Physical Fitness and Physical Activity in Adolescent Childhood Cancer Survivors and Controls: The PACCS Study

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ABSTRACT

EDVARDSEN, E., E. RUUD, C. S. RUEEGG, H. K. KVIDALAND, I. K. TORSVIK, L. P. V. BOVIM, M. GRYDELAND, N. VON DER WEID, S. A. ANDERSSEN, S. KRIEMLER, and T. RAASTAD. Physical Fitness and Physical Activity in Adolescent Childhood Cancer Survivors and Controls: The PACCS Study. *Med. Sci. Sports Exerc.*, Vol. 57, No. 10, pp. 2286–2293, 2025. **Objectives:** This study aimed to compare physical fitness, function, and physical activity (PA) in adolescent childhood cancer survivors (CCSs) to age- and sex-matched controls and across different cancer diagnoses. **Methods:** This multicenter cross-sectional study (Physical Activity among Childhood Cancer Survivors) included CCSs aged 9–18 yr (≥1-yr after cancer treatment) and age- and sex-matched controls. Physical fitness tests included cardiorespiratory fitness ($\dot{V}O_{2max}$) and muscular strength (maximal isometric handgrip, knee extension, and chest press). Physical function tests included a 1-min sit-to-stand test (STS) and countermovement jump (CMJ). PA was measured by accelerometer for 7 d. We used linear mixed-effects models to compare outcomes between CCSs and controls, and across diagnostic groups. **Results:** We included 157 CCSs and 113 controls aged 13.4 ± 2.6 yr (mean ± SD). Cancer types were leukemia (*n* = 78), central nervous system (CNS) tumors (*n* = 18), lymphoma (*n* = 16), and other solid tumors (*n* = 45). CCSs had lower $\dot{V}O_{2max}$ (marginal mean (95% confidence interval), 41.7 (38.4–45.0) vs 46.4 (42.9–49.8) $mL \cdot kg^{-1} \cdot min^{-1}$; $P < 0.001$), knee-extension strength (35.4 (34.1–36.8) vs 38.2 (36.7–39.7) kg, $P = 0.003$), chest-press strength (30.0 (28.4–31.6) vs 32.8 (31.0–34.7) kg, $P = 0.007$), STS repetitions (57.5 (55.8–59.3) vs 60.0 (58.0–62.0) $P = 0.017$), and CMJ height (22.1, (20.5–23.8) vs 24.9 (23.2–26.6) cm, $P < 0.001$). PA levels and sedentary time were similar in both groups (8513 (7993–9034) vs 9000 (8404–9596) steps per day, $P = 0.174$, respectively). Survivors of CNS tumors had the lowest values for $\dot{V}O_{2max}$, muscular strength, physical function, and PA. **Conclusions:** Despite no significant difference in PA levels, adolescent CCSs had 4.2% to 11% lower physical fitness and function compared with controls, where survivors of CNS tumors performed the poorest. **Key Words:** ACCELEROMETRY, CARDIORESPIRATORY FITNESS, EXERCISE TESTING, FUNCTIONAL PERFORMANCE, MUSCLE STRENGTH

In childhood cancer, improvements in multimodal cancer treatment together with better risk stratification and supportive care have contributed to a significant decline in mortality. The general 5-yr overall survival rate today exceeds 80% (1,2). However, childhood cancer survivors (CCSs) remain at elevated risk for adverse chronic health problems, which may persist for years after treatment completion due to treatment-induced medical conditions (3–5), alterations in body composition (6–8), and cancer-related fatigue (9). These factors may contribute to sedentary behavior, thereby further de-escalating the health of CCSs. Furthermore, there is evidence that adult CCSs have premature conditions that are typically associated with accelerated aging, such as reduced cardiorespiratory fitness (CRF) (10) and muscular strength (11,12), measured 5–20 yr after diagnosis, and they are less likely to

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meet physical activity (PA) recommendations (13). For CCSs during childhood and adolescence, there is a significant knowledge gap regarding their physical fitness levels and PA. Compared with studies in adults, high-quality studies in young CCSs remain scarce (14,15), often being outdated (16), of small sample size (17,18), or limited to specific cancer diseases, primarily acute lymphoblastic leukemia (ALL) (17,19,20). Furthermore, key aspects of cardiopulmonary function and PA level have been insufficiently described for this age group (21), and no studies to date have comprehensively assessed multiple dimensions of physical fitness. A recently systematic review and meta-analysis summarized CRF data from 786 CCSs, reporting that their peak oxygen uptake was as much as 7.08 $mL \cdot kg^{-1} \cdot min^{-1}$ lower compared with healthy controls (22). However, a notable limitation of this review was the inclusion of 334 (42%) adult CCSs, which may have influenced the findings and reduced their applicability to younger CCSs. Our study group has recently published results from the Physical Activity among Childhood Cancer Survivors (PACCS) study reporting lower levels of PA and higher sedentary time in CCSs compared with references (23,24). In a subpopulation of the PACCS study, we also reported on PA and physical fitness in relation to cardiovascular disease risk (25). In the present study, we included age- and sex-matched controls and report the main results from more comprehensive physical fitness measurements and PA. Accordingly, the purpose of this study was to 1) compare physical fitness, physical function, and PA levels in CCSs aged 9–18 yr with age- and sex-matched controls, and 2) to explore differences in these outcomes across cancer types.

