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What are the effects of exercise training in childhood cancer survivors? A systematic review

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Abstract
This systematic review aimed to summarize evidence on the effects of physical exercise interventions in childhood cancer survivors (CCS) who had finished anticancer therapy ≥ 1 year before the study. Relevant articles were identified in the electronic databases PubMed, Web of Science, and SPORTDiscus (from inception to June 27, 2019). The PEDro scale was used to assess methodological quality. Twelve studies including 109 CCS met all inclusion criteria and were included in the systematic review. The quality of the included studies was overall low. Physical exercise improved endothelial function, reduced waist circumference, and waist-to-hip ratio and increased physical activity levels. Preliminary evidence was found regarding benefits on brain volume and structure after exercise interventions in childhood brain tumor survivors. Only two studies reported exercise-related adverse events. Physical exercise seems to be safe and effective for improving several health markers in CCS, but further high-quality research and especially randomized controlled trials are needed to confirm these results.

Keywords Endothelial function · Exercise is medicine · Cardiometabolic health · Brain health · Physical activity

1 Introduction

Treatment strategies for childhood cancer have improved considerably over the last decades, as reflected by a 5-year survival rate of ~ 80% [1]. As a consequence, the prevalence of childhood cancer survivors (CCS) continues to rise, and the total number of CCS is estimated to reach 500,000 in the USA by 2020 [2]. However, despite treatment advances and improvements in survival rates, CCS frequently experience adverse events related to the disease and its treatment, of which many can persist after treatment has ended (e.g., impaired left ventricular function and low and high levels of HDL cholesterol and adiposity, respectively) [3]. Thus, the development of interventions to counteract the adverse effects of cancer and its treatment is clinically relevant.

There is a strong rationale to expect that physical exercise interventions help reduce the side effects of cancer treatment in CCS, as well as to attenuate the functional decline commonly observed in this population, as supported by meta-analytical evidence [4, 5]. In line with these findings, higher levels of vigorous exercise after cancer treatment have been recently associated with a lower risk of mortality in adult CCS [6]. Two meta-analysis studies have previously assessed the effects of exercise interventions in CCS, but both of them included participants who were still under treatment or who had recently finished the treatment (< 1 year) [5, 7]. Thus, the evidence is inconclusive regarding the role of physical exercise as a lifestyle intervention to mitigate cancer-/treatment-related adverse effects in CCS who are off treatment. In the present study, we aimed to systematically review the evidence available on the effects of exercise training intervention (duration ≥ 4 weeks) in CCS after the first year after finishing treatment.

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2 Patients and methods

2.1 Literature search

Relevant articles written in English were identified and preliminarily screened by title and abstract in the electronic databases PubMed, Web of Science, and SPORTDiscus (from inception to June 27, 2019). Keywords were (child* OR adolescen* OR pediatric) AND (exercise OR "physical activity" OR training) AND (cancer OR tumor OR neoplasm OR maligna* OR leukemia OR leukaemia OR oncology). We also checked the bibliography of potentially relevant studies and reviews to find additional publications on the subject. Gray literature (e.g., abstracts, conference proceedings, and editorials) and reviews were excluded.

2.2 Study selection and data extraction

Two authors (J.S.M. and P.L.V.) independently performed the study selection, and disagreements were resolved by discussion with a third reviewer (A.M.H-O.). We only included in the systematic review those studies meeting each of the following criteria: (i) assessing CCS who had finished anticancer therapy ≥ 1 year before the study, (ii) including an exercise intervention of ≥ 4 weeks composed of aerobic and/or strength exercises, and (iii) including a pre- and post-intervention assessment performed upon completion of the exercise intervention. Having a control group (i.e., a group performing no exercise) was not required for a study to be included. Case studies were excluded from the analyses. Articles initially selected by systematic search were preliminarily screened by title and abstract. The full text of those studies that met the inclusion criteria was assessed to elucidate their eligibility.

