Body Composition, Muscle Strength Deficits and Mobility Limitations in Adult Survivors of Childhood Acute Lymphoblastic Leukemia

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Background. Chronicity of muscle weakness from cancer and its treatment may be problematic, particularly in those treated for cancer during childhood. We compared body composition, muscle strength, and mobility between 75 adult survivors of childhood acute lymphoblastic leukemia (ALL) and expected values based on population normative data. ***Methods.*** Subjects were young adults treated for childhood ALL between 1970 and 1986, selected randomly from participants in an ongoing study of cancer survivors. DeXA scans were performed to evaluate body composition, and myometry used to measure strength. Mobility was evaluated with the Timed Up and Go (TUG) and 2-min walk (TMW). One sample *t*-tests compared ALL survivors to population norms. ***Results.*** Males had 4.5% and females had 2.3% more body fat than expected (expected males 21.5%, females 36.0%). Males were 76.7 Newtons and females were 58.6 Newtons weaker in quadriceps strength than expected (expected males 569.87 N, females 464.67 N). Males walked 100.88 m and females walked 85.38 m less on the TMW (expected values: males 304.23 m, females 276.26 m), and took longer to complete the TUG (males 5.82 vs. 2.84 sec, females 5.88 vs. 3.00 sec) than expected. Treatment with cranial radiation and current growth hormone (GH) deficiency were associated with lower body weakness among females. ***Conclusions.*** Young adult survivors of childhood ALL have strength and mobility deficits. Decreased strength may reduce ability to participate in physical activity, perpetuating fitness deficits in survivors of childhood ALL. Pediatr Blood Cancer 2007;49:975–981. © 2006 Wiley-Liss, Inc.

Key words: body composition; functional mobility; growth hormone deficiency; leukemia; muscle strength; radiation

INTRODUCTION

Muscle atrophy is associated with acute disease states, including malignancies [1,2]. In animal models, loss of muscular mass can occur from protein degradation in response to physiologic triggers from the tumor [3], lack of adequate nutritional intake, chemotherapy or radiation-induced toxicities [4], and prolonged inactivity, including bed rest. For children and adolescents who survive post-treatment, muscle catabolism can impact performance from muscle weakness and rapid fatigue long after treatment ends [5]. Losses in muscle strength and mass impact physical function and interfere with the ability to perform physical tasks necessary for everyday life [6,7]. The chronicity of muscle weakness in long-term cancer survivors is not well documented and may be problematic, particularly in those treated during childhood. Early loss of muscle mass during periods of rapid physical development may deplete protein stores such that full recovery is unlikely. Muscle weakness and associated frailty may result in a lifetime of sub-optimal physical ability and associated ill health [5–7].

A recent analysis from the Childhood Cancer Survivor Study (CCSS) indicated that at least 20% of childhood cancer survivors, including 15% of those with a previous leukemia diagnosis, reported problems with physical performance as young adults [8]. The self-reported design of this large epidemiologic study did not allow direct measurement of impairments underlying functional losses. Physical fitness deficits in adult survivors of childhood acute lymphoblastic leukemia (ALL) have been documented [9], and are attributed either to a lack of physical activity [10], or, in individuals who received high doses of anthracyclines, to underlying cardio-structural problems [11–13]. Although fitness deficits are reported to be associated with adiposity, defined as percent body fat, it is not clear whether the changes in body composition leads to reduced fitness or whether the reduced fitness leads to changes in body composition, or both [14].

Body composition imbalances, defined, for instance, as having more fat and less lean body mass, have the potential to reduce muscular strength, and decreased strength may impair the ability to participate in physical activity and thus perpetuate fitness deficits. Although lower extremity weakness was reported in a small group of children (N = 8) during treatment for ALL [15] and in a larger group (N = 43) of adolescent and young adult survivors of childhood ALL [5], there is scant data in the literature about muscle strength in adult survivors of childhood ALL, or the impact of body composition and growth hormone (GH) status on muscle performance. Based on the premise that muscle strength may be abnormal in long-term cancer survivors, the aims of these analyses were to: (1) ascertain body composition, strength, and functional mobility among adult survivors of childhood ALL, and to compare these values to population normative values; (2) evaluate the impact of cranial radiation treatment and GH deficiency on muscle strength in survivors; and (3) evaluate the impact of muscle strength on functional mobility in survivors.