METHODS

Study design and participants. This cross-sectional multicenter study is part of the larger PACCS study, which includes four work packages (WPs): WP1, PA; WP2, physical fitness; WP3, facilitators and barriers for PA; and WP4, PA pilot intervention. The PACCS study included CCSs from Norway, Denmark, Finland, Germany, and Switzerland (26). The current study is based on WP2, recruiting participants from WP1 in Oslo and Bergen (Norway), and Basel (Switzerland) between January 2019 and January 2021. Eligible CCSs were 9–18 yr of age and ≥1-yr post-treatment at enrollment in WP1. Exclusion criteria were language difficulties, limited cognitive functioning, and unable to perform a cardiopulmonary exercise test (CPET) until exhaustion. Participants were consecutively recruited during scheduled follow-up consultations at their local hospitals. In addition, age- and sex-matched controls were recruited via the participating CCSs (Norway) or through the hospital staff (Switzerland). The study was approved by the South-East Regional Committee for Medical Ethics in Norway (2018/739/REK Sør-Øst) and the Ethics Committee of Northwestern and Central Switzerland in Switzerland (2019-00410). All participants and/or their legal guardians signed written informed consent.

Outcomes. *CRF* in Norway was assessed as maximal oxygen uptake ($\dot{V}O_{2max}$) during a progressive CPET conducted on a treadmill (27) (Woodway PPS Med, Waukesha, WI, or RL2700E X 1000, Rodby, Vänge, Sweden). In Switzerland, $\dot{V}O_{2max}$ was assessed by CPET on a cycle ergometer (Lode, Excalibur Sport, Groningen, the Netherlands) following Godfrey's protocol (28). Gas exchange measurements were collected breath-by-breath by experienced exercise physiologists and reported as 30-s averages. Three types of gas analyzers were used: Oxycon Pro (Erich Jaeger GmbH, Würzburg, Germany), Jaeger Vyntus CPX (Erich Jaeger GmbH), and MetaMax II (Cortex Biophysik GmbH, Leipzig, Germany). Complete volume and gas calibration was performed daily. Heart rate was monitored continuously during CPET using electrocardiography (Custo Cardio 200, CustoMed, Ottobrunn, Germany). Perceived exertion was assessed immediately after test termination using the Borg scale (6–20) (29). $\dot{V}O_{2max}$ was set to missing in participants with a respiratory exchange ratio (RER) <1.0 and a Borg scale <17 ($n = 3$). $\dot{V}O_{2max}$ values in both absolute terms ($L \cdot min^{-1}$) and relative to body mass ($mL \cdot kg^{-1} \cdot min^{-1}$) were used as outcomes in the analysis.

Isometric knee extension and chest press were performed using a custom-built strength ergometer (Gym 2000, Vikersund, Norway) designed for testing children. For the knee-extension test, the participants were seated with straight backs and arms down. During the maneuver, both hip and knee joint angles were flexed at 90°. For the bench press test, the participants were instructed to push an immovable bar upward with maximal effort with an elbow angel of 90° in order to position the upper arm horizontally. For both tests, participants were instructed to perform at least three maximal attempts until maximal force was achieved. The highest value (kg) in each test was used in the analysis.

Maximal handgrip strength was measured three times in each hand (alternating) in standing position (Baseline Lite Hand Dynamometer, New York, NY). The highest value (kg) of the six trials was used in the analysis.

Muscular endurance was evaluated twice with at least 20-min break in-between with the 1-min sit-to-stand (STS) test (30), where the maximal number of repetitions of standing up and sitting down was recorded. The highest number of repetitions from the two trials was used in the analysis.

Countermovement jump (CMJ) was performed to assess jump height, standing on a portable force platform (FP4; HUR Labs, Tampere, Finland) while executing jumps from an upright position to a self-selected depth (31). The jump height was calculated from the impulse during take-off by the provided software (Force Platform Software Suite, Version 2.6.51, Kokkola, Finland), and the highest jump (cm) was used in the analysis.

PA level was measured by an ActiGraph GT3X+ accelerometer worn on the right hip for 7 consecutive days during wake time (ActiGraph LLC, Pensacola, FL). The accelerometers recorded accelerations on the vertical axis at a sampling rate of 30 Hz, and raw files were processed using ActiLife software (ActiGraph LLC, Pensacola, FL) and averaged over 10-s epochs using the KineSoft analytical software (version 3.3.80, Loughborough, UK). Nonwear criteria were defined as ≥20 consecutive minutes of zero counts with no interruptions and a valid day as ≥480 $min \cdot d^{-1}$ of wear time. Participants with ≥3 valid days of registration were included in the analysis.