We collected the following data from each study, if available: number, sex and age of participants, main cancer characteristics (cancer type, age at diagnosis, time since diagnosis and treatment, time of remission, and anticancer treatment received), interventions' characteristics, endpoints assessed, and main study results.

2.3 Quality assessment of the included studies

Study quality was evaluated with the PEDro scale, which is based on the Delphi list [8]. Two authors (J.S.M. and A.C.G.) independently scored the studies, and disagreements were resolved by discussion with a third author (A.M.H-O.). A total score out of 10 was determined by counting the number of criteria satisfied by each study (criteria are detailed in Table 1).

Table 1 Quality of the studies included in the systematic review

Items												
Study	1	2	3	4	5	6	7	8	9	10	11	Total score*
Dubnov-Raz et al. [9]	+	–	N/A	+	–	–	–	+	?	+	+	4
Järvelä et al. [10]	+	N/A	N/A	N/A	N/A	N/A	N/A	+	?	N/A	+	2
Järvelä et al. [11]	+	N/A	N/A	N/A	N/A	N/A	N/A	+	?	N/A	+	2
Järvelä et al. [12]	+	N/A	N/A	N/A	N/A	N/A	N/A	+	?	N/A	+	2
Kim and Park [13]	+	N/A	N/A	N/A	N/A	N/A	N/A	+	?	N/A	+	2
Long et al. [14]	+	–	–	–	–	–	–	+	?	+	+	3
Piscione et al. [15]	+	+	+	–	–	–	–	+	?	+	+	5
Rath et al. [16]	+	–	–	N/A	–	–	–	–	?	N/A	+	1
Riggs et al. [17]	+	+	+	–	–	–	–	+	?	+	+	5
Smith et al. [18]	+	N/A	N/A	N/A	N/A	N/A	N/A	+	?	N/A	–	1
Szulc-Lerch et al. [19]	+	+	+	–	–	–	–	+	?	+	+	5
Takken et al. [20]	+	N/A	N/A	N/A	N/A	N/A	N/A	–	?	N/A	–	0

Column numbers correspond to the following criteria on the PEDro scale:

1: eligibility criteria were specified; 2: subjects were randomly allocated to groups (or, in a crossover study, subjects were randomly allocated an order in which treatments were received); 3: allocation was concealed; 4: groups were similar at baseline; 5: subjects were blinded; 6: therapists who administered the treatment were blinded; 7: assessors were blinded; 8: measures of key outcomes were obtained from more than 85% of subjects; 9: data were analyzed by intention-to-treat; 10: statistical comparisons between groups were conducted; 11: point measures and measures of variability were provided

* A total score out of 10 is determined from a number of criteria that are satisfied, except that scale item 1 is not used to generate the total score

"+" indicates the criterion was clearly satisfied; "–" indicates that it was not; "?" indicates that it is not clear whether the criterion was satisfied; *N/A* not applicable

3 Results

3.1 Included studies

Twelve studies [9–20] were finally included and evaluated (Fig. 1), and the details are summarized in Table 2.

3.2 Quality assessment and publication bias

The quality of the included studies was overall low (Table 1). Four [9, 15, 17, 19] out of 12 studies had fair quality (total score of 4–5), and the remaining studies were deemed to have a poor quality (total score ≤ 3).

3.3 Participants' and intervention characteristics

The retrieved articles included a total of 109 CCS. We excluded two participants of one study because they had been less than 1 year off treatment [13], and two other participants in two studies because they had hematological disorders that were not cancers [9, 13]. Some studies shared the same sample (Järvelä et al. [10–12] and Riggs et al. [17], Piscione et al. [15] and Szulc-Lerch et al. [19]), and thus, we used only one study in each case to compute the total number of subjects.

The included studies analyzed children/adolescents and adult survivors with different types of childhood cancer, with the most common being hematological malignancies (leukemia) and brain tumors. Participants' age ranged from 6 to 41 years. The age at diagnosis, the time since diagnosis, and the time since the end of treatment ranged from 0 to 15 years, from 1 to 22 years, and from 1 to 21 years, respectively. Three of the included studies did not report the age at diagnosis, four did not report the time since diagnosis, and four did not report the time since the end of treatment.