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METHODS

Sampling and Recruitment

Eligible subjects were those diagnosed with ALL between 1970 and 1986 at age 20 years or younger who participated in the CCSS [16] and were treated at the University of Minnesota or Children's Hospitals and Clinical of Minneapolis and St. Paul. Details on the study design and methods of CCSS are provided elsewhere [16]. The evaluations reported here were included in a clinical study evaluating long-term effects of childhood ALL treatment, including the metabolic syndrome and GH deficiency [17]. In order to detect differences of at least 10% between our survivor group and population expected values, we recruited 75 participants from 213 potentially eligible individuals, 25 in each of 3 cranial radiation treatment groups (none, <24 Gy, ≥24 Gy). Six cases (2.8%) were no longer eligible. Of the remaining 207, 29 (14%) actively or passively refused participation, 22 were lost to follow-up (10.6%), 10 agreed to participate (4.8%) but were not scheduled because recruitment goals were met, and 71 (34.3%) were never contacted because their random number was not reached in our recruitment protocol. The protocol was approved by the Human Subjects Review Committees (IRB) at both the University of Minnesota and Children's Hospitals and Clinics of Minneapolis/St. Paul.

Measures

The primary outcomes of interest for this analysis were body composition and functional mobility. Cranial radiation treatment and GH deficiency were considered as risk factors for the strength outcomes. Chemotherapy agents were evaluated and oxygen consumption was estimated [18], so that we could account for them in models that evaluated the associations between cranial radiation treatment with strength and functional mobility.

Anthropometrics. Height in centimeters and weight in kilograms were measured with a wall-mounted stadiometer, and on an electronic scale (Model 5002, Scale-Tronix, Inc., Wheaton, IL). Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared.

Body composition. Percent body fat, lean body mass, skeletal muscle mass, and bone mineral content were determined by having participants undergo dual X-ray absorbtiometry (DEXA) scans. (Prodigy, 3M, Madison, WI; software version 6.7). Body regions were isolated from each other using DEXA regional computer generated default lines, with manual adjustment as described by Kim et al. [19]. Reference data described by McDowell et al. [20], Gallagher et al. [21,22], and Janssen et al. [23] were used as age and gender-specific population normative values.

Muscle strength. Knee extension strength, the maximal voluntary force participants could exert during a single contraction, was measured with a break test. A single tester used a Chattilion hand held myometer (model CSD 200, Ametek, Inc., Largo, FL). Participants were seated in a firm chair with the back and thighs fully supported, the pelvis and distal femurs secured. Resistance was applied just proximal to the malleoli [24]. Intraclass correlation coefficients (ICCs) from 0.90 to 0.99 are reported for this device using this technique, within and between sessions [26–32]. Hand grip strength in kilograms was measured using a Jamar hand grip dynamometer (Sammons Preston Rolyan, Nottinghamshire, UK). Participants were seated with the shoulder at 0–10 degrees, the

elbow flexed to 90 degrees, and the forearm in neutral [33]. ICCs for this hand grip device range from 0.85 to 0.98 [34,35]. Each participant completed three trials with each extremity for both knee extension and hand grip. Averages were used for analysis [25].

Oxygen consumption. Peak VO$_2$, the volume of oxygen consumed per minute relative to body mass was estimated with the Duke Activity Status Index (DASI) [18]. This 12 item questionnaire is correlated with peak oxygen uptake (recorded via expired gas analysis) during graded exercise testing (r = 0.81) [18]. The DASI has been compared to and validated with exercise testing in both healthy and sick populations [36–43]. It's value as a prognostic tool for myocardial ischemia and angiographically defined coronary disease has recently been reported [44]. Test scores were converted to VO$_2$ max values where VO$_2 = 0.43 \times$ DASI + 9.6.

Functional mobility. Mobility was evaluated by having each subject perform the "Timed Up and Go" (TUG) measure [45], the time in seconds it takes to stand up from a 46 cm height arm chair, walk a distance of 3 m, turn, walk back to the chair and sit down. Each subject performed both a practice and a timed trial. Participants also completed the modified Cooper test where they walked in a corridor as fast as possible for 2 min. Distance was recorded in meters [46].