APPLIED SCIENCES

Activity counts were translated into time spent in sedentary time (<101 counts per minute), moderate-to-vigorous intensity PA (MVPA) (≥2296 counts per minute), and vigorous intensity PA (≥4012 counts per minute) (32). Sedentary time, mean steps per day, and minutes per day spent in MVPA and vigorous-intensity PA averaged over the number of valid days were used in the analysis.

Covariates. *Demographic (age, sex) and cancer-related background information* (cancer type, cancer treatment) were extracted from medical records. *Puberty status* was determined by clinical examination based on the Tanner puberty scale (33) and/or by a self-reported digital standardized questionnaire (Pubertal Category Scores) (34) that included body hair growth, voice and facial hair, and breast development and menarche. Participants were grouped into three categories: prepubertal, pubertal, and postpubertal. *Body composition* was in Norway assessed by Lunar dual-energy x-ray absorptiometry (DXA) (GE Healthcare) using the enCORE Software Version 14.10.022 and 18. In Switzerland, body composition was assessed by Horizon A DXA (Hologic Inc.) using the InnerCORE software version 13. Total lean body mass (LBM; kg), total fat mass (kg), and fat percentage (%, continuous and proportion ≥ 35%) were used in the analysis. Body mass index (BMI; $kg \cdot m^{-2}$) was calculated based on measured height and weight.

Statistical analysis. All data were entered into the REDCap database and analyzed using STATA v18 (StataCorp LLC). Descriptive results are presented as means ± standard deviations (SD), numbers with proportions (%), or medians with minimum and maximum, overall and for boys and girls separately. Differences in physical fitness, physical function, and PA between CCSs and controls were estimated using linear mixed-effects models for each outcome with the study site (Oslo, Bergen, and Basel) and survivor–control pair as random intercept and age and sex as fixed effects. Models were run overall and separately for boys and girls (including only age as fixed effect). In a *post-hoc* sensitivity analysis, we additionally adjusted for fat percentage to investigate whether this could explain some of the differences observed. Differences in physical fitness, physical function, and PA between the cancer types were estimated using linear mixed-effects models for each outcome with study site as random intercept and cancer diagnosis, age, and sex as fixed effects. We exported marginal means with 95% confidence intervals (CIs) from the models using the delta method. A *P* value ≤0.05 was considered statistically significant. Data were analyzed based on available information (complete case analysis), and number of missing values is reported in each table.

RESULTS

A total of 296 CCSs were invited to participate in WP2, and 96 declined. In total, 157 CCSs and 113 age- and sex-matched controls were included in the current study (Fig. 1). Basic characteristics such as sex, age, diagnosis, age at diagnosis, and time since diagnosis did not differ between participants and nonparticipants in WP2 (35).

Characteristics of the participants. Time since diagnosis and end of treatment in CCSs were 8.2 ± 3.6 and 6.3 ± 3.5 yr, respectively. Background characteristics were comparable between survivors and controls except for a higher BMI, total fat mass, fat percentage, and proportion of obesity among CCSs (Table 1).

Physical fitness, physical function, and PA. All individuals, except for seven participants not performed or fulfilling the CPET criteria, successfully completed the CPET. At maximal effort, the mean RER, and ratings of perceived exertion for all participants (CCSs and controls, n = 263) were 1.15 ± 0.09, and 18.5 ± 1.4, respectively. No significant differences were observed between CCSs and controls, indicating comparable exertion levels.

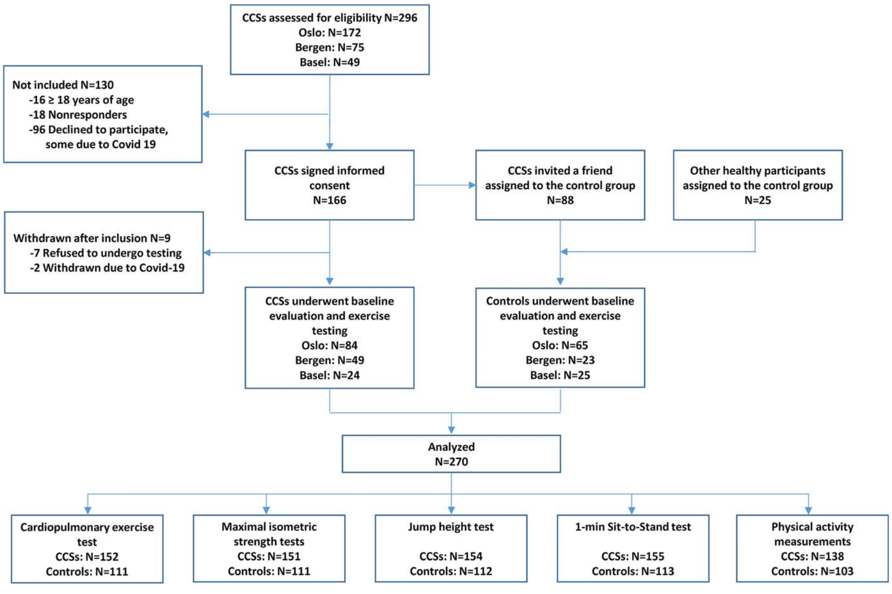

FIGURE 1—Flow of inclusion and number of tests performed.