Five studies included a non-exercising control group [9, 14, 15, 17, 19], of which one study used a parallel design [9] and four used a crossover design [14, 15, 17, 19]. The remaining studies were noncontrolled trials. Exercise interventions consisted of aerobic exercise [15, 17, 19] or a combination of both aerobic and resistance exercise [9–14, 16, 18, 20]. Frequency and duration of the interventions ranged from two to five sessions/week and from 8 weeks to 6 months, respectively. Intensity ranged from 50 to 60% of one-repetition maximum for resistance exercise, and between 40% of heart rate (HR) reserve and > 90% of maximum HR for aerobic exercise. Six of the included studies did not register the intensity of the intervention. None of the 12 studies included a nutrition (either interventional or educational) intervention.

3.4 Outcomes

3.4.1 Physical capacity

There was mixed evidence on the benefits of exercise on physical performance. Six studies [9, 10, 14, 15, 18, 20]

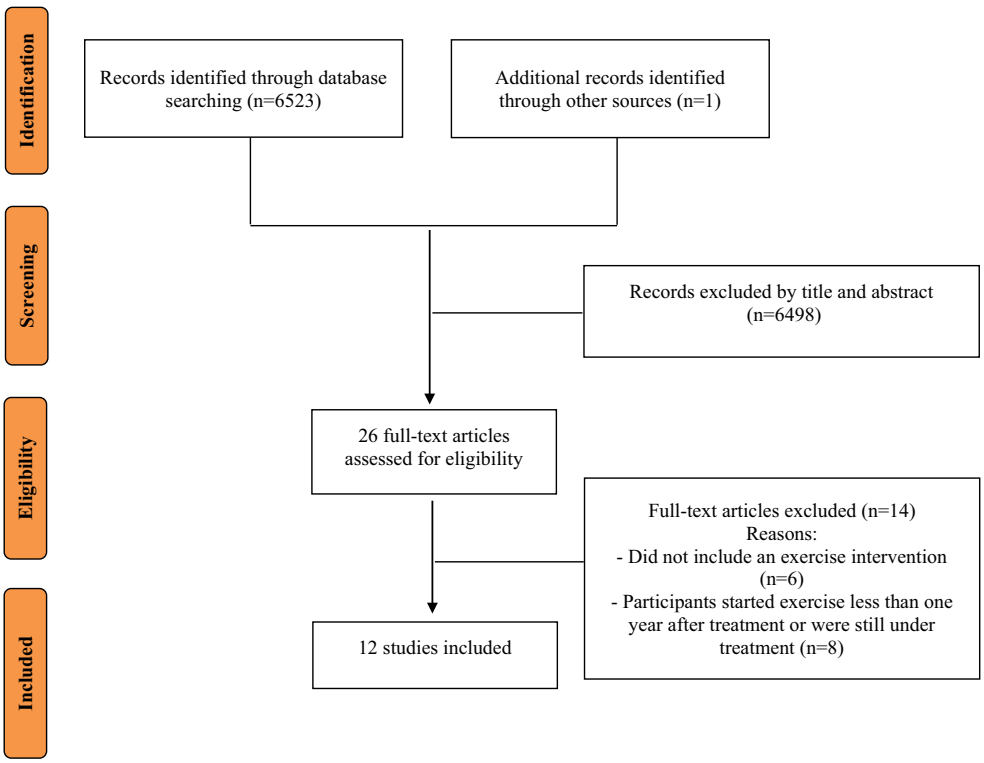

Fig. 1 Flowchart of literature search

Table 2 Studies analyzing the effects of exercise intervention on CCS

Study	Study design	Sample demographics (*n*, sex, age)	Main cancer characteristics	Intervention	Endpoints	Main results
Dubnov-Raz et al. [9]	Non-randomized controlled trial	− EXP: *n* = 10 CCS (6 female), 11 years (8–14) − CT: *n* = 10* CCS (5 female), 12 years (9–13)	*Type of cancer*: different types *Age at diagnosis*: N/R *Time since diagnosis*: N/R *Time since treatment*: EXP: 3 years (1–6); CT: 3 years (2–4) *Time of remission*: N/R *Treatment*: chemotherapy and/or HSCT and/or radiotherapy	*Type*: aerobic and resistance exercise *Frequency*: 3 days/week *Duration*: 6 months *Intensity*: N/R *Supervised*: yes	− CRF (VO_{2peak}) − Fat and lean mass, BMC and BMD (DXA) − QoL (PedsQL 4.0) − Mood (CDI)	− No changes in CRF − ↑ lean mass, total body and lumbar spine BMD − No changes in fat mass − ↑ total body BMC and femoral neck BMD − ↓ QoL − No changes in mood