Growth hormone stimulation test. GH function was evaluated for 72 of the 75 participants with the GH-releasing hormone/ arginine stimulation test (GHRH/ARG) as described by Biller et al. [47] GH levels were obtained at 30, 40, 60, 90, and 120 min following a 1.0 µg/kg intravenous bolus administration of GHRH and a 0.5 g/kg intravenous infusion of arginine [48]. Consistent with prior studies, participants with peak GH levels less than 9.0 µg/L were classified as GH deficient [48,49].

Treatment data. Cranial radiation exposure and chemotherapy treatment data were obtained from the CCSS database. These data were previously abstracted from medical records for each CCSS participant by trained personnel [17].

Data Analysis

Descriptive statistics were calculated for demographic and treatment variables and compared between participants and eligible non-participants with two sample t-tests or Chi-squared tests. Mean values for body composition, strength, and mobility outcomes were calculated using sampling weights to account for our block randomization sampling scheme, and compared to age, gender, height, and weight-specific population normative values with paired t-tests. Pearson correlation coefficients were calculated to evaluate the association between body composition variables and strength and mobility outcomes. Based on previous research that demonstrated improved model fitting with non-linear strength variables [50–53], leg strength was dichotomized to those in the lower 10th percentile (−1.3 standard deviations or more below the population mean) versus higher than the 10th percentile, for use in regression analyses. The 10th percentile corresponds to a ratio of strength to body weight of 3.3 N/kg. Individuals with strength to body weight ratios between 3.0 and 3.5 N/kg are at risk for impaired function [54]. Multiple variable linear regression models were used to evaluate the associations between cranial radiation treatment and continuous outcomes of strength, GH deficiency and strength, strength and distance walked in 2 min, and strength and seconds required to perform the TUG. Cranial radiation was first classified as

none, <24 Gy and 24+ Gy; however, there were no significant differences in outcomes between the two groups who received radiation, so the two groups who received radiation were combined for the final models. All models were adjusted for age and gender. The evaluations of the impact of knee extension strength on the 2-min walk and the TUG were adjusted for peak oxygen consumption. Chemotherapy agents and total anthracycline doses were evaluated in the predictive models, however they were not found to be independent predictors of the outcome or confounders of the tested associations, so were not included in the final models. Stata version 8.1 was used for all analyses.

RESULTS

Participants

The characteristics of the participants and eligible non-participants are shown in Table I. Participants did not differ statistically from non-participants by age, gender, or chemotherapy agents received. Study participants were 41.3% male, had a mean age at interview of 30.2 years (standard deviation (SD) 7.1), a mean age at diagnosis of 5.6 years (SD 4.3), and had survived on average 24.6 years (SD 4.8). Participants differed from non-participants by cranial radiation dose by sampling design.

TABLE I. Demographic and Treatment Variables Between Study Participants and Eligible Non-Participants