TABLE 1. Characteristics of study participants, overall and stratified for boys and girls.

Variables	All		Boys		Girls	
	Survivors (n = 157)	Controls (n = 113)	Survivors (n = 84)	Controls (n = 57)	Survivors (n = 73)	Controls (n = 56)
Age, yr	13.4 ± 2.6	13.3 ± 2.6	13.5 ± 2.5	13.6 ± 2.4	13.4 ± 2.7	13.0 ± 2.8
Body mass, kg	50.3 ± 14.9	47.8 ± 13.7	51.5 ± 15.2	50.3 ± 16.0	48.9 ± 14.4	45.3 ± 10.5
Height, cm	157.5 ± 13.6	157.6 ± 14.6	159.6 ± 13.9	161.0 ± 16.3	155.2 ± 13.0	154.1 ± 11.8
BMI, kg·m^{-2}	**19.9 ± 3.7**	**18.8 ± 2.6**	19.8 ± 3.6	18.9 ± 2.8	19.9 ± 3.8	18.8 ± 2.4
Puberty score						
Prepubertal	36 (23)	28 (25)	23 (27)	17 (30)	13 (18)	11 (20)
Pubertal	112 (71)	74 (65)	59 (70)	36 (67)	53 (73)	38 (68)
Postpubertal	9 (5.7)	6 (5.0)	2 (2.4)	1 (2)	7 (9.6)	5 (8.9)
Body composition						
LBM total, kg	34.2 ± 9.5	33.9 ± 10.6	36.7 ± 10.1	37.0 ± 12.4	31.4 ± 8.1	30.8 ± 7.4
Fat total, kg	**15.0 ± 7.6**	**12.4 ± 5.1**	**14.0 ± 7.8**	**11.5 ± 5.7**	**16.2 ± 7.3**	**13.2 ± 4.2**
Fat total, %	**29.0 ± 8.4**	**26.1 ± 7.2**	**26.2 ± 8.8**	**23.0 ± 7.4**	**32.2 ± 6.6**	**29.1 ± 5.6**
Obese[a]	**70 (45)**	**31 (27)**	**36 (43)**	**17 (30)**	**34 (47)**	**14 (25)**
Fat percentage ≥35	42 (27)	10 (8.8)	15 (18)	3 (5.3)	27 (37)	7 (13)
Resting BP						
Systolic BP, mm Hg	117.1 ± 13.5	120.3 ± 13.8	119.0 ± 13.2	121.6 ± 14.5	114.9 ± 13.5	118.9 ± 13.1
Diastolic BP, mm Hg	67.0 ± 10.6	67.6 ± 10.7	66.7 ± 10.9	67.9 ± 10.4	67.2 ± 10.3	67.3 ± 11.1
Cancer type						
Leukemia	78 (50)		39 (46)		39 (53)	
Brain tumor/CNS	18 (11)		11 (13)		7 (10)	
Lymphoma	16 (10)		12 (14)		4 (5.5)	
Solid tumors[b]	45 (29)		22 (26)		22 (30)	
Cancer treatment						
Chemotherapy	152 (97)		83 (99)		69 (95)	
Anthracyclines	121 (78)		64 (77)		57 (79)	
Cumulative dose[c], mg·m^{-2}	154 (45–450)		149 (45–400)		159 (80–450)	
Radiation therapy	44 (28)		24 (29)		20 (27)	
Surgery	59 (38)		34 (41)		25 (34)	
Stem cell transplantation	16 (10)		9 (11)		7 (10)	

Data are presented as means ± standard deviations, no. (%), or median with (minimum, maximum). We had the following missing information: puberty score (n = 5), body composition (n = 3), cancer type (n = 1), and fat percent (n = 3). Proportions were calculated based on available numbers. Bold = statistically significant at $P \leq 0.05$.
[a]Weight status for obesity was defined by gender and age according to McCarthy and coworkers.
[b]Solid tumors included Erwing sarcoma (n = 5), neuroblastoma (n = 9), abdominal PNET (n = 1), pleuropulmonal blastoma (n = 1), hepatoblastoma (n = 2), retinoblastoma (n = 2), fibroblastic osteosarcoma (n = 1), renal cell carcinoma (n = 1), rhabdomysarcoma (n = 5), and Wilms tumor (n = 13).
[c]The cumulative anthracycline dose was calculated as doxorubicin isotoxic equivalent dose (mg·m^{-2}).
BP, blood pressure.

The mean peak heart rate was 197 beats per minute (95% CI, 195–198) in CCSs and 198 beats per minute (95% CI, 196–200) in controls (P = 0.322). In contrast, peak systolic blood pressure was significantly lower among CCSs compared with controls with means of 160 mm Hg (95% CI, 155–164) and 170 mm Hg (CI: 164 to 175), respectively (P < 0.001).

