147)		Comparison Group (n=166)		Survivors (n=146)		Comparison Group (n=139)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Anthropometrics								
BMI (kg/m ²)	27.9	0.5	29.3	0.5	27.3	0.6	28.4	0.7
Waist circumference (cm)	92.2	1.1	94.1	1.1	84.6	1.4	85.1	1.4
Body fat percentage	25.4	0.6	24.8	0.6	35.2	0.7	35.1	0.7
Muscular Strength								
Knee extension (n-m/kg)	218.0	4.2	218.6	3.9	145.7	4.0	163.4	4.0
Hand grip strength (kg)	51.8	0.8	51.7	0.7	29.8	0.5	32.2	0.5
Muscular Endurance								
Left knee work fatigue (%)	36.3	2.3	35.1	2.2	30.9	2.4	28.9	2.4
Left knee work fatigue (%)	38.5	1.7	34.3	1.6	33.1	3.7	36.2	3.7
Flexibility								
Sit and reach distance (cm)	19.0	0.7	21.3	0.6	23.2	0.7	29.6	0.8
Cardiopulmonary Fitness								
Resting heart rate (bpm)	77.6	1.0	71.2	0.9	85.4	1.1	76.6	1.2
Six minute walk distance (m) ^a	604.4	7.9	637.7	7.5	564.5	6.9	590.6	7.0
Sensory Organization Test (Composite Score)	80.9	0.5	80.1	0.5	78.9	0.7	78.8	0.7
Peripheral nervous system integrity	2.7	0.2	1.3	0.2	3.2	0.2	1.4	0.3

43 survivors were removed from the model due to incomplete data; reasons for the missed assessments were due to cardiovascular abnormalities (23), musculoskeletal abnormalities (9), uncontrolled diabetes (2), over the machine weight limit (5), cerebrovascular abnormalities (2), general doctor's restrictions (1), and cognitive limitations (1)

21 controls were removed from the model due to incomplete data; reason for missed assessments were due to exceeding testing equipment limitations (7), musculoskeletal injury (2), patient refusal (12); survivors and controls who were missing data were list-wise deleted

SE = standard error, β = beta coefficient, CI = confidence interval BMI = body mass index, n-m = newton meters, kg = kilograms, cm = centimeters, m = meters, bpm = beats per minute, mmHg = millimeter of mercury

All models adjusted for age, race, physical activity, smoking status

^a: model adjusted for age, race, height, weight, smoking status, and physical activity

Center for Disease Control's 2008 recommendations of 450 metabolic equivalent hours per week

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TABLE 3

Associations between the presence of chronic conditions (by organ system) and fitness impairment (1.5 SD below (or above) calculated Z-scores of age-sex- race-matched comparison group) in HL survivors.