	Participants	Non-participants	
	N = 75	N = 132	
	N (%)	N (%)	P-value
Sex			
Male	31 (41.3)	64 (48.5)	0.42
Female	44 (58.7)	68 (51.5)	
Age group at interview			
19–29 years	40 (53.3)	61 (46.2)	0.19
30–39 years	27 (36.0)	63 (47.7)	
40–45 years	8 (10.7)	8 (6.1)	
Mean age at interview (SD) in years	30.2 (7.1)	30.9 (6.3)	0.50
Mean age at diagnosis (SD) in years	5.6 (4.3)	5.4 (4.0)	0.72
Mean years of survival (SD) in years	24.6 (4.8)	25.5 (4.6)	0.20
Body mass index-1995–1996 survey: mean (SD)	23.6 (5.9)	24.5 (4.6)	0.28
Race			
White	74 (98.7)	127 (96.2)	0.98
Non-white	1 (1.3)	5 (3.8)	
Cranial radiation treatment group			
None	25 (33.3)	17 (12.9)	0.001
<24 Gy	25 (33.3)	70 (53.0)	
24+ Gy	25 (33.3)	45 (34.1)	
Body areas in radiation fields			
Brain	50 (66.7)	115 (87.1)	<0.001
Spine	17 (22.7)	27 (20.5)	0.71
Total body	5 (6.7)	4 (3.0)	0.22
Chemotherapy agents received			
Actinomycin	1 (1.3)	0 (0.0)	0.18
Cytoxan	33 (44.0)	64 (48.5)	0.53
Ara-C	33 (44.0)	58 (43.9)	0.99
Daunorubicin	21 (28.0)	30 (22.7)	0.39
Dexamethasone	11 (14.7)	20 (15.2)	0.92
Doxorubicin	21 (28.0)	51 (38.6)	0.12
Isofosfomide	1 (1.3)	1 (0.8)	0.68
L-aspariginase	72 (96.0)	122 (92.4)	0.31
6-Mercaptopurine	69 (92.0)	119 (90.2)	0.66
Methotrexate	75 (100.0)	132 (100.0)	0.99
Prednisone	74 (98.7)	129 (97.7)	0.64
6-Thioguanine	18 (24.0)	29 (22.0)	0.74
Vincristine	75 (100.0)	131 (99.2)	0.45
VM-26	2 (2.7)	1 (0.8)	0.27
Allopurinol	2 (2.7)	1 (0.8)	0.27
Anthracycline dose			
None	46 (61.3)	77 (58.3)	0.07
1–100 mg/m^2	10 (13.3)	6 (4.5)	
101–300 mg/m^2	11 (14.7)	31 (23.5)	
301+ mg/m^2	8 (10.7)	18 (13.6)	

Body Composition

Observed and expected means of body composition, strength, and mobility values for the ALL survivors are shown in Table II. BMI and bone mineral content did not differ between study participants and expected population normative values, however percent fat mass was higher and percent skeletal and lean body mass were lower in study participants when compared to population normative values. Mean BMI among study participants was 26.8 kg/m^2 for males and 27.9 kg/m^2 for females, compared to expected mean values [20] of 27.5 kg/m^2 ($P = 0.45$) and 26.8 kg/m^2 ($P = 0.37$), respectively. Fat mass among males was 5.5%, and among females was 2.0%, higher than expected from population norms. Lean body mass was 4.7% ($P = 0.001$) lower among males and 2.2% ($P = 0.13$) lower among females, and skeletal lean body mass was 2.5% ($P = 0.007$) lower among males and 2.2% ($P = 0.007$) lower among females than expected when compared to population normative values [21–23].

Strength

Hand grip strength among our study participants was slightly, but not significantly lower than population normative values [33]. Knee extension strength was significantly lower among both male and female survivors of childhood ALL when compared to population normative values. On average, males had knee extension strength values slightly more than one standard deviation below, and females had knee extension strength nearly one standard deviation below the expected population mean [24]. Quadriceps strength was positively correlated with percent skeletal muscle mass ($r = 0.27$, $P = 0.02$), but not with BMI, percent lean body mass, or percent fat mass.

Cardio-Pulmonary Fitness

Self reported cardio-pulmonary fitness levels in the study population were also significantly lower than would be expected for same age and gender members of the normative population.

Based on participants' answers to the 12 questions on the DASI, males in our study had estimated mean peak VO$_2$ levels 8.60 mg/kg/min ($P < 0.001$) and females had estimated mean peak VO$_2$ levels 4.62 mg/kg/min ($P < 0.001$) lower than predicted for their age and gender [55]. Peak VO$_2$ was positively correlated with percent lean body mass ($r = 0.26$, $P = 0.03$) and percent skeletal muscle mass ($r = 0.24$, $P = 0.04$), and negatively correlated with percent fat mass ($r = -0.26$, $P = 0.02$) and BMI ($r = -0.23$, $P = 0.04$).

Mobility

The time it took for participants to complete the TUG was 3.0 sec ($P < 0.001$) longer for males and 2.9 sec ($P < 0.001$) longer for females than expected for same age, same gender, same height members of the normal population [45,56,57]. Study participants also walked significantly shorter distances in 2 min than expected for their same height, age, and gender members of the normal population (Table II) [46,56–58]. Time to complete the TUG was positively correlated with BMI ($r = 0.34$, $P = 0.003$).