Except for handgrip strength (P = 0.179), CCSs performed lower in all outcomes of physical fitness and physical function (all P < 0.017; Table 2). Compared with controls, CCSs had 10% lower $\dot{V}O_{2max}\cdot kg^{-1}$, 7.3% lower leg strength, 8.5% lower chest press strength, and 4.2% fewer repetitions in the 1-min STS, and jumped 11% lower in the CMJ. By sex, there was a significant difference in the number of repetitions in the 1-min STS (5.8%) and CMJ (9.5%) for boys, and in the 1-repetition maximum in knee extension (8.0%), chest press (9.1%), and CMJ (12%) for girls. Overall, the largest difference between CCSs and controls was seen in $\dot{V}O_{2max}$ (mL·kg^{-1}·min^{-1}) in boys (13%) and in CMJ height in girls (12%).

After adjusting for fat percentage (Supplemental Table 1, Supplemental Digital Content http://links.lww.com/MSS/D247), the overall difference between CCSs and controls decreased for $\dot{V}O_{2max}\cdot kg^{-1}$ (from 10% to 4.8%), 1RM in chest press (from 8.5% to 5.5%), number of repetitions in the 1-min STS (from 4.2% to 1.3%), and CMJ height (from 11% to 4.5%).

Regarding PA and sedentary behavior, there were no significant differences in sedentary time, number of steps per day, minutes spent in MVPA per day, or minutes spent in vigorous PA between CCSs and controls (Table 2).

Physical fitness, physical function, and PA by cancer diagnosis. Survivors of central nervous system (CNS) performed lower on all measures of physical fitness, physical function, and PA compared with survivors of the other diagnostic groups, reaching statistical significance for absolute $\dot{V}O_{2max}$ (P = 0.025), 1-min STS (P = 0.007), and CMJ height (P = 0.003) (Table 3). Furthermore, lymphoma survivors demonstrated 24% poorer muscular strength in chest press compared with leukemia survivors (P = 0.005).

DISCUSSION

Our study showed that CCSs had, on average, 4%–11% lower physical fitness levels across three fitness domains compared with age- and sex-matched controls. By sex, the largest differences between CCSs and controls were observed in $\dot{V}O_{2max}$ for males (11% and 13% for absolute and relative $\dot{V}O_{2max}$, respectively), and in CMJ height for females (12%). PA levels were similar between CCSs and controls. Adjustment for percent body fat reduced the difference in physical fitness between survivors and controls dramatically. CCSs treated for CNS cancer performed poorest for most measures of physical fitness and PA, whereas CCSs treated for leukemia performed best.

Previous studies have suggested that physical impairments in CCSs may be related to increased sedentary behavior, possibly

TABLE 2. Physical fitness, physical function, and PA for CCSs and controls, overall and by sex.

Variables	All: Survivors (n = 157)	All: Controls (n = 113)	All: Mean Difference (P Value)	Boys: Survivors (n = 84)	Boys: Controls (n = 57)	Boys: Mean Difference (P Value)	Girls: Survivors (n = 73)	Girls: Controls (n = 56)	Girls: Mean Difference (P Value)
CRF									
$\dot{V}O_{2max}$, L·min^{-1}	2.04 (1.84–2.24)	2.25 (2.04–2.45)	**−0.21 (<0.001)**	2.25 (2.1–2.44)	2.53 (2.32–2.73)	**−0.27 (0.002)**	1.85 (1.66–2.04)	1.97 (1.77–2.16)	**−0.12 (0.034)**
$\dot{V}O_{2max}$, mL·kg^{-1}·min^{-1}	41.7 (38.4–45.0)	46.4 (42.9–49.8)	**−4.7 (<0.001)**	44.2 (40.9–47.6)	50.5 (46.9–54.1)	**−6.3 (<0.001)**	39.3 (35.9–42.8)	42.2 (38.7–45.8)	**−2.9 (0.002)**
Muscular strength									
1RM knee extension, kg	35.4 (34.1–36.8)	38.2 (36.7–39.7)	**−2.7 (0.003)**	38.7 (36.6–40.5)	41.1 (38.6–43.6)	−2.4 (0.115)	32.1 (30.6–33.5)	34.9 (33.3–36.6)	**−2.8 (0.009)**
1RM chest press, kg	30.0 (28.4–31.6)	32.8 (31.0–34.7)	**−2.8 (0.007)**	36.0 (33.7–38.4)	38.6 (35.7–41.5)	−2.6 (0.140)	24.1 (21.5–26.7)	26.5 (23.8–29.2)	**−2.4 (0.027)**
1RM handgrip, kg	26.6 (25.6–27.6)	27.4 (26.3–28.6)	−0.9 (0.179)	29.9 (28.4–31.3)	31.0 (29.3–32.7)	−1.1 (0.277)	23.4 (21.9–25.0)	23.4 (21.8–25.0)	0.0 (0.963)
Physical function									
1-min STS, No.	57.5 (55.8–59.3)	60.0 (58.0–62.0)	**−2.5 (0.017)**	58.3 (54.7–62.0)	61.9 (58.1–65.7)	**−3.5 (0.002)**	57.2 (54.3–60.0)	58.9 (55.7–62.1)	−1.8 (0.309)
CMJ, cm	22.1 (20.5–23.8)	24.9 (23.2–26.6)	**−2.8 (<0.001)**	24.7 (23.8–26.0)	27.3 (25.8–28.8)	**−2.5 (0.003)**	19.8 (18.4–21.2)	22.4 (21.0–23.9)	**−2.6 (<0.001)**
PA									
Steps per day, No.	8513 (7993–9034)	9000 (8404–9596)	−486 (0.174)	8504 (7746–9262)	9259 (8360–10,158)	−755 (0.148)	8507 (7818–9195)	8825 (8064–9586)	−319 (0.515)
Sedentary time, min·d^{-1}	543 (529–557)	549 (533–564)	−5 (0.512)	541 (521–562)	560 (536–584)	−19 (0.166)	545 (526–564)	539 (19–559)	6 (0.537)
MVPA, min·d^{-1}	52.0 (48.0–56.0)	55.3 (50.7–60.0)	−3.3 (0.229)	53.9 (47.9–59.9)	58.9 (51.7–66.1)	−5.0 (0.259)	50.1 (44.9–55.2)	51.9 (46.2–57.6)	−1.8 (0.593)
VPA, min·d^{-1}	20.8 (18.4–23.2)	21.5 (18.7–24.3)	−0.7 (0.700)	21.9 (18.5–25.2)	23.6 (19.6–27.5)	−1.7 (0.473)	19.8 (16.2–23.3)	19.5 (15.6–23.5)	0.3 (0.927)