Chronic Condition	Impaired muscular strength (n=86)				Impaired handgrip strength (n=57)				Impaired right muscular fatigue (n=43)				Impaired left muscular fatigue (n=47)			
	n	Row% ^a	OR (99% CI)	Row% ^a	OR (99% CI)	Row% ^a	OR (99% CI)	Row% ^a	OR (99% CI)	Row% ^a	OR (99% CI)	Row% ^a	OR (99% CI)	Row% ^a	OR (99% CI)	
Cardiovascular dysfunction																
Yes	166	33.1	1.89 (0.81,4.44)	21.1	0.84 (0.33,2.15)	19.3	2.82 (0.95,8.37)	20.5	2.16 (0.76,6.10)							
No	170	18.2		12.9		6.5		7.7								
Endocrine dysfunction																
Yes	282	24.1	1.65 (0.53,5.01)	16.3	0.85 (0.30,2.34)	13.5	1.48 (0.38,5.80)	14.9	1.88 (0.49,7.42)							
No	54	33.3		20.4		9.3		9.3								
Neurological dysfunction																
Yes	72	38.9	2.94 (1.24,6.96)	27.8	2.16 (0.87,5.30)	18.1	1.88 (0.65,5.46)	18.1	1.59 (0.55,4.60)							
No	264	22.0		14.0		11.4		12.9								
Muscular dysfunction																
Yes	45	28.9	0.83 (0.28,2.42)	22.8	2.16 (0.78,5.94)	11.1	0.56 (0.14,2.18)	11.1	0.48 (0.12,1.89)							
No	291	25.1		13.1		13.1		14.4								
Pulmonary dysfunction																
Yes	148	38.5	1.90 (0.89,4.04)	22.3	1.57 (0.70,3.52)	14.2	1.01 (0.40,2.51)	16.9	1.33 (0.55,3.26)							
No	188	15.4		12.8		11.7		11.7								
Chronic Condition	n	Impaired flexibility (n=80)		Impaired six minute walk distance (n=77)		Impaired sensory organization test (n=72)		Impaired peripheral nervous system integrity (n=145)								
		Row% ^a	OR (99% CI)	Row% ^a	OR (99% CI)	Row% ^a	OR (99% CI)	Row% ^a	OR (99% CI)							
Cardiovascular dysfunction																
Yes	166	27.1	0.84 (0.38,1.85)	34.9	2.36 (1.00,5.61)	26.5	1.47 (0.65,3.30)	49.4	1.29 (0.67,2.49)							
No	170	20.6		11.2		16.5		37.1								
Endocrine dysfunction																
Yes	282	24.5	1.31 (0.49,3.52)	24.5	2.04 (0.63,6.54)	20.6	0.69 (0.27,1.75)	44.3	1.36 (0.60,3.08)							
No	54	20.4		14.8		25.9		37.0								
Neurological dysfunction																
Yes	72	31.9	1.41 (0.62,3.22)	44.4	2.96 (1.28,6.69)	36.1	2.56 (1.13,5.79)	59.7	2.23 (1.06,4.69)							

Chronic Condition	Impaired muscular strength (n=86)			Impaired handgrip strength (n=57)			Impaired right muscular fatigue (n=43)			Impaired left muscular fatigue (n=47)		
	n	Row% ^a	OR (99% CI)	Row% ^a	OR (99% CI)	Row% ^a	Row% ^a	OR (99% CI)	Row% ^a	OR (99% CI)	Row% ^a	OR (99% CI)
No	264	21.6		17.1		17.4	38.6					
Muscular dysfunction												
Yes	45	20.0	0.68 (0.83,3.41)	33.3	1.60 (0.58,4.40)	20.0	51.1	0.75 (0.26,2.66)	51.1	1.29 (0.54,3.05)		
No	291	24.4		21.3		21.7	41.9					
Pulmonary dysfunction												
Yes	148	29.7	1.02 (0.50,2.08)	34.5	2.78 (1.30,5.94)	25.7	48.7	1.37 (0.65,3.88)	48.7	1.34 (0.74,2.43)		
No	188	19.2		13.8		18.1	38.8					

Organ system dysfunctions defined by the CTC/AE; alpha was set at .01 to control for multiple comparisons; models were adjusted for age and sex CI = confidence interval

^a = percent of survivors with/without chronic conditions who have impaired fitness

TABLE 4

Associations between survivors' fitness status, sex and health-related quality of life

	SF-36 Physical Component Summary (n=326)			SF-36 Mental Component Summary (n=326)		
	β	SE	p	β	SE	p
Fitness Measures						
Fat percentage Z-score > 1.5	-0.80	2.19	0.37	5.09	2.86	0.06
Quadriceps weakness Z-score < -1.5	-6.44	2.01	< 0.01	-0.31	2.47	0.90
Grip strength Z-score < -1.5	0.58	1.61	0.72	0.68	1.96	0.72
Sit and reach Z-score < -1.5	-0.99	1.35	0.46	-0.13	1.65	0.94
Resting heart rate Z-Score > 1.5	-2.41	1.35	0.07	1.13	1.65	0.50
Six minute walk distance Z-score < -1.5	-4.63	1.54	< 0.01	-1.26	1.86	0.50
Sensory organization test Z-score < -1.5	-1.91	1.40	0.17	-0.77	1.72	0.65
Peripheral nervous system integrity Z-score > 1.5	-4.98	1.14	< 0.01	-4.42	1.40	< 0.01
Age	-0.30	0.08	< 0.01	0.14	0.10	0.15
Sex (Female)	-0.07	1.11	0.94	-1.73	1.37	0.21

10 survivors did not complete all components of the SF-36; models adjusted for age and sex

SF-36 = medical outcomes survey 36 item short form