Strength and Mobility

The association between knee extension strength and the mobility outcomes are shown in Figure 1A,B. After adjusting for age and peak V0$_2$, study participants whose knee extension strength was at or less than -1.3 standard deviation below the population expected mean took slightly, but not significantly longer to perform the TUG and showed a trend toward walking shorter distances in 2 min when compared to those with knee extension strength greater than -1.3 standard deviations below the population mean.

Cranial Radiation Treatment, Growth Hormone Deficiency, and Knee Extension Strength

The impact of cranial radiation treatment on subsequent muscular strength is shown in Figure 2A. Both males and females

TABLE II. Mean Comparisons Body Composition, Strength, Mobility Study Participants, and Population Normative Values

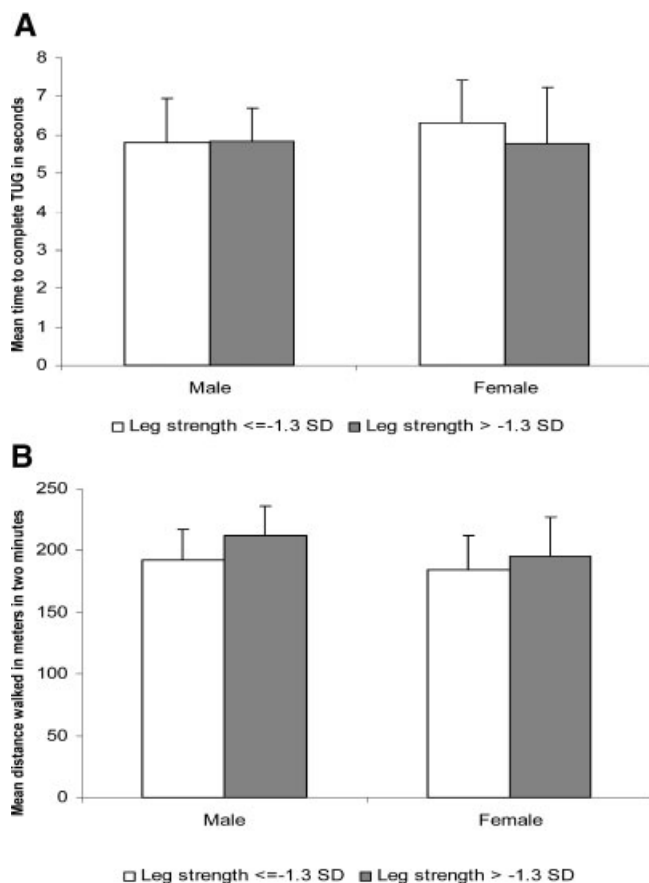|	Males					Females				
	Cases		Normative values			Cases		Normative values		
	Mean	SD	Mean	SD	P-value	Mean	SD	Mean	SD	P-value
Body composition										
BMI (kg/meter squared)	26.8	5.3	27.5	0.3	0.45	27.9	8.1	26.8	0.3	0.37
Bone mineral content %	4.0	0.6	3.8	0.5	0.16	3.6	0.6	3.8	0.5	0.15
Lean mass %	70.0	7.7	74.7	8.4	0.001	58.0	10.0	60.2	5.3	0.13
Fat mass %	26.0	8.0	21.5	7.6	<0.001	38.0	9.6	36.0	9.7	0.001
Skeletal muscle mass %	38.1	4.1	40.7	4.7	0.007	30.1	5.0	32.3	5.7	0.007
Strength										
Left knee extension (Newtons)	490.25	122.98	569.87	60.17	0.001	405.39	122.18	464.67	75.04	0.01
Right knee extension (Newtons)	494.45	118.34	567.97	62.06	0.002	414.20	113.14	472.15	72.38	0.01
Left hand grip (kg)	49.30	10.05	50.18	1.80	0.63	30.40	8.16	29.00	1.23	0.26
Right hand grip (kg)	54.13	9.43	55.36	1.69	0.47	32.44	8.76	34.00	1.32	0.24
Cardiopulmonary fitness										
Peak V02 (ml/kg/min)	32.40	4.68	41.00	5.68	<0.001	29.18	7.12	33.80	4.89	<0.001
Mobility										
Timed up and go (seconds)	5.82	0.99	2.84	0.22	<0.001	5.88	1.32	3.00	0.28	<0.001
Modified Cooper/2 min walk (meters)	203.35	25.72	304.23	8.13	<0.001	190.88	29.59	276.26	9.46	<0.001

Fig. 1. Means and standard deviations, adjusted for age and VO_2 max, for mobility tests show that females with decreased knee extension strength take longer to complete the timed up and go (TUG) (**A**) and that both males and females with decreased knee extension strength walk a shorter distance in the 2-min corridor walk (**B**) than those with knee extension strength—1.3 standard deviation or closer to the population mean. A: Male ranges: 4.08–7.82 sec (leg strength $<=-1.3$ SD) versus 4.51–8.03 sec (leg strength >-1.3 SD), $P = 0.47$. Female ranges: 4.58–8.10 sec (leg strength $<=-1.3$ SD) versus 3.82–11.11 sec (leg strength >-1.3 SD), $P = 0.53$. B: Male ranges: 155.45–233.78 m (leg strength $<=1.3$ SD) versus 165.58–266.38 m (leg strength >1.3 SD), $P = 0.10$. Female ranges: 134.72–242.01 m (leg strength $<=1.3$ SD) versus 131.06–263.04 m (leg strength >1.3 SD), $P = 0.16$.

who received cranial radiation had lower strength than those who did not, however, the impact of the treatment is statistically significant only in females. In an age-adjusted model, females who received cranial radiation had mean knee extension strength values 58.15 Newtons lower than those who did not receive radiation. GH deficiency also was associated with impaired strength among females (Fig. 2B). Again, adjusting for age, females with peak GH levels $\leq 9.0\,\mu g/L$ had an average knee extension strength value 69.14 Newtons less than those who had peak GH levels $>9.0\,\mu g/L$ ($P = 0.05$). The correlation between radiation treatment group and peak GH levels was -0.63 ($P < 0.001$).

DISCUSSION

Adult survivors of childhood ALL have lower lean body and skeletal muscle mass, weaker leg strength, and impaired mobility
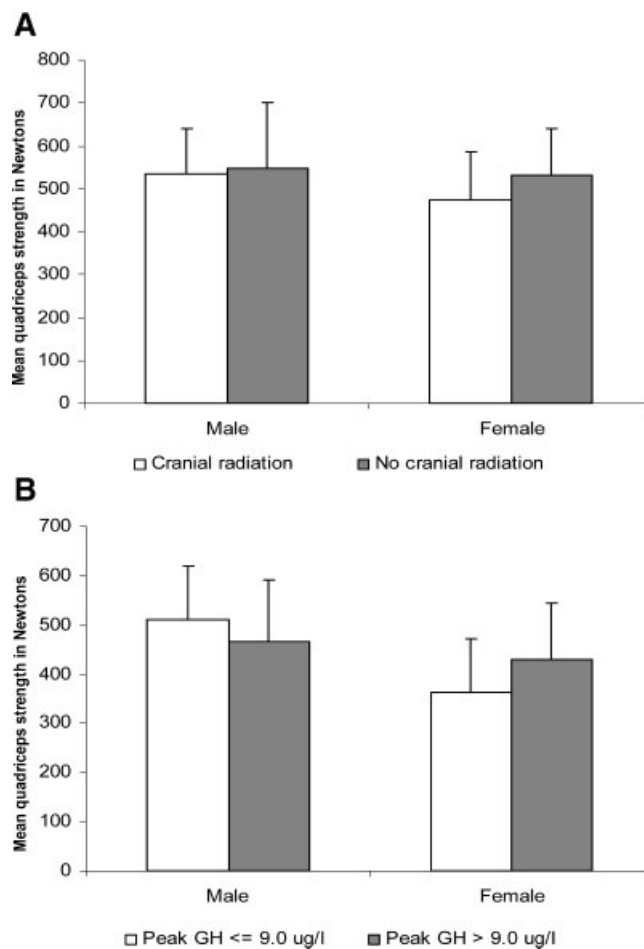
Fig. 2. Means and standard deviations for quadriceps strength from a multiple variable model adjusted for age show that a history of cranial radiation (**A**) and growth hormone insufficiency (**B**) are associated with decreased quadriceps strength among females. A: Male ranges: 243.23–627.20 Newtons (cranial radiation) versus 214.67–665.47 Newtons (no cranial radiation), $P = 0.75$. Female ranges: 185.73–607.60 Newtons (cranial radiation) versus 274.40–697.20 Newtons (no cranial radiation), $P = 0.05$. B: Male ranges: 289.33–665.47 Newtons (growth hormone deficiency) versus 214.67–622.52 Newtons (no growth hormone deficiency), $P = 0.37$. Female ranges: 185.73–548.80 Newtons (growth hormone deficiency) 215.60–697.20 Newtons (no growth hormone deficiency), $P = 0.05$.