Data are presented as marginal means and marginal mean differences with 95% CIs, from linear mixed-effects model with study site and survivor–control pair as random intercept and age and sex as fixed effects. The sex-stratified models included only age as fixed effect. We had the following missing information: $\dot{V}O_{2max}$ (n = 7), muscular strength (n = 8), physical function (n = 2), and PA (n = 29). Bold = statistically significant at $P \leq 0.05$.
No., number; RM, repetition maximum; VPA, vigorous PA.

as a consequence of cancer-related fatigue and post-treatment discomfort (14). However, using objective accelerometer-based measurements in the present study, we found no significant differences in either sedentary time or PA levels between CCSs and controls. This suggests that former cancer disease and its treatment may play a significant role for the impaired physical fitness in younger CCSs, even for those currently maintaining an active lifestyle. Our findings are in line with a similar study showing significantly lower quadriceps strength compared with healthy siblings, despite identical PA levels (11). Moreover, emerging evidence suggests that CCSs may respond differently to exercise and might not experience the same benefits as their healthy peers. Specifically, exposure to anthracyclines and radiation to the heart has been linked to an abnormal hypertrophic response to exercise, potentially interfering with cardiac and vascular adaptive mechanisms (36). This is supported by echocardiographic measures in a subgroup of our participants (37). In the Norwegian population of CCSs, left ventricular global longitudinal strain was 20% lower compared with the controls, indicating impaired myocardial function. Furthermore, lower myocardial function was associated with lower $\dot{V}O_{2max}$ and higher doses of anthracyclines during treatment.

These physiological alterations could contribute to persistent impairments in cardiovascular and muscular fitness, despite engagement in regular PA. In light of this finding, to facilitate and encourage increased PA alone seems insufficient to counteract the reduction in physical fitness. Consequently, more insight into explanatory factors is needed for targeting the most important factors in further development of effective countermeasures.

Overweight and obesity are well-known late effects following treatment in CCSs (38) and highly prevalent participants of the present study. Full-body DXA scans revealed that 27% of CCSs had a fat mass >35% compared with 8.8% of controls. When adjusted for fat percentage in the analysis, the difference in $\dot{V}O_{2max}$ between CCSs and controls was reduced by 2.5 mL·kg^{-1}·min^{-1} (~50%), which underline the impact of obesity on CRF between CCSs and controls. This effect was most pronounced among girls, whereas for the boys, $\dot{V}O_{2max}$ was still 4.4% lower in CCSs after the adjustment. The pathophysiology of obesity in CCSs remains unclear but is likely influenced by a positive energetic balance during and after treatment, affecting physical function, PA levels, and overall health.

Cardiorespiratory fitness. CRF measured as $\dot{V}O_{2max}$·kg^{-1} was 10% lower in CCSs compared with controls, consistent with a smaller US study (39). Notably, our survivors had a 20% higher $\dot{V}O_{2max}$·kg^{-1} compared with the US CCSs likely due to their significantly lower body mass in the present study (49.2 kg vs 56.4 kg for all participants, respectively). Another Italian study reported ~10% lower $\dot{V}O_{2max}$·kg^{-1} in survivors of childhood ALL compared with controls (17). They had high PA levels, but they were younger than our CCSs (7.8 yr vs 13.4 yr). Nevertheless, CCSs in our study revealed a substantial 18% higher $\dot{V}O_{2max}$·kg^{-1} than ALL survivors. The discrepancy may be related to difference in levels of effort during CPET in the Italian study as opposed to our study (Borg 15.3 vs 18.5, respectively), which emphasizes the importance of motivating subjects to their

TABLE 3. Physical fitness, physical function, and PA for CCSs according to main diagnostic groups.