Järvelä et al. [10]	Noncontrolled trial	− EXP: *n* = 17 CCS (9 female), 22 years (16–30) − No CT	*Type of cancer*: ALL *Age at diagnosis*: ≤ 16 years *Time since diagnosis*: 16 years (11–21) *Time since treatment*: N/R *Time of remission*: first remission *Treatment*: anthracyclines and/or CRT	*Type*: aerobic and resistance exercise *Frequency*: 3–4 days/-week *Duration*: 16 weeks *Intensity*: N/R *Supervised*: no	− CRF (VO_{2peak}) − LV function (echocardiography) − Dynamic muscle strength (sit-up and back tests, a 30-s full squat test, and lifting weights) − Muscle power of the lower extremities (vertical squat jump) − Maximal isometric handgrip strength (dynamometer) − BMI, weight, waist circumference, and waist-to-hip ratio − % fat mass (skinfold) − BP − PA levels (questionnaire) − Plasma glucose, insulin, HOMA-IR, HDL, LDL and total cholesterol, and triglyceride concentrations (blood analysis)	− ↑ CRF − No changes in LVEF and FS − ↑ sit-up and back test, and full squat test − ↓ waist circumference, waist-to-hip ratio, and % fat mass − No changes in weight and BMI − ↓ diastolic BP − ↑ PA levels − ↓ plasma insulin and HOMA-IR − No changes in plasma glucose, HDL, LDL and total cholesterol, and triglyceride concentrations
Järvelä et al. [11]	Noncontrolled trial	− EXP: *n* = 17 CCS (9 female), 22 years (16–30) − No CT	*Type of cancer*: ALL *Age at diagnosis*: ≤ 16 years *Time since diagnosis*: 16 years (11–21) *Time since treatment*: N/R *Time of remission*: first remission *Treatment*: anthracyclines and/or CRT	*Type*: aerobic and resistance exercise *Frequency*: 3–4 days/-week *Duration*: 16 weeks *Intensity*: N/R *Supervised*: no	− IMT and FMD (vascular ultrasound)	− ↓ IMT − ↑ FMD40 − No changes in FMDmax and FMDauc
Järvelä et al. [12]	Noncontrolled trial	− EXP: *n* = 17 CCS (3 female),	*Type of cancer*: ALL	*Type*: aerobic and resistance exercise	− LV structure and function (echocardiography)	− No changes in LVEF and FS

Table 2 (continued)