when compared to same sex, same age, same body weight population norms. Previous treatment with cranial radiation and current GH deficiency are associated with decreased strength in female ALL survivors. After adjusting for age and peak VO_2, female ALL survivors with leg strength in the lowest 10th percentile of population norms take longer to complete the TUG and walk fewer meters in 2 min than do ALL survivors who have knee extension strength above the population 10th percentile, although these values were not statistically significant in our sample.

Our findings regarding body composition, muscle strength, and cardio-respiratory fitness are consistent with other research [5,14,59]. We found increased fat mass values slightly higher than those reported by Warner et al. [14] in ALL survivors who were still children perhaps indicating that treatment-related changes in body

composition continue well into adulthood. Lower extremity strength deficits in our study participants were not as severe as than those reported by Marchese et al. [15] in children undergoing treatment for ALL. Strength deficits in our female participants were also less marked than those reported by Hovi et al. in a younger (mean age = 19 years) cohort of female ALL survivors, suggesting that either some recovery of strength occurs with distance from leukemia treatment or that members of the normal population also experience strength losses during early adult years. Both cranial radiation and GH deficiency were associated with strength deficits among the females in our study. These findings support previous reports of an association between cranial radiation and muscle weakness [5], and an association between GH deficiency and percent body fat in ALL survivors [59]. The deficit in peak oxygen consumption in our study cohort of childhood ALL survivors, as expected, was similar to the −5.97 ml/kg/min value reported in a systematic review of the literature reporting cardio-respiratory fitness among ALL survivors [9].

Although the body composition, strength, and cardio-respiratory findings we describe provide support to the small body of existing literature, the magnitudes of functional limitations in our study participants, and the potential association of functional limitations with lower extremity strength deficits, are novel findings. Strengthening interventions to improve muscle weakness may help ALL survivors overcome functional loss. The association between weakness and function during treatment has been reported previously among children [15]; our findings of similar losses in long-term adult survivors, however, indicate a potential need for intervention strategies even many years following treatment.

There are several limitations that should be taken into account when interpreting the results of this study. First, our sample size was largely limited to a Caucasian population reflective of the racial and ethnic make-up of Minneapolis and St. Paul between 1970 and 1986. We were unable to determine if body composition, strength, or mobility differed as a function of race or ethnicity. Although larger than other studies specific to muscle strength and function among ALL patients or survivors [5,15], our sample size of 75 is still relatively small and some associations may reflect random variability as a statistical explanation for the differences. Third, if muscle strength deficits are attributable to cranial irradiation and subsequent GH deficiency, our findings have less relevance to ALL survivors diagnosed in a more recent era because of the substantially reduced reliance on cranial radiation treatment in modern risk-based ALL therapy. Nevertheless, our findings are important to the thousands of ALL survivors who were treated with cranial irradiation in an earlier era and to those with T-cell phenotype, those with central nervous system disease at diagnosis, and those with relapsed ALL who are still treated with cranial radiation. They potentially are also important for children diagnosed with brain and spinal cord tumors who receive cranial radiation, and for children who received total body irradiation in preparation for hematopoietic stem cell transplantation. Lastly, because our study participants received very similar chemotherapeutic regimens, we were unable to evaluate the effects of neurotoxic agents, like vincristine, on muscle strength and function.

In summary, long-term adult survivers of childhood ALL in this study had significant lower extremity muscle weakness and also subtle limitations in mobility that may interfere with activities that require lower extremity power, sustained mobility and movement transitions. These limitations in strength and mobility may have a deleterious effect on functional capabilities, including participation in leisure and physical activity.

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