Variables	Leukemia (n = 78)	Lymphoma (n = 16)	CNS Tumor (n = 18)	Solid Tumors[a] (n = 45)	Global P Value for Difference between Groups
CRF					
$\dot{V}O_{2max}$, $L\cdot min^{-1}$	**2.21 (2.05–2.37)**	2.02 (1.76–2.27)	**1.87 (1.62–2.12)**	1.99 (1.80–2.17)	0.008
$\dot{V}O_{2max}$, $mL\cdot kg^{-1}\cdot min^{-1}$	43.7 (40.5–46.9)	39.6 (34.8–44.4)	38.6 (33.8–43.3)	41.7 (38.2–45.3)	0.069
Muscular strength					
1RM knee extension, kg	36.3 (34.7–38.0)	35.3 (31.7–38.9)	32.6 (29.2–36.1)	35.8 (33.6–38.0)	0.307
1RM chest press, kg	32.6 (30.3–34.9)	24.7 (19.7–29.6)	28.2 (23.5–33.0)	29.6 (26.7–32.5)	0.249
1RM handgrip, kg	**28.3 (26.9–29.7)**	24.7 (21.7–27.7)	**23.2 (20.4–26.0)**	26.9 (25.1–28.7)	0.007
Physical function					
1-min STS test, No.	58.5 (55.9–61.1)	58.6 (53.0–64.3)	50.3 (45.0–55.7)	57.2 (53.9–60.6)	0.602
CMJ, cm	**24.0 (22.7–25.2)**	21.5 (18.8–24.1)	**19.7 (17.2–22.3)**	22.0 (20.6–23.8)	0.017
PA					
Steps per day, No.	8503 (7710–9296)	9006 (7289–10,722)	7723 (5276–8770)	8813 (7789–9839)	0.332
MVPA, min	53.2 (47.2–59.2)	56.3 (43.3–69.2)	38.1 (24.9–51.3)	53.1 (45.3–60.8)	0.185

Data are presented as marginal means with 95% CIs, from linear mixed-effects model with study site as random intercept and age and sex as fixed effects.
[a] Solid tumors included Erwing sarcoma (n = 5), neuroblastoma (n = 9), abdominal PNET (n = 1), pleuropulmonal blastoma (n = 1), hepatoblastoma (n = 2), retinoblastoma (n = 2), fibroblastic osteosarcoma (n = 1), renal cell carcinoma (n = 1), rhabdomysarcoma (n = 5), Wilms tumor (n = 13).
Bold = statistically significant at $P \leq 0.05$.
No., number; RM, repetition maximum.

maximum potential during CPET. Furthermore, a recent systematic review including 786 CCSs found that $\dot{V}O_{2max}$ was, on average, 7.08 $mL\cdot kg^{-1}\cdot min^{-1}$ lower compared with controls (22), whereas we observed a smaller difference of 4.7 $mL\cdot kg^{-1}\cdot min^{-1}$. This suggests that our CCSs cohort may have preserved CRF to a greater extent than reported in the broader CCS population. Possible explanations for this difference may include differences in treatment regimens, supportive care, lifestyle behaviors, or methodological variations in CPET protocols and participant motivation between studies. Furthermore, more than 40% of the CCSs included in the systematic review were tested as adults. Minor impairments in physical fitness during adolescence may escalate into adulthood if PA level is further reduced. Despite lower CRF in our CCSs compared with controls, their $\dot{V}O_{2max}$ was surprisingly high compared with predictions for healthy adolescents, suggesting potentially reduced treatment-related negative effects than previously thought.

$\dot{V}O_{2max}$ differences between CCSs and controls were more pronounced in males than in females. There is limited information on the physiological factors contributing to this greater impairment in male CCSs. However, LBM tended to be lower in male CCSs compared with their matched controls, whereas in females, LBM tended to be higher in CCSs. Consequently, male CCSs had a reduced amount of skeletal muscle mass to consume oxygen. As already discussed, differences in fat percentage could explain some of the differences between CCSs and controls, especially in girls, but still other determinants of CRF like impaired myocardial function (37) are involved and need to be determined.

By cancer type, CCSs treated for CNS tumors showed a 12% lower $\dot{V}O_{2max}$ compared with patients treated for leukemia, which is in line with other findings (40). This deficit, specific to brain tumors, may be related to treatment related factors (CNS radiation and surgery), higher fat percentage, and lower PA levels compared with CCSs treated for leukemia, lymphoma, and solid tumors. However, these results should be interpreted cautiously due to the relatively small number of CNS survivors included.

Muscular strength. Except for handgrip strength, muscular strength in CCSs was notably lower than controls, especially among girls. Interestingly, there was no difference in LBM between CCS and controls, and in girls, LBM tended to be higher in CCS, indicating less strength per kg LBM. This is of clinical relevance due to its negative impact on physical health-related quality of life (21), walking speed, and CRF (41).