Study	Study design	Sample demographics (*n*, sex, age)	Main cancer characteristics	Intervention	Endpoints	Main results
		23 years (17–30) – No CT	*Age at diagnosis*: 5 years (2–13) *Time since diagnosis*: 16 years (11–21) *Time since treatment*: N/R *Time of remission*: first remission *Treatment*: anthracyclines and/or CRT	*Frequency*: 3–4 days/-week *Duration*: 16 weeks *Intensity*: N/R *Supervised*: no		– No changes in LV end-systolic and end-diastolic dimensions and volumes, intraventricular septum thickness, and left ventricle posterior wall thickness or mass – ↑ early diastolic mitral inflow velocity – No changes in late diastolic mitral inflow velocity and ratio early and late diastolic mitral inflow velocity – ↑ peak circumferential strain rate and diastolic strain rate
Kim and Park [13]	Noncontrolled trial	– EXP: *n* = 2* CCS (1 female), 11 years – No CT	*Type of cancer*: ALL, AML, and severe aplastic anemia *Age at diagnosis*: N/R *Time since diagnosis*: N/R *Time since treatment*: 2 years (1–3) *Time of remission*: N/R *Treatment*: chemotherapy and/or HSCT	*Type*: aerobic and resistance exercise *Frequency*: 2 days/week *Duration*: 8 weeks *Intensity*: N/R *Supervised*: yes	– Physical fitness (PAPS) – QoL (PedsQL 4.0)	– ↑ muscle strength and overall physical fitness – ↑ school functioning and overall QoL
Long et al. [14]	Crossover controlled trial	– EXP: *n* = 13 CCS (7 female), 19 years (16–23) – CT: *n* = 13 CCS (7 female), 19 years (16–23)	*Type of cancer*: brain tumor, ALL and rhabdomyosar-coma *Age at diagnosis*: 3 years (0–10) *Time since diagnosis*: 15 years (7–22) *Time since treatment*: 13 years (7–21) *Time of remission*: N/R *Treatment*: surgery and/or HSCT and/or chemotherapy and/or radiotherapy	*Type*: aerobic and resistance exercise *Frequency*: 3 days/week *Duration*: 24 weeks *Intensity*: ~ 50–60% 1-RM (resistance exercise) and ~ 60% HR_{max} (aerobic exercise) *Supervised*: yes	– Dynamic muscle strength (latissimus dorsi pulldown and biceps curl) – Muscular endurance (squats, sit-ups, and push-ups) – CRF (submaximal and VO_{2peak}) – Lean and fat mass, peripheral and visceral adipose tissue (DXA) – Weight and BMI – HR and BP – FMD and delta diameter of the brachial artery (vascular ultrasound) – PA levels (accelerometer)	– ↑ biceps curl strength – ↑ V_E, RER and relative VO_{2peak} and ↓ absolute and relative VO_{2peak} – No changes in lean and fat mass, peripheral and visceral adipose tissue – No changes in weight and BMI – No changes in HR and BP – ↑ delta diameter and FMD – ↑ breaks in sedentary time
Piscione et al. [15]	Crossover controlled trial	– EXP: *n* = 28 CCS (12 female), 12 years (8–17)	*Type of cancer*: brain tumor *Age at diagnosis*: 6 years (2–9)	*Type*: aerobic exercise *Frequency*: 2–3 days/-week	– CRF (VO_{2peak} and pro-rated work rate) – Motor performance (BOTF-2)	– ↑ pro-rated work rate – ↑ bilateral coordination

Table 2 (continued)

Study	Study design	Sample demographics (*n*, sex, age)	Main cancer characteristics	Intervention	Endpoints	Main results
		– CT: $n = 28$ CCS (12 female), 12 years (8–17)	*Time since diagnosis*: 5 years (1–10) *Time since treatment*: 1–10 years *Time of remission*: N/R *Treatment*: surgery and/or CRT and/or chemotherapy	*Duration*: 12 weeks *Intensity*: ~ 80% HR_{max} *Supervised*: yes		
Rath et al. [16]	Noncontrolled trial	– EXP: $n = 20$ CCS (10 female), 20 years (16–24) – No CT	*Type of cancer*: different types *Age at diagnosis*: 4 years (0–15) *Time since diagnosis*: N/R *Time since treatment*: 11 years (11–21) *Time of remission*: N/R *Treatment*: surgery and/or CRT and/or chemotherapy	*Type*: aerobic and resistance exercise *Frequency*: 3 days/week *Duration*: 6 months *Intensity*: N/R *Supervised*: yes	– BP – BMI and waist/hip circumference – Trunk:limb fat mass ratio (DXA) – Plasma glucose, insulin, HbA1c, HOMA-IR, HDL, LDL and total cholesterol, triglyceride, and C-peptide concentrations (blood analysis) – Psychological function (WASI-II and ABAS-II) – Mental health (ASEBA)	– ↑ diastolic BP – ↓ trunk:limb fat mass ratio – ↑ insulin 1 h – ↑ ABAS-II
Riggs et al. [17]	Crossover controlled trial	– EXP: $n = 28$ CCS (12 female), 12 years (8–17) – CT: $n = 28$ CCS (12 female), 12 years (8–17)	*Type of cancer*: brain tumor *Age at diagnosis*: 6 years (2–9) *Time since diagnosis*: 5 years (1–10) *Time since treatment*: 1–10 years *Time of remission*: N/R *Treatment*: surgery and/or CRT and/or chemotherapy	*Type*: aerobic exercise *Frequency*: 2–3 days/-week *Duration*: 12 weeks *Intensity*: ~ 80% HR_{max} *Supervised*: yes	– CRF (6MWD) – Attention, processing speed, and short-term memory (CANTAB) – White matter architecture and hippocampal volume (MRI)	– No differences in CRF – ↓ reaction time – ↑ white matter fractional anisotropy and hippocampal volume
Smith et al. [18]	Noncontrolled trial	– EXP: $n = 5$ CCS (2 female), 38 years (33–41) – No CT	*Type of cancer*: Osteosarcoma and Ewing sarcoma *Age at diagnosis*: 12 years (3–15) *Time since diagnosis*: ≥ 10 years *Time since treatment*: N/R *Time of remission*: N/R *Treatment*: surgery and chemotherapy	*Type*: aerobic and resistance exercise *Frequency*: 3–5 days/-week *Duration*: 12 weeks *Intensity*: 40–70% $HR_{reserve}$ (aerobic exercise) and N/R (resistance exercise) *Supervised*: no	– CRF (RER and VO_{2peak}) – Muscle strength (knee extension peak torque) – LV function (echocardiography) – Fat mass (DXA) – Weight – BP and HR_{max}	– ↑ CRF – No changes in RER – ↑ muscle strength – ↑ LVEF – ↓ fat mass – ↓ weight – No changes in BP and HR_{max}

Table 2 (continued)

Study	Study design	Sample demographics (*n*, sex, age)	Main cancer characteristics	Intervention	Endpoints	Main results
Szulc-Lerch et al. [19]	Crossover controlled trial	− EXP: *n* = 28 CCS (12 female), 12 years (8–17) − CT: *n* = 28 CCS (12 female), 12 years (8–17)	*Type of cancer*: brain tumor *Age at diagnosis*: 6 years (2–9) *Time since diagnosis*: 5 years (1–10) *Time since treatment*: 1–10 years *Time of remission*: N/R *Treatment*: surgery and/or CRT and/or chemotherapy	*Type*: aerobic exercise *Frequency*: 2–3 days/-week *Duration*: 12 weeks *Intensity*: ~ 80% HR_{max} *Supervised*: yes	− Cortical thickness and brain volume (MRI)	− ↑ cortical thickness − ↑ white matter volume
Takken et al. [20]	Noncontrolled trial	− EXP: *n* = 4 CCS (1 female), ~ 9 years (6–14) − No CT	*Type of cancer*: ALL *Age at diagnosis*: N/R *Time since diagnosis*: N/R *Time since treatment*: 1–3 years *Time of remission*: continued remission *Treatment*: chemotherapy	*Type*: aerobic and resistance exercise *Frequency*: 4 days/week *Duration*: 12 weeks *Intensity*: 66–> 90% of HR_{max} *Supervised*: yes	− Maximal isometric handgrip strength (dynamometer) − CRF (VO_{2peak}) − Fatigue (CIS-20) − BMI, weight − Fat mass (skinfold) − Functional mobility (TUDS and TUG)	− No changes in any variable

ABAS-II Adaptive Behavior Assessment Scale, second edition; *ALL* acute lymphoblastic leukemia; *AML* acute myeloid leukemia; *ASEBA* Achenbach System Empirically of Based Assessment; *BMC* bone mineral content; *BMD* bone mineral density; *BMI* body mass index; *BOT-2* the Bruininks-Oseretsky Test of Motor Performance 2nd edition; *BP* blood pressure; *CANTAB* the Cambridge Neuropsychological Test Automated Battery; *CCS* childhood cancer survivors; *CDI* children's depression inventory; *CIS-20* checklist individual strength questionnaire; *CRF* cardiorespiratory fitness; *CRT* cranial radiation therapy; *CT* control group; *DXA* dual-energy X-ray absorptiometry; *EXP* experimental group; *FMD40* flow mediation dilation at 40 s after the cuff release; *FMDauc* flow mediation dilation area under curve; *FS* fractional shortening; *HbA1c* glycated hemoglobin; *HOMA-IR* homeostasis model assessment, insulin resistance; *HR* heart rate; HR_{max} maximum heart rate; *HSCT* hematopoietic stem cell transplantation; *IMT* intima media thickness; *LVEF* left ventricular ejection fraction; *MRI* magnetic resonance imaging; *MWD* minute walk distance; *N/R* not reported; *PA* physical activity; *PAPS* physical activity promotion system; *PedsQL* Pediatric Quality of Life Inventory; *QoL* quality of life; *RER* respiratory exchange ratio; *RM* repetition maximum; *TUDS* timed up and down stairs test; *TUG* timed up-and-go test; *VAT* visceral adipose tissue; V_E minute ventilation; VO_{2peak} peak oxygen uptake; *WASI-II* Wechsler Abbreviated Scale of Intelligence, second edition; *FMD* flow mediated dilation *FMDmax* maximum flow mediated dilation

*Two participants were excluded because they had hematological disorders that were not cancers [9, 13] or had been less than a year off treatment [13]

analyzed cardiorespiratory fitness through the measurement of peak oxygen uptake (VO_{2peak}), with two studies reporting an increase in VO_{2peak} after exercise [10, 18] and the remaining studies finding no changes. One study [9] found an improvement in VO_{2peak} with exercise, but this trend was also observed in the non-exercising control group. Furthermore, one study [17] evaluated CRF using the 6-min walk distance, but no changes were found.

Four studies analyzed different markers of muscle strength [10, 14, 18, 20], of which one study [18] found an increase in knee extension peak torque, one [10] found an increase in performance during sit-up, back extensor, and full squat tests—but not when lifting weights—and one [14] found an increase in performance during the biceps curl exercise—but not during the latissimus dorsi pulldown. Two studies found no changes in maximal isometric handgrip strength [10, 20], and one of these studies [10] found no changes in a vertical squat jump test used to measure lower extremity muscle power.

One study [13] reported an improvement in muscle strength and overall physical fitness as measured through the physical activity promotion system, a standardized measurement table for primary schoolchildren in Korea that measures cardiorespiratory endurance, flexibility, muscle strength, quickness, and body mass index (BMI).

No changes were reported in the only study that assessed functional mobility by means of the timed up-and-go test and timed up and down stairs test [20].

Improvements were observed in bilateral coordination as measured with the Bruininks-Oseretsky Test of Motor Performance, 2nd edition [15], and benefits in reaction time measured by means of the Cambridge Neuropsychological Test Automated Battery were reported in childhood brain tumor survivors [17].

Two studies assessed physical activity (PA) levels by means of a questionnaire [10] and an accelerometer [14] and both observed benefits, with one study finding an increase in PA levels [10] and the other reporting an increase in the number of breaks in sedentary time [14].

3.4.2 Cardiovascular function and structure

Three studies assessed left ventricular systolic function [10, 12, 18]. Of these, one reported an improvement in ejection fraction (EF) after exercise [18], but no benefits on EF or shortening fraction were found in the other two studies [10, 12]. One study [12] analyzed the left ventricular structure and found an increase in early diastolic mitral inflow velocity and peak circumferential strain rate and diastolic strain rