Received: 15 December 2019 | Revised: 14 September 2020 | Accepted: 20 September 2020

DOI: 10.1002/pbc.28751

Pediatric Blood & Cancer

ONCOLOGY: RESEARCH ARTICLE

A randomized controlled trial of a structured exercise intervention after the completion of acute cancer treatment in adolescents and young adults

Morgan Atkinson[1] | Andrew Murnane[2,3] | Thomas Goddard[4,5] | Cathy Pendergrast[4] | Paul Rogers[4] | Rebecca Manudhane[4] | Michael Osborn[1,4]

[1] Youth Cancer Service SA/NT, Royal Adelaide Hospital, Adelaide, Australia

[2] ONTrac at Peter Mac, Victorian Adolescent and Young Adult Cancer Service, Melbourne, Australia

[3] Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Faculty of Health, Deakin University, Geelong, Australia

[4] Department of Haematology and Oncology, Women's and Children's Hospital, North Adelaide, Australia

[5] School of Paediatrics and Reproductive Health, Faculty of Medicine, The University of Adelaide, Adelaide, Australia

Correspondence
Morgan Atkinson, Royal Adelaide Hospital Mail DP 46 (6E-351) Port Road, Adelaide, South Australia 5000.
Email: morgan.atkinson@sa.gov.au

Funding information
Australian and New Zealand Children's Haematology/Oncology Group Concept Validation Scheme; the Royal Adelaide Hospital Research Foundation; CanTeen Australia

Abstract

Background: Cancer treatments are frequently associated with impaired physical fitness, quality of life (QOL), and fatigue, often persisting into survivorship. Studies in older adults with cancer have demonstrated benefits from exercise; however, this has not been rigorously investigated in adolescents and young adults (AYA). The aim of this study was to determine whether a structured 10-week exercise intervention was associated with improved cardiorespiratory fitness (VO_{2peak}), fatigue, and QOL in AYA who have recently completed cancer treatment.

Method: Forty-three AYA (median age 21 ± 6 years) were randomly assigned to an exercise group ($n = 22$) or a control group ($n = 21$). The exercise group received a structured 10-week exercise program comprising progressive aerobic and resistance exercise; the control arm received routine care. VO_{2peak} was measured at baseline, 10 weeks, and six months. Fatigue and QOL were assessed by the FACIT fatigue scale and the PEDS QL, respectively.

Results: Mean VO_{2peak} at baseline was 26.5 ± 7.2 $mL.kg^{-1}.min^{-1}$, which is substantially lower than population norms. The exercise group demonstrated significant improvement in VO_{2peak} at 10 weeks compared with controls (33.8 ± 8.1 vs 29.6 ± 7.6 $mL.kg^{-1}.min^{-1}$, $P = 0.0002$), but by six months, the difference was no longer significant (32.9 ± 7.0 vs 30.9 ± 11.0 $mL.kg^{-1}.min^{-1}$, $P = 0.21$). There were no significant differences in fatigue or total QOL scores between groups.

Conclusion: Cancer treatment is associated with reduced VO_{2peak} in AYA. Improvement in VO_{2peak} was accelerated by a 10-week exercise program; however, no significant benefit was observed in QOL or fatigue. The plateau in VO_{2peak} at six months suggests that a maintenance exercise program may be beneficial.

KEYWORDS
adolescent and young adult, cancer, cardiopulmonary exercise testing, exercise, VO_{2peak}

Abbreviations: 10RM, 10-repetition maximum; 1RM, 1-repetition maximum; ACSM, American College of Sports Medicine; AEP, accredited exercise physiologist; ATS/ACCP, American Thoracic Society/American College of Chest Physicians; ATS/ERS, American Thoracic Society/European Respiratory Society; AYA, adolescents and young adults; BMI, body mass index; CI, confidence interval; CPET, cardiopulmonary exercise testing; FACIT-F, Functional Assessment of Chronic Illness Therapy - Fatigue; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; GSLTPAQ, The Godin-Shephard Leisure Time Physical Activity Questionnaire; ICC, intraclass correlation coefficient; kg/m^2, kilograms per meter squared; LSI, leisure score index; PEDS QL™, The Pediatric Quality of Life Inventory; PFT, pulmonary function test; QOL, quality of life; RCT, randomized controlled trial; RPM, revolutions per minute; VO_{2peak}, peak oxygen uptake

1 | INTRODUCTION

With five-year survival for adolescents and young adults (AYA) with cancer now exceeding 80%,[1,2] a growing number of survivors are at risk of the physical and psychosocial complications of cancer and its treatment.[3,4] In particular, cardiorespiratory fitness is reduced in cancer survivors across the age spectrum. This often persists into long-term survivorship, and is associated with increased cardiovascular disease risk and late mortality.[5–10] Impaired fitness may also contribute to the well-documented worse physical functioning, poorer health-related quality of life (QOL),[11] and excessive fatigue experienced by AYA cancer survivors.[12] Despite 85% wanting exercise information, this need was unmet in 55% of AYA attending a quaternary cancer center.[13] Consequently, there is interest in developing effective physical activity interventions to improve cardiorespiratory fitness in AYA cancer survivors.[14]

Studies in survivors of adult onset cancers consistently demonstrate that exercise increases cardiorespiratory fitness and may improve QOL and fatigue.[15,16] However, because randomized controlled trials (RCTs) have predominantly evaluated individuals with breast cancer and prostate cancer,[7,15,17] it is unclear whether these outcomes can be generalized to AYA or to the predominant tumor types seen in this age group which are often treated more intensively.[14,18]

Little is known about exercise capacity or the benefits of exercise following acute cancer treatment in AYA. Currently, there are no published RCTs investigating the effects of a structured exercise program in AYA. Previous studies in AYA have largely examined exercise programming preferences,[13,19–22] and the small number of intervention studies conducted to date have had methodological limitations.[23,24] Specifically, a recent systematic review of exercise interventions in AYA with cancer reported that only two studies had included a control group (and these were nonrandomized),[25,26] most had small sample sizes, and the few that reported physical fitness outcomes used surrogate measures rather than the more robust cardiopulmonary exercise testing (CPET) with VO_{2peak} analysis.[14] CPET with gas analysis (measured as VO_{2peak}) is considered the gold-standard measurement of cardiorespiratory fitness.[27] VO_{2peak} is a strong predictor of cardiovascular and all-cause mortality in childhood and adult cancer survivors and is correlated with survival, risk of recurrence, QOL, fatigue, and functional independence.[5,27,28]

The purpose of this current RCT was to determine whether a 10-week structured exercise intervention was associated with improved cardiorespiratory fitness, as measured by VO_{2peak}, when compared with controls in AYA patients who had recently completed acute systemic cancer treatment. AYA were defined as per the Australian definition of 15-25 years.[29] Other primary endpoints were muscular strength and flexibility, fatigue scores, and QOL. Secondary endpoints were whether the benefits derived from the intervention were sustained at six months after commencement, and whether the intervention was associated with increased participation in physical activity during that six-month period compared with controls. Adherence to the exercise intervention and tolerability of exercise testing were also evaluated.

2 | METHODS

This was a multicenter, parallel group randomized controlled trial with 1:1 allocation. Multisite ethics approval was obtained from the Women's and Children's Health Network Human Research Ethics Committee (HREC/14/WCHN/171) and the study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12615000527561). Written informed consent was obtained from all participants, with data collection taking place between July 2015 and March 2018. The manuscript was prepared in line with CONSORT guidelines.[30]

Patients were eligible if they were diagnosed with a hematological malignancy or solid tumor, aged 15-25 years at the time of diagnosis and recruitment, had completed systemic cancer treatment (chemotherapy, radiation therapy, or both) within the previous two months (or had started maintenance therapy for acute lymphoblastic leukemia within the past two months). Exclusion criteria included cognitive impairment, less than six months life expectancy, absolute contraindications to CPET (Supporting Information Table S1), previous participation in an exercise intervention during active treatment, or insufficient English to participate in the study. The rationale for excluding participants who had previously engaged in an exercise intervention during treatment was to accurately capture participants' $VO_{2\ peak}$ at the end of active therapy and to ensure that both groups were well matched at baseline.

CPET, pulmonary function tests (PFT), strength and flexibility assessments were conducted in the pulmonary function testing laboratories at Women's and Children's Hospital (North Adelaide, South Australia) and Peter McCallum Cancer Centre (Melbourne, Victoria).

2.1 | Exercise group versus standard care

Participants randomized to the exercise intervention group were asked to attend two supervised exercise sessions per week for 10 weeks. Exercise sessions were conducted at hospital and community-based gymnasiums. Exercise interventions were tailored to each individual participant utilizing aerobic and resistance training guidelines as recommended by the American College of Sports Medicine and Exercise and Sports Science Australia.[7,31] Exercise sessions were supervised by accredited exercise physiologists (AEP) with exercise intensity monitored using heart rate monitors and the Borg scale.[32] The goal of the exercise intervention was to increase VO_{2peak} and muscular strength.

The format of the exercise intervention is summarized in Table 1. Initially, aerobic exercise was performed at moderate intensity (50%-60% maximum heart rate) with progressive increases in intensity every 2-3 sessions, such that participants were ultimately exercising at high intensity (> 85% maximum heart rate). Aerobic exercise was conducted on a bicycle ergometer, arm ergometer, or treadmill depending on the participant's preference.

Resistance training utilized machines and free weights. Each participant completed 6-8 resistance exercises alternating between upper and lower limbs. Participants completed 2-3 sets of 8-12 repetitions

TABLE 1 Format of exercise sessions

	Aerobic training			Resistance training		
Training week[a]	No. sessions per wk	Duration (min/session)[b]	Intensity % HR max	Duration (min/session)	Sets, *n*	Reps, *n*
1-3	2	15-20	50-60	~15-20	1-2	8-12
3-6	2	20-25	60-85	~20-25	2-3	8-12
6-10	2	25-30	>85	25-30	3	8-10

Abbreviations: %HR max, percentage of heart rate maximum; Reps, number of repetitions.
[a]The training program above is a guideline only; clinical judgment was applied in order to regress or progress the exercise program as tolerated. All exercise sessions were supervised by accredited exercise physiologists.
[b]Aerobic exercise was performed in shorter bouts (5-10 min) initially to account for fatigue or reduced exercise capacity.

at > 80% of 10-repetition maximum (10RM). Resistance exercises were progressed either via increased load, repetitions, or set as tolerated every 2-3 sessions. If a participant was unable to progress aerobic or resisted exercises, no changes were made to the exercise prescription. If a participant was feeling unwell, exercise intensity was regressed or progressed as tolerated. Participants with physical impairments (e.g., limb-salvage surgery and weight-bearing restrictions) completed individually adapted exercise programs. These adhered to the aerobic and resistance training guidelines mentioned above but could include exercise with resistance bands, joint range of motion exercises, balance training, and modifications to exercise intensity if indicated.

The control group received usual care, with no specific exercise guidance or restrictions.

2.2 | Assessment and outcome measures

Participants completed assessments at baseline, 10 weeks (±2 weeks), and 6 months (±2 weeks). Questionnaires were administered electronically. Blinded outcome assessors were used for strength and flexibility measures, and laboratory staff were blinded to group allocation when conducting CPET and PFT.

2.3 | Cardiopulmonary exercise testing (VO_{2peak})

CPET was conducted according to the American Thoracic Society/American College of Chest Physicians (ATS/ACCP) guidelines.[33] All tests were conducted on an electronically braked cycle ergometer (Howard Keller EK Ergoline, Germany), with breath-by-breath gas analysis (MasterScreen CPX metabolic cart, Vyaire Medical, Mettawa, Illinois). The equipment was controlled by Jaeger software (JLAB V5.32.0, Vyaire Medical, Mettawa, Illinois). All equipment in the Lung Lab met 2005 American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines.[34] Metabolic equipment was calibrated prior to each individual test. Participants underwent a pretest medical screen to identify absolute or relative contraindications to CPET as per ATS/ACCP guidelines.[33] Testing was supervised by an AEP, a laboratory technician, and a medical professional trained in CPET. Resting data were collected for blood pressure, continuous electrocardiogram, pulse oximetry, and breath-by-breath gas exchange data for five minutes. The patient was then instructed to cycle at 60-70 RPM at a predetermined wattage for one minute, with continuous monitoring of vital signs. Workloads were then increased between 3 and 8 watts (depending on predicted peak wattages as described in ref. 35) every 20 seconds until volitional exhaustion or symptom limitation. During exercise, oxyhemoglobin saturation (Nellcore forehead oximeter, Hayward, California) and blood pressure (Welch Allyn manual auscultatory sphygmomanometer, Skaneateles Falls, New York) were monitored every two minutes, and continuous 12-lead electrocardiogram was monitored for ischemic changes or arrhythmias. Dyspnea and leg fatigue were assessed every two minutes using the Borg scale.[32]

2.4 | Strength and flexibility

Strength and muscular endurance were assessed by maximal grip strength using a hydraulic hand grip dynamometer (Saehan, SH5001, Masan, Korea), maximal back and leg strength using a hydraulic back and leg dynamometer (Baseline Back-Leg-Chest Dynamometer, Via Industrial, Bogotá, DC Colombia), the maximal push-ups test for males and modified maximal push-ups test for females, and the maximal sit-up test.[36] Trunk flexibility was measured using a sit and reach box (Flex-Tester Sit and Reach Flexibility Test Box, Novel Products Inc. Rockton, Illinois) and shoulder flexibility by the back scratch test using a 30-cm ruler.[37,38] Outcome assessors were blinded to group allocation and completed intra- and interrater reliability testing. Intraclass correlation coefficients (ICC) were used to assess the reliability of outcome assessors. All ICC were above 0.90, indicating good reliability.[39]

2.5 | Pulmonary function

PFT were conducted as per ATS/ERS guidelines.[40–42] Forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and diffusing capacity for the lungs using carbon monoxide were measured on a spirometer (Carefusion Masterscreen PFT 2004, Vyaire Medical, Mettawa, Illinois) and controlled by SentrySuite software V2.19.96.

2.6 | Quality of life and fatigue

The Pediatric Quality of Life Inventory (PEDS QL) Cancer Module (Teen version 4 [13-18 years] and Young Adult version, 4 [18-25 years]) was used to assess QOL.[43] Fatigue was assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F).[44] These questionnaires were administered at baseline, 10-week, and 6-month assessments.

2.7 | Leisure time physical activity

The Godin-Shephard Leisure Time Physical Activity Questionnaire (GSLTPAQ)[45] was used to assess leisure time physical activity at baseline, 10-week, and 6-month assessments. The GSLTPAQ is a four-item self-administered questionnaire seeking information on the number of times respondents engage in mild, moderate, and strenuous leisure time physical activity for bouts of at least 15 minutes in a typical week. The resulting leisure score index (LSI) is a measure of total weekly leisure time physical activity of moderate and strenuous intensity. LSI scores can be used to rank individuals from highest to lowest physical activity levels or to classify respondents into sufficiently active (LSI > 24) or insufficiently active (LSI≤23) categories according to published guidelines.[45]

2.8 | Anthropometric measures

Height was measured using a stadiometer (SECA 285, Seca, Hamburg, Germany) and body mass using standard medical scales (AND UC-321 Precision Scale, A&D Company Limited, Saitama, Japan).[36] Body mass index (BMI) was calculated as weight/height^2. Waist circumference was measured in the horizontal plane at the superior border of the right iliac crest. The average of three measurements to the nearest 0.5 cm was recorded.[36]

2.9 | Exercise adherence and adverse events

Adherence was measured by the number of sessions attended during the 10-week intervention. Any adverse events were recorded and graded according to the Common Terminology Criteria for Adverse Events Version 4.[46]

2.10 | Sample size

A power calculation for sample size estimation, based on data from Jones et al.,[47] assumed a between-group equivalent effect size of d = 0.65 mL/kg/min for VO_{2peak} (considered to be medium using Cohen's criteria). With an alpha = 0.05 and power = 0.80, a sample of $n = 38$ in each of the control and intervention groups was required to detect this effect between the two groups at 10 weeks post baseline size for VO_{2peak} mL.kg^{-1}.min^{-1}.

2.11 | Randomization

Participants were randomly assigned to either the exercise intervention group or control group following baseline assessment. Participants were stratified according to gender and treatment intensity (high vs moderate; adapted from the Intensity of Treatment Rating Scale[3,48] (Supporting Information Table S2) and randomized by block randomization with a 1:1 allocation using mixed block sizes of 2 and 4. Allocation was concealed by opaque envelopes at the coordinating site.

2.12 | Statistical analysis

Continuous outcome variables were analyzed using a linear mixed-effects model to test for the effect of treatment at 10 weeks and 6 months after baseline. Each model included terms for time period (10 weeks, 6 months), treatment group (exercise group vs standard care), and the interaction of time period and treatment group, with control for the outcome measure at baseline. As gender and treatment intensity were used to stratify the randomization, these variables were also controlled for in the model. An unstructured covariance matrix was used to account for repeated measurements over time. Assumptions of a linear mixed-effects model were found to be upheld by inspection of histograms and scatter plots of residuals, variance, and predicted values. Treatment effects are described as mean differences at 10 weeks and 6 months with 95% confidence intervals.

3 | RESULTS

3.1 | Participants

One hundred eighty-one AYA cancer patients were assessed for eligibility: 43 consented to study, 20 declined, and 118 did not meet the inclusion criteria (Figure 1). The high screen failure rate largely related to the fact that one of the three recruiting centers offered exercise during cancer treatment as standard of care and listed all of these patients as assessed but ineligible. That site only recruited participants who were externally referred after completing their cancer treatment in neighboring hospitals. Specifically, of the 118 participants who did not meet the inclusion criteria, 70 participants had participated in an exercise intervention during active treatment, 20 declined participation, and 48 did not meet other eligibility criteria.

The median age was 20 ± 3 years, 47% were female, and the mean BMI was 25 ± 6 kg/m^2. The most common tumor type was Hodgkin lymphoma (37%). The mean number of days from the last dose of therapy to baseline assessment was 24 ± 10 days (Table 2).

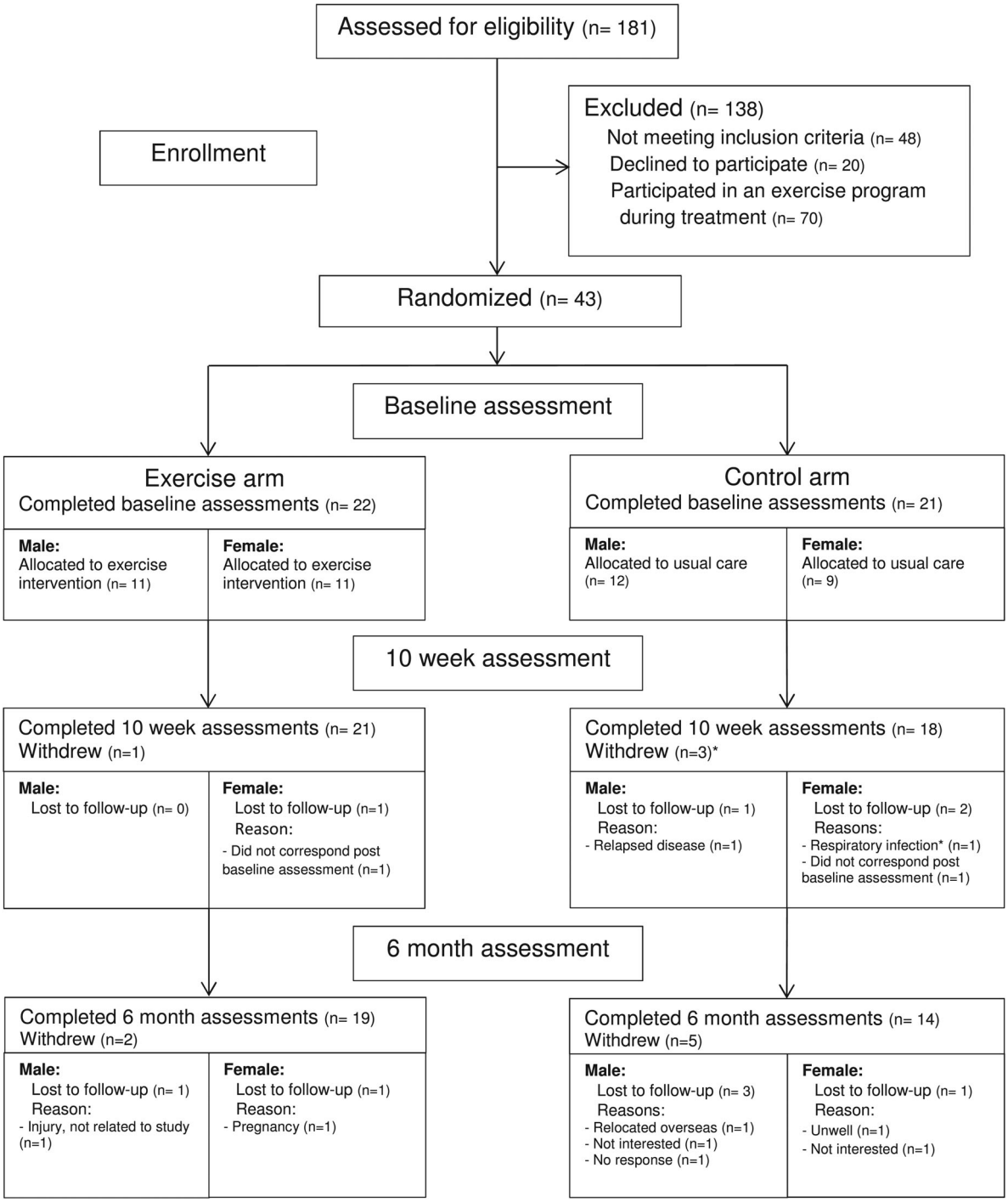

FIGURE 1 Flow chart of study protocol. *Unable to complete the 10 week assessment due to respiratory infection, completed 6 month assessment

3.2 | Cardiopulmonary fitness

CPET data at baseline, 10 weeks, and 6 months are presented in Table 3. Of the 115 tests conducted during the study, 114 (99%) were considered maximal intensity according to the ATS/ACCP guidelines.[33]

Mean VO_{2peak} at baseline prior to randomization was 26.5 $mL.kg^{-1}.min^{-1}$, with a mean percent predicted VO_{2peak} of 69% ± 15%. There was no significant difference between VO_{2peak} in the exercise versus control arms at baseline. At the 10-week follow-up, mean VO_{2peak} in the exercise versus control arm was 33.8 ± 8.1 vs 29.6 ± 7.6 $mL.kg^{-1}.min^{-1}$ ($P = 0.0002$) and percent predicted was 87.6% ± 12.5% vs 77.4% ± 16.9% ($P = 0.0012$); however, there were no significant differences at six months between groups.

TABLE 2 Baseline characteristics of participants ($n = 43$)

Variable	No.		%
Age mean ±SD, y		20 ± 3	
Female %	20		47
Weight, mean ± SD, kg		73 ± 16	
BMI, mean ± SD, kg/m^2		25 ± 6	
Diagnosis			
Sarcoma			12
Ewing sarcoma	3		
Synovial sarcoma	2		
Leukemia			9
Acute myeloid leukemia	1		
Acute promyelocytic leukemia	1		
Acute lymphoblastic leukemia	2		
Hodgkin lymphoma			37
Classical Hodgkin lymphoma	14		
Nodular lymphocyte predominant	2		
Non-Hodgkin lymphoma			21
Diffuse large B-cell	4		
Pre-B lymphoblastic lymphoma	1		
T-cell lymphoblastic lymphoma	1		
Burkitt lymphoma	1		
Gray zone lymphoma	1		
Follicular lymphoma	1		
Germ cell			19
Mixed germ cell tumor of the testis	3		
Ovarian germ cell tumor	2		
Retroperitoneal nonseminomatous	1		
Pineal germinoma	1		
Intracranial germinoma	1		
Other			2
Medulloblastoma	1		
Treatment intensity			
Moderate intensity	28		65
High intensity	15		35

Abbreviations: BMI, body mass index; SD, standard deviation; y, year.

3.3 | Strength and flexibility

Maximal push-ups was superior in the exercise group ($P = 0.015$) when compared with controls at 10 weeks; however, the benefit was not sustained at 6 months. All other strength and flexibility measures did not reach statistical significance (Table 4). Both groups demonstrated improvements in strength, muscular endurance, and flexibility across multiple outcome measures, including maximal back and leg strength, right and left grip strength, maximal sit-ups, hamstring flexibility, and right and left shoulder flexibility.

3.4 | Quality of life and fatigue

There were no significant differences in total QOL, domains of QOL, and fatigue between groups at 10 weeks or 6 months (Table 5). However, both groups demonstrated improvements in total QOL, and certain QOL domains including pain, nausea, cognitive, appearance, communication and worry, and fatigue.

3.5 | Leisure time physical activity

Both groups were considered to be insufficiently active at baseline as indicated by an LSI ≤23 (exercise 21.6 ± 31.9 vs control 21.6 ± 26.7). There was no significant difference in total leisure time physical activity according to the GSLTPAQ at 10 weeks ($P = 0.17$) and 6 months ($P = 0.61$). Both groups were sufficiently active as indicated by an LSI > 23 at the 10-week (41.4 ± 18.6 vs 32.9 ± 26.8) and 6-month assessments (34.4 ± 29.1 vs 34.3 ± 18.6).

3.6 | Anthropometric measures

At baseline, there were no significant differences between groups in mean height (171 vs 173 cm, $P = 0.29$), weight (71.0 ± 14.9 vs 76.1 ± 17.2 kg, $P = 0.0514$), or BMI (24.6 ± 6.3 vs 25.2 ± 4.6 kg/m^2, $P = 0.072$). There were no significant differences in body mass or BMI at 10 weeks; however, at 6 months there were significant differences in body mass (70.1 ± 11.3 kg vs 77.7 ± 12.5 kg [adjusted mean difference −3.7 95% CI, −6.40 to −1.00, $P = 0.0086$]) and BMI (24.1 ± 4.8 vs 26.0 ± 4.3 [adjusted mean difference −1.26, 95% CI, −2.13 to −0.38, $P = 0.0062$]) favoring the exercise arm.

3.7 | Exercise adherence and adverse events

The adherence rate to the exercise intervention was 90% (range, 70%-100%), with participants completing a mean of 18 ± 2 of the planned 20 sessions. Three participants required modifications to their exercise program (as described in Methods) due to physical limitations post-Ewing sarcoma treatment (one limb-salvage surgery of the humerus; two with weight-bearing restrictions).

Five minor adverse events were recorded during CPET (all grade 1) and one participant experienced an adverse event during PFT (grade 2). Adverse events included post-CPET nausea (two episodes), vomiting (two episodes), and one participant had a drop in systolic blood pressure > 20 mm Hg following CPET, which rapidly normalized with rest.

TABLE 3 Exercise capacity and pulmonary function ($n = 43$)

Variable	Time period	Exercise (mean STD)	Usual care (mean STD)	Adjusted mean difference (95% CI)[a]	P[b]
Age	Baseline	20.59 (3.2)	20.9 (2.6)		0.4874
Weight	Baseline	71.00 (14.96)	76.05 (17.22)		0.0514
BMI	Baseline	24.61 (6.30)	25.12 (4.66)		0.0720
VO_{2peak} mL . kg^{-1} . min^{-1}	Baseline	27.20 (7.11)	25.82 (7.38)		0.2431
	10 weeks	**33.84 (8.10)**	**29.61 (7.60)**	**4.06 (2.07, 6.06)**	**0.0002**
	6 months	32.88 (7.02)	30.95 (11.02)	2.26 (−1.37, 5.89)	0.2146
VO_{2peak} %Pred	Baseline	70.59 (13.39)	68.19 (16.49)		0.1174
	10 weeks	**87.57 (12.46)**	**77.39 (16.94)**	**8.63 (13.59, 3.67)**	**0.0012**
	6 months	85.79 (12.24)	84.14 (21.70)	3.17 (10.47, 4.14)	0.3844
RR @ Peak, breaths min^{-1}	Baseline	44.98 (8.95)	42.74 (10.08)		0.6350
	10 weeks	45.68 (11.32)	44.13 (11.06)	−0.50 (4.84, −5.83)	0.8507
	6 months	49.66 (26.54)	46.63 (9.30	2.75 (16.55, −11.04)	0.6874
Anaerobic threshold	Baseline	17.15 (4.17)	17.14 (6.32)		0.8384
	10 weeks	20.31 (5.79)	18.56 (6.92)	2.27 (−0.41, 4.96)	0.0947
	6 months	20.98 (6.43)	20.54 (7.76)	1.84 (−2.18, 5.85)	0.3596
VO_{2peak} L . min^{-1}	Baseline	1906 (408.71)	1973 (665.94)		0.0398
	10 weeks	**2347 (537.79)**	**2311 (704.58)**	**145 (283.28, 7.34)**	**0.0396**
	6 months	2293 (476.33)	2509 (810.28)	−88.45 (137, −314)	0.4317
Workload, watts	Baseline	158 (38.12)	167.38 (59.30)		0.0770
	10 weeks	**196 (47.91)**	**192.72 (62.04)**	**16.28 (26.45, 6.12)**	**0.0025**
	6 months	193 (43.48)	202.57 (72.04)	4.69 (19.20, 9.82)	0.5163
RER	Baseline	1.33 (0.12)	1.33 (0.11)		0.5517
	10 weeks	1.26 (0.07)	1.29 (0.09)	0.03 (0.02, 0.08)	0.2816
	6 months	1.27 (0.09)	1.27 (0.12)	0.01 (0.05, 0.07)	0.7600
$V_{E\ @peak}$ L . min^{-1}	Baseline	92.26 (21.96)	96.23 (38.78)		0.5965
	10 weeks	100.03 (33.39)	105.46 (42.28)	−3.11 (11.11,−17.34)	0.6592
	6 months	98.06 (29.69)	112.44 (39.26)	−6.87 (5.69, 19.43)	0.2740
Pulmonary function					
FEV_1, L	Baseline	3.53 (0.90)	3.98 (0.88)		
	10 weeks	3.57 (0.90)	4.05 (1.02)	−0.05 (0.11, 0.20)	0.5491
	6 months	3.63 (0.89)	4.03 (0.84)	0.00 (0.12, −0.12)	0.9721
FVC, L	Baseline	4.24 (1.23)	4.79 (1.31)		
	10 weeks	4.32 (1.22)	4.90 (1.29)	−0.08 (0.07, −0.22)	0.2926
	6 months	4.46 (1.23)	4.87 (1.19)	0.00 (0.13, −0.13)	0.9882
$D_{LCO\ (adj.)}$ mL . min^{-1} . mm Hg	Baseline	23.44 (6.21)	26.93 (8.29)		
	10 weeks	24.61 (6.11)	28.78 (7.76)	−0.86 (0.58, −2.31)	0.2327
	6 months	25.61 (6.02)	28.86 (6.87)	0.73 (−0.93, 2.40)	0.3753

Abbreviations: 95% CI, 95% confidence interval; BMI, body mass index; DLCO, diffusion capacity of the lung for carbon monoxide adjusted for alveolar ventilation; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; RER, respiratory exchange ratio; RR, respiratory rate; VE @peak, minute ventilation at peak exercise; VO_{2peak}, peak oxygen consumption.

[a]Exercise group versus control group. Model is adjusted for gender, treatment intensity, and outcome at baseline.

[b]The first row P value for each outcome is the interaction P value. Bold font indicates statistical significance.

TABLE 4 Strength and flexibility ($n = 43$)

Variable	Time period	Exercise (mean SD)	Usual care (mean SD)	Adjusted mean difference (95% CI)[a]	P[b]
Max back leg strength	Baseline	96.55 (29.67)	91.90 (43.00)		0.0084
	10 weeks	114.00 (33.62)	103.33 (46.14)	5.47 (−8.55, 19.49)	0.4333
	6 months	117.58 (35.22)	118.21 (52.54)	−8.51 (−23.12, 6.10)	0.2446
Max grip strength right	Baseline	36.77 (9.52)	36.05 (16.31)		0.0433
	10 weeks	40.10 (9.52)	40.26 (17.74)	−0.55 (−4.47, 3.38)	0.7795
	6 months	39.63 (10.62)	42.96 (18.42)	−4.02 (−9.15, 1.10)	0.1200
Max grip strength left	Baseline	35.35 (9.92)	36.83 (14.24)		0.3049
	10 weeks	37.58 (9.62)	39.49 (13.85)	−0.17 (−2.95, 2.61)	0.9025
	6 months	38.75 (9.90)	41.64 (13.50)	−1.50 (−4.60, 1.60)	0.3324
Max sit-ups	Baseline	11.55 (8.53)	14.29 (10.90)		0.4519
	10 weeks	19.00 (12.58)	18.17 (10.43)	3.85 (−1.83, 9.53)	0.1776
	6 months	20.84 (12.13)	21.50 (11.58)	1.87 (−5.32, 9.07)	0.6004
Max push-ups	Baseline	12.73 (9.91)	11.38 (9.52)		0.6360
	10 weeks	**21.33 (11.00)**	**15.22 (12.95)**	**5.29 (1.11, 9.46)**	**0.0146**
	6 months	23.68 (10.04)	19.43 (12.80)	4.36 (−1.50, 10.23)	0.1401
Hamstring flexibility	Baseline	16.43 (13.69)	17.74 (7.06)		0.0749
	10 weeks	21.19 (11.23)	20.50 (8.37)	1.29 (−2.90, 5.47)	0.5373
	6 months	21.53 (11.65)	24.68 (8.21)	−1.40 (−6.22, 3.43)	0.5606
Back scratch right	Baseline	−3.14 (7.72)	−2.60 (7.51)		0.1348
	10 weeks	−4.26 (7.38)	−3.31 (7.23)	−0.01 (−3.06, 3.04)	0.9936
	6 months	−6.11 (4.95)	−2.43 (7.92)	−2.16 (−5.63, 1.30)	0.2130
Back scratch left	Baseline	1.68 (8.32)	0.62 (8.89)		0.6656
	10 weeks	−0.29 (8.22)	1.81 (7.71)	−1.95 (−5.55, 1.64)	0.2779
	6 months	−1.13 (8.11)	0.89 (7.17)	−1.26 (−4.07, 1.54)	0.3660

Note. Max back and leg strength measured using Baseline Back-Leg-Chest Dynamometer; max grip strength measured using a Saehan, SH5001 grip dynamometer on the right and left hand; max sit ups indicates maximal sit ups in 60 seconds; max push up indicates maximal push up; hamstring flexibility measured using a Flex-Tester Sit and Reach Flexibility Test Box; back scratch test measured using a 30 cm ruler on the right and left arm.
Abbreviations: 95% CI, 95% confidence interval; SD, standard deviation.
[a]Exercise group versus control group. Model is adjusted for gender, treatment intensity, and outcome at baseline.
[b]The first row *P* value for each outcome is the interaction *P* value. Bold font indicates statistical significance.

One participant experienced a spontaneous nosebleed during PFT. No adverse events occurred during supervised exercise sessions. Six participants were referred for cardiology review due to arrhythmias or abnormal responses to exercise during CPET that were hitherto undetected, including one participant with transient ST elevation. No treatment was required.

4 | DISCUSSION

The primary finding of this study was that a 10-week structured exercise program was associated with a highly significant improvement in VO_{2peak} in AYA who had recently completed cancer treatment. However, the extent of this difference diminished by the six-month assessment. This suggests that such an exercise program accelerates improvement in cardiorespiratory fitness following cancer treatment.

Before discussing the primary outcome further, one of our most striking findings was the extent of deconditioning at baseline assessment. The mean VO_{2peak} at baseline for our entire cohort (26.5 $mL.kg^{-1}.min^{-1}$) was below the fifth percentile for age- and sex-matched normative data from the general population. Specifically, it was more than 40% lower than the median VO_{2peak} for healthy 20-29-year-olds without a history of cancer (54 ± 8.7 $mL.kg^{-1}.min^{-1}$ for men; 42.9 ± 7.6 $mL.kg^{-1}.min^{-1}$ for women), and more than 30% lower than that seen in inactive healthy 20-29-year-olds (i.e., those exercising less than once per week or never; men 46.9 ± 9.1 $mL.kg^{-1}.min^{-1}$, women 36.7 ± 7.7 $mL.kg^{-1}.min^{-1}$).[49] The baseline mean VO_{2peak} for our AYA cancer cohort was lower than the results observed in cystic fibrosis and other chronic diseases, and was similar to that of sedentary persons aged in their seventies.[49,50] Schneider and colleagues observed comparable impairments in the cardiorespiratory fitness of young adult cancer survivors,[6] reporting that the average VO_{2peak}

TABLE 5 Quality of life and fatigue ($n = 43$)

Quality-of-life domain	Time period	Exercise arm mean SD	Control arm mean SD	Adjusted mean difference (95% CI)[a]	P[b]
Pain	Baseline	68.18 (23.69)	61.90 (22.87)		0.6364
	10 weeks	82.74 (13.96)	73.03 (23.30)	9.59 (−2.32, 21.50)	0.1110
	6 months	81.25 (23.47)	78.57 (18.62)	6.13 (−8.29, 20.55)	0.3939
Nausea	Baseline	58.41 (26.43)	63.10 (24.31)		0.6556
	10 weeks	86.19 (16.35)	79.74 (20.03)	7.46 (−4.37, 19.30)	0.2090
	6 months	90.00 (15.13)	82.14 (23.59)	9.67 (−3.22, 22.57)	0.1367
Procedural anxiety	Baseline	78.79 (21.01)	80.56 (21.62)		0.5333
	10 weeks	83.33 (19.54)	89.04 (19.45)	−5.45 (−14.79, 3.89)	0.2440
	6 months	80.00 (26.55)	91.67 (20.41)	−8.04 (−20.22, 4.14)	0.1889
Treatment anxiety	Baseline	77.65 (25.64)	76.59 (27.59)		0.6560
	10 weeks	76.19 (26.52)	78.51 (28.37)	−3.88 (−13.77, 6.01)	0.4312
	6 months	73.33 (30.66)	85.12 (22.45)	−6.78 (−20.36, 6.81)	0.3180
Worry	Baseline	53.03 (27.76)	58.33 (24.44)		0.8893
	10 weeks	63.10 (20.00)	61.40 (30.71)	5.01 (−7.59, 17.62)	0.4250
	6 months	67.50 (26.06)	69.64 (22.07)	3.83 (−9.44, 17.09)	0.5618
Cognitive	Baseline	72.05 (18.17)	66.19 (24.95)		0.8977
	10 weeks	76.90 (17.06)	73.95 (25.85)	−1.88 (−10.90, 7.15)	0.6755
	6 months	74.50 (22.41)	70.00 (21.84)	−1.07 (−12.73, 10.60)	0.8540
Appearance	Baseline	65.53 (29.80)	61.90 (30.80)		0.4739
	10 weeks	70.24 (26.30)	64.47 (28.98)	2.73 (−8.36, 13.81)	0.6207
	6 months	75.42 (27.90)	67.26 (28.95)	7.37 (−5.60, 20.35)	0.2566
Communication	Baseline	76.14 (21.87)	74.21 (23.56)		0.8052
	10 weeks	80.16 (19.63)	73.25 (29.86)	4.38 (−7.16, 15.92)	0.4464
	6 months	80.83 (21.98)	77.98 (25.45)	3.12 (−9.19, 15.44)	0.6098
PEDS QL total score	Baseline	20.36 (5.10)	20.10 (5.37)		0.8828
	10 weeks	22.92 (4.27)	21.98 (6.08)	0.66 (−1.47, 2.80)	0.5337
	6 months	23.07 (5.43)	23.05 (4.78)	0.80 (−1.63, 3.24)	0.5075
FACIT fatigue subscore	Baseline	38.23 (10.41)	32.95 (10.92)		0.0354
	10 weeks	44.62 (9.64)	42.00 (10.24)	−0.43 (−5.68, 4.81)	0.8673
	6 months	41.35 (10.28)	45.43 (6.56)	−4.63 (−11.01, 1.75)	0.1496

Abbreviations: 95% CI, 95% confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; PEDSQL Pediatric Quality of Life Inventory; SD, standard deviation.

[a]Exercise group versus control group. Model is adjusted for gender, treatment intensity, and outcome at baseline.

[b]The first row *P* value for each outcome is the interaction *P* value.

for 19-39-year-olds after treatment was 23.8-26.7 $mL.kg^{-1}.min^{-1}$ for females and 25.0-27.6 $mL.kg^{-1}.min^{-1}$ for males. This degree of impairment is comparable to that observed post-cancer treatment in older adults.[51] Moreover, studies of older adults and adult survivors of childhood cancer have consistently demonstrated that impaired cardiorespiratory fitness persists long after treatment, and is associated with increased mortality, highlighting the importance of recognizing and addressing this potentially modifiable risk factor.[5,51]

The magnitude of the exercise-induced improvement in cardiorespiratory fitness in our study was at least comparable to that reported for exercise interventions in older adult cancer survivors.[27,50] Specifically, a systematic review in adult cancer patients with a mean ± SD age of 55 ± 7.5 years reported that exercise therapy was associated with an increase in VO_{2peak} of 2.80 $mL.kg^{-1}.min^{-1}$,[28] whereas our exercise participants exhibited an increase of 6.64 $mL.kg^{-1}.min^{-1}$ between baseline and 10-week measures. Although studies of older adults usually report no improvement or a decline in the control group's VO_{2peak},[28,51] our control group unexpectedly improved by 3.79 $mL.kg^{-1}.min^{-1}$. This surprising improvement may be explained by our study design not restricting controls from exercising, and indeed the GSLTPAQ results indicated that controls increased their leisure

time physical activity from baseline to 10-week assessment, although not to the same degree as the exercise intervention group. Ultimately, the difference in VO_{2peak} between exercise participants and controls at 10 weeks (2.85 $mL.kg^{-1}.min^{-1}$) was comparable to the between-group difference of 2.13 $mL.kg^{-1}.min^{-1}$ reported in a meta-analysis of exercise studies involving older adult cancer survivors.[28]

Although both of our groups exhibited an increase in VO_{2peak} at 10 weeks, the greater degree of improvement in VO_{2peak} in the exercise arm may result from the receipt of a structured program. The benefit of a structured program may relate to greater accountability and/or motivation, opportunity for additional exercise, and the AEP's expertise in individualizing therapy and progressively increasing the intensity of exercise.[16]

It is interesting to note that the difference in VO_{2peak} between groups at 10 weeks was no longer evident by 6 months. Specifically, the exercise group's VO_{2peak} plateaued between 10 weeks and 6 months, whereas the controls' VO_{2peak} continued to improve such that both groups had comparable cardiorespiratory function by 6 months. This suggests that the exercise program accelerated recovery, but that this trajectory was not sustained over time. Even if the two groups ultimately achieved a similar measure of cardiorespiratory function, an earlier recovery may facilitate a more rapid return to physically demanding activities that are important to AYA such as employment, education, and peer activities.[52,53] Despite the improvement in VO_{2peak} at six-month follow-up (exercise 32.88 ± 7.02 $mL.kg^{-1}.min^{-1}$ vs control 30.95 ± 11.02 $mL.kg^{-1}.min^{-1}$), both groups remained not only below age-matched population norms (men, 54 ± 8.7 $mL.kg^{-1}.min^{-1}$; women, 42.9 ± 7.6 $mL.kg^{-1}.min^{-1}$), but also below the population norms for inactive healthy young adults (men, 46.9 ± 9.1 $mL.kg^{-1}.min^{-1}$; women, 36.7 ± 7.7 $mL.kg^{-1}.min^{-1}$).[49] This observation together with the plateau in VO_{2peak} after completing the exercise program indicates that a maintenance exercise program should be investigated to determine whether continued improvement can be achieved.

Despite the exercise arm demonstrating a substantially better VO_{2peak} at 10 weeks compared with controls, the trend toward better muscular strength in the exercise group did not reach statistical significance. This may indicate that the intensity of our resistance training was insufficient, and perhaps needed to include assessment of 1RM as opposed to 10RM and higher training intensities at the start of the exercise program. Despite overall improvements in muscular strength, grip strength in our cohort remained below population reference values (male 47 ± 9.5 kg, female 30 ± 7 kg, right hand). Impaired grip strength is associated with physical frailty and increased mortality from cardiovascular disease.[54]

Some studies in older adult cancer survivors have demonstrated exercise-related improvements in QOL and fatigue,[10,17,44,55] although this has not been consistent.[56] We did not observe significant differences in QOL (total score or within QOL domains) or fatigue scores between groups at the 10-week or 6-month assessment, although our study was not powered to demonstrate a change in these measures. Additionally, the fact that our control arm recorded a similar volume of leisure time physical activity to the intervention arm (as indicated by the GSLTPAQ) at the six-month assessment and demonstrated improvements in VO_{2peak} superior to control groups in other studies may explain why both groups exhibited similar improvements in QOL and fatigue scores. Because aerobic exercise is more effective than combined aerobic and resistance exercise for cancer-related fatigue in older adults,[57] future studies addressing fatigue in AYA could focus on aerobic exercise rather than our combined approach.

The high adherence and low adverse event rates observed in our study indicate that a structured exercise program is acceptable, safe, feasible, and well tolerated in AYA soon after cancer treatment. However, as highlighted by our CONSORT diagram (Figure 1), a large number of patients were excluded due to either cancer-related physical disability or a preference for an exercise intervention during rather than after treatment. Consequently, future research priorities include developing alternative approaches for individuals whose disability precludes participation in conventional exercise programs, and evaluating the safety and feasibility of AYA undertaking exercise programs during active treatment.

A strength of the study was the use of CPET testing with VO_{2peak} analysis as the primary outcome measure. Efforts to minimize bias included blinding outcome assessors to the randomization outcome, ensuring similarity of groups at baseline by stratifying according to treatment intensity and gender, and standardization of the intervention. The study also had a high level of adherence and, although we experienced 23% attrition by six months, there was only 10% attrition for the primary outcome assessment at 10 weeks. Unlike many adult studies, measures of safety and fidelity were reported. In particular, six participants were referred to cardiology after detection of hitherto unrecognized arrhythmias or abnormal responses to exercise during CPET. Given the risk of cardiovascular late effects in AYA,[9] future studies may investigate whether CPET assessment could facilitate early identification of treatment-related cardiac dysfunction.

Several limitations need to be considered. Due to many potential patients preferring to participate in an exercise program during treatment, our study was unable to recruit the number of participants required to achieve appropriate power. This may have particularly affected the six-month comparison, which suffered from 23% attrition. Low patient numbers have been a common deficiency in most published studies of exercise in children and young adults.[23] Additionally, because cancer in AYA is infrequent, we elected to recruit a mixture of cancer types. Despite attempting to stratify for treatment intensity, this heterogeneity still may have affected the results. Also, the nature of the study may have attracted participants with a preexisting positive attitude to exercise. This may have influenced the volume of leisure time physical activity performed by the control arm. Given that our control arm reported more leisure time physical activity than previous studies of AYA cancer patients,[13] we speculate that our controls' results may overestimate the cardiorespiratory fitness of patients receiving usual care.

In conclusion, this study demonstrated that a structured 10-week exercise program improved VO_{2peak} more rapidly in AYA who had recently completed cancer treatment. However, this improvement plateaued such that results were similar to controls by six months,

suggesting that a continuing maintenance exercise program warrants investigation. Baseline VO_{2peak} in our entire cohort was considerably lower than expected for age, and, despite both groups improving, the six-month results remained below population norms. Future studies should investigate whether exercise during cancer treatment in AYA may offset this degree of deconditioning. Additionally, alternative approaches are warranted for AYA who are unable to participate in conventional exercise programs due to their cancer- or treatment-related disability.

CONFLICTS OF INTEREST

None declared.

DATA SHARING

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ACKNOWLEDGMENTS

The authors would like to acknowledge the funding support provided by the Australian and New Zealand Children's Haematology/Oncology Group Concept Validation Scheme, the Royal Adelaide Hospital Research Foundation, and CanTeen Australia. The authors would also like to thank Associate Professor Carol Maher from the University of South Australia for assisting with interpreting results and preparation of the manuscript, and acknowledge the additional in-kind support provided by staff at the Women's and Children's Hospital, Royal Adelaide Hospital, and the Peter MacCallum Cancer Centre.

ORCID

Morgan Atkinson https://orcid.org/0000-0002-7713-8361
Andrew Murnane https://orcid.org/0000-0002-5992-9311
Thomas Goddard https://orcid.org/0000-0002-7062-843X
Michael Osborn https://orcid.org/0000-0002-1288-9930

REFERENCES

1. Australian Institute of Health and Welfare 2018. Cancer in adolescents and young adults in Australia. Cat. no. CAN 110. Canberra: AIHW. https://www.aihw.gov.au/reports/cancer/cancer-adolescents-young-adults/contents/table-of-contents. Published 18 April, 2018. Accessed June 11, 2019.
2. Keegan TH, Ries LA, Barr RD, et al. Comparison of cancer survival trends in the United States of adolescents and young adults with those in children and older adults. *Cancer*. 2016;122(7):1009-1016.
3. Hayashi RJ. Adolescent and young adult cancer survivorship: the new frontier for investigation. *Cancer*. 2019;125(12):1976-1978.
4. Fidler MM, Frobisher C, Hawkins MM, et al. Challenges and opportunities in the care of survivors of adolescent and young adult cancers. *Pediatr Blood Cancer*. 2019. 66e27668. https://doi.org/10.1002/pbc.27668.
5. Ness KK, Plana JC, Joshi VM, et al. Exercise intolerance, mortality, and organ system impairment in adult survivors of childhood cancer. *J Clin Oncol*. 2020;38:29-42. https://doi.org/10.1200/JCO.19.01661
6. Schneider CM, Repka CP, Lalonde TL, et al. Demonstration of the need for cardiovascular and pulmonary normative data for cancer survivors. *Int J Sports Med*. 2014;35:1134-1137
7. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine round table on exercise guidelines for cancer patients. *Med Sci Sports Exerc*. 2010;42(7):1409-1426.
8. Koelwyn GJ, Khouri M, Mackey JR, et al. Running on empty: cardiovascular reserve capacity and late effects of the therapy in cancer survivorship. *J Clin Oncol*. 2012;30(36):4456-4461.
9. Chao C, Xu L, Bhatia S, et al. Cardiovascular disease risk profiles in survivors of adolescent and young adult (AYA) cancer: the Kaiser Permanente AYA cancer survivors study. *J Clin Oncol*. 2016;34(14):1626-1633.
10. Cormie P, Zopf EM, Zhang X, Schmitz KH The impact of exercise on cancer mortality, recurrence and treatment-related adverse effects. *Epidemiol Rev*. 2017;39(1):71-92.
11. Smith AW, Bellizzi KM, Keegan TH, et al. Health-related quality of life in adolescent and young adult patients with cancer in the United States: the Adolescent and Young Adult Health Outcomes and Patient Experience study. *J Clin Oncol*. 2013;31:2136-2145
12. Daniel L, Kazak AE, Li Y, et al. Relationship between sleep problems and psychological outcomes in adolescent and young adult cancer survivors and controls. *Support Care Cancer*. 2016;24:539-546.
13. Murnane A, Gough K, Thompson K, et al. Adolescents and young adult cancer survivors: exercise habits, QOL and physical activity preferences. *Support Care Cancer*. 2015;23(2):501-510.
14. Munsie C, Ebert J, Joske D, et al. The benefit of physical activity in adolescent and young adult cancer patients during and after treatment: a systematic review. *J Adolesc Young Adult Oncol*. 2019;8(5):512-524. https://doi.org/10.1089/jayao.2019.0013.
15. Cormie P, Peddle-McIntyre C, Hayes S, et al. Exercise and cancer survivorship. *Cancer Forum*. 2015;39(2):105-112.
16. Cormie P, Atkinson M, Bucci L, et al. Clinical Oncology Society of Australia position statement on exercise in cancer care. *Med J Aust*. 2018;209(4):184-187.
17. Fuller JT, Hartland MC, Maloney LT, et al. Therapeutic effects of aerobic and resistance exercises for cancer survivors: a systematic review of meta-analyses of clinical trials. *Br J Sports Med*. 2018;52:1311. https://doi.org/10.1136/bjsports-2017-098285
18. Bleyer A. Young adult oncology: the patients and their survival challenges. *CA Cancer J Clin*. 2007;57:242-255.
19. Wurz A, Brunet J. The effects of physical activity on health and QOL in adolescent cancer survivors: a systematic review. *JMIR Cancer*. 2016;24(1):1-11. https://doi.org/10.2196/cancer.5431.
20. Belanger LJ, Plotnikoff RC, Clark A, et al. A survey of physical activity programming and counselling preferences in young-adult cancer survivors. *Cancer Nurs*. 2012;35(1):48-54.
21. Belanger L, Plotnikoff R, Clark A, Courneya KS. Physical activity and health-related QOL in young adult cancer survivors: a Canadian provincial survey. *J Cancer Surviv*. 2011;5(1):44-53.
22. Murnane A, Thompson K, Mancuso S, Lewin J, Orme L. Exploring the effect of exercise physiology intervention among adolescent and young adults diagnosed with cancer. *Rehabil Oncol*. 2019;37(2):55-63
23. Braam KI, van der Torre P, Takken T, et al. Physical exercise training interventions for children and young adults during and after treatment for childhood cancer. *Cochrane Database Syst Rev*. 2016;3:1-61. https://doi.org/10.1002/14651858.CD008796.pub3.
24. Huang TT, Ness KK. Exercise interventions in children with cancer: a review. *Int J Pediatr*. 2011; 2011:461512.
25. Corr AM, Liu W, Bishop M, et al. Feasibility and functional outcomes of children and adolescents undergoing preoperative chemotherapy prior to a limb-sparing procedure or amputation. *Rehabil Oncol*. 2017;35:38-45.

26. Müller C, Winter C, Boos J, et al. Effects of an exercise intervention on bone mass in pediatric bone tumor patients. *Int J Sports Med*. 2014;35:696-703.
27. Jones LW, Eves ND, Haykowsky M, Joy AA, Douglas PS. Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. *Lancet Oncol*. 2008;9(8):757-765.
28. Scott JM, Zabor EC, Schwitzer E, et al. Efficacy of exercise therapy on cardiorespiratory fitness in patients with cancer: a systematic review and meta-analysis. *J Clin Oncol*. 2018;36(22):2297-2305. https://doi.org/10.1200/JCO.2017.77.5809.
29. Australian Government, Cancer Australia, *CanTeen. National Service Delivery Framework for Adolescents and Young Adults with Cancer*. Commonwealth of Australia, Canberra. https://canceraustralia.gov.au/sites/default/files/publications/national_service_delivery_framework_for_adolescents_and_young_adults_with_cancer_teen_52f301c25de9b.pdf. Published 2008. Accessed June 26, 2019.
30. Altman DG, Schulz KF, Moher D, et al. CONSORT GROUP (Consolidated Standards of Reporting Trials) The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med*. 2001;134(8):663-694.
31. Hayes SC, Newton RU, Spence RR, Galvão DA. The Exercise and Sports Science Australia position statement: exercise medicine in cancer management. *J Sci Med Sport*. 2019;22:1175-1199.
32. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. 1982;14:377-381.
33. Weisman IM. ATS/ACCP statement on the cardiopulmonary exercise testing. *Am J Respir Care Med*. 2003;167(2):211-277.
34. Miller MR, Crapo R, Hankinson J, et al. SERIES "ATS/ERS task force: standardisation of lung function testing" number 1 in this Series General considerations for lung function testing. *Eur Respir J*. 2005;26:153-161. https://doi.org/10.1183/09031936.05.00034505
35. Cooper DM, Weiler-Ravell D, Whipp BJ, et al. Growth-related changes in oxygen uptake and heart rate during progressive exercise in children. *Pediatr Res*. 1984;18(9):845-851.
36. Marlow N, Hastings K, Hansson J. *Exercise and Sports Science Australia's Outcome Measures for Exercise Physiologists: Ensuring Evidence-Based Practice*. Brisbane, Australia: Exercise and Sports Science Australia; 2014.
37. Reese NB, Brandy WD. *Joint Range of Motion and Muscle Length Testing*. 2nd ed. MI: Saunders Elsevier; 2010:47-79.
38. Rikli RE, Jones CJ. *Senior Fitness Test Manual*. Australia: Human Kinetics; 2001.
39. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med*. 2016;15:155-163.
40. Miller MR, Hankinson J, Brusasco V, et al. Series "ATS/ERS task force: standardisation of lung function testing" Edited by V. Brusasco, R. Crapo and G. Viegi. Number 2 in this Series Standardisation of spirometry. *Eur Respir J*. 2005;26:319-338.
41. Moore VC. Spirometry: step by step. *Breathe*. 2012;8(3):232-240.
42. MacIntyre N, Crapo RO, Viegi G, et al. Series "ATS/ERS task force: standardisation of lung function testing". Edited by V. Brusasco, R. Crapo and G. Viegi. Number 4 in this Series Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J*. 2005;26:720-735.
43. Ewing JE, King MT, Smith NF. Validation of modified forms of the PedsQL generic core scales and cancer module scales for adolescents and young adults (AYA) with cancer or a blood disorder. *Qual Life Res*. 2009;18:231-244. https://doi.org/10.1007/s11136-008-9424-4.
44. Storic L, Linder J, Kane L, Foster C, Gugliotti M. Does exercise provide a positive therapeutic effect for patients with cancer related fatigue?: a systematic review. *Rehabil Oncol*. 2013;31(4):14-22.
45. Amireault S, Godin G, Lacombe J, Sabiston CM. The use of the Godin-Shephard leisure-time physical activity questionnaire in oncology research: a systematic review. *BMC Med Res Methodol*. 2015;15(60);1-11. https://doi.org/10.1186/s12874-015-0045-7.
46. National Cancer Institute. *Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events*. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm. Published June 14 2010. Accessed January 29, 2019.
47. Jones LW, Peddle CJ, Eves ND, et al. Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. *Cancer*. 2007;1;110(3):590-598.
48. Kazak AE, Hocking MC, Ittenbach RF, et al. A revision of the intensity of treatment rating scale: classifying the intensity of pediatric cancer treatment. *Pediatr Blood Cancer*. 2012;59(1):96-99.
49. Aspenes ST, Nilsen TIL, Skaug EA, et al. Peak oxygen uptake and cardiovascular risk factors in 4631 healthy women and men. *Med Sci Sports Exerc*. 2011;43(8):1465-1473. https://doi.org/10.1249/MSS.0b013e31820ca81c.
50. Torvanger O, Os A, Skjønsberg OH, Edvardsen E Cardiorespiratory fitness in an adult Norwegian cystic fibrosis population. *Eur Respir J*. 2018;52: https://doi.org/10.1183/13993003.congress-2018.PA1320
51. Jones LW, Liang Y, Pituskin EN, et al. Effect of exercise training on peak oxygen consumption in patients with cancer: a meta-analysis. *Oncologist*. 2011;16:112-120.
52. Parsons HM, Harlan LC, Lynch CF, et al. Impact of cancer on work and education among adolescent and young adult cancer survivors. *J Clin Oncol*. 2012;30:2393-2400.
53. Husson O, Zebrack BJ, Aguilar C, et al. Cancer in adolescents and young adults: who remains at risk of poor social functioning over time? *Cancer*. 2017:123:2743-2751.
54. Massy-Westropp NM, Gill TK, Taylor AW, Bohannon RW, Hill CL Hand grip strength: age and gender stratified normative data in a population-based study. *BMC Research Notes*, 2011;4:127.
55. Oberoi S, Robinson PP, Cataudella D, et al. Physical activity reduces fatigue in patients with cancer and hematopoietic stem cell transplant recipients: a systematic review and meta-analysis of randomized trials. *Crit Rev Oncol Hematol*. 2018;122:52-59.
56. Mishra SI, Scherer RW, Geigle P, et al. Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst Rev*. 2012;Issue 8:CD007566. https://doi.org/10.1002/14651858.CD007566.pub2.
57. Kessels E, Husson O, van der Feltz-Cornelis CM. The effect of exercise on cancer-related fatigue in cancer survivors: a systematic review and meta-analysis. *Neuropsychiatr Dis Treat*. 2018;14:472-494.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Atkinson M, Murnane A, Goddard T, et al. A randomized controlled trial of a structured exercise intervention after the completion of acute cancer treatment in adolescents and young adults. *Pediatr Blood Cancer*. 2020;e28751. https://doi.org/10.1002/pbc.28751