Reduced muscular strength after radiotherapy and chemotherapy are well-known late effects (42). Several studies have demonstrated the impairment of muscular strength in CCSs (12,21,43,44), where the greatest impairment seems to be located in the knee extensors (12). The physiological mechanism, possibly involving cellular senescence, inflammation, and mitochondrial dysfunction related to initial cancer or treatment toxicity, have been postulated to have an impact on muscle quality (45). Reduced specific force is indicated by the lower strength per kg LBM in the CCS, and in a substudy from the PACCS project, peripheral polyneuropathy was observed in 14% of CCSs, indicating potential impact on muscle quality (46).

No difference in handgrip strength between CCS and controls is in line with previous findings in 13 ALL survivors (44). However, results from the handgrip test should be interpreted with caution because it may not reflect general muscle strength.

Survivors treated for CNS tumors and lymphomas demonstrated the lowest muscular strength, with lymphomas particularly affected in the upper body. Further investigation is needed to confirm and explain these findings.

Physical function. Significant performance differences were observed between CCSs and controls in both the 1-min STS and CMJ tests. The difference was smallest for the 1-min STS (4.2% vs 11%, respectively) indicating less impairment in lower body muscular endurance compared with CMJ performance, which assesses power and coordination. Although STS performance was lower among CCS, their results were within normative values on healthy children (47). To our knowledge, no other studies have performed the 1-min STS test in young CCSs.

The 11% lower CMJ performance is similar to the differences observed for CRF and muscular strength. The lower jump height in CCSs may be explained by the lower strength in knee extensors and a higher incidence of obesity, even when adjusting for body fat (Supplemental Table 1, Supplemental Digital Content, http://links.lww.com/MSS/D247). Coordination problems for the CNS cancer survivors may also contribute, as CMJ demands high coordination.

PA level. Our findings that PA levels—including sedentary time, step count, MVPA, and vigorous PA—did not differ significantly between CCSs and controls contrast with previous studies reporting lower PA engagement among CCSs compared with references (23). This finding is particularly notable given the higher obesity prevalence in CCSs, as higher adiposity is typically associated with reduced PA (15,23). The use of friend or sibling controls in the present study may partly explain these findings. Given the strong influence of peer relationships on PA behaviors during childhood and adolescence, social matching may have minimized differences in daily activity patterns between groups. This approach likely reduced selection bias compared with comparisons with general population references and strengthens the internal validity of our group comparisons.

Importantly, despite similar sedentary time and PA levels, CCSs demonstrated significantly lower physical fitness and function compared with controls. These findings suggest that treatment-related physiological impairments, altered metabolism, or reduced exercise efficiency may contribute to reduced fitness and increased adiposity, independent of daily PA behaviors. Evaluating both PA and physical fitness is therefore essential to fully understand the health profile of CCSs.

Future research directions. Future studies are needed to investigate whether CCSs require a higher volume or intensity of exercise to achieve similar fitness adaptations as their healthy peers. In addition, individualized exercise interventions tailored to cancer type, treatment exposures, and current physical status should be explored to optimize training responsiveness. Longitudinal studies are also warranted to assess how physical fitness, PA levels, and training responses evolve over time based on cancer type and history of treatment, to better inform the development of effective, personalized rehabilitation strategies.

Strengths and limitations. The strengths of this study include the inclusion of healthy, age- and sex-matched controls and the extensive use of clinical and functional tests in an adolescent population with diverse childhood cancer diagnosis and treatment exposures. Nonetheless, certain limitations should be considered.

First, combining treadmill and bike CPET may have influenced CRF results, because treadmill-testing tends to yield higher $\dot{V}O_{2max}$ (48). We addressed this potential source of bias by including the study site as a random intercept in the analysis, and importantly, survivor–control pairs were assessed using the same CPET modality.

Second, emphasizing exercise testing may introduce selection bias by discouraging less fit and frail CCSs from participating. However, this bias might also be true for the controls and thus would not be expected to significantly bias group comparisons.

Third, the low number of CNS tumor survivors, partly due to change in inclusion criteria, limits the power to detect differences between subgroups. Results from this diagnostic group should be interpreted with caution.

CONCLUSIONS

Although the physical fitness and PA levels were high, adolescent CCSs in the present comprehensive study exhibit lower physical fitness and physical function in comparison to their healthy controls, despite similar levels of sedentary time and PA. Overall impairments were at the same level across all physical fitness domains investigated (range from 4.2% to 11%) and strongly influenced by the level of obesity. Survivors treated for leukemia managed to maintain their physical fitness well, whereas those treated for CNS tumors demonstrated the lowest results. The findings are important for personalized guidance of CCSs according to cancer type to prevent and delay negative late effects of treatment.

Despite CCSs demonstrating relatively good function in their youth, the potential for a gradual decline in function over time remains. Hence, further research into the mechanisms behind these physical fitness impairments is essential to target interventions for recovering and maintaining physical fitness and function after cancer treatment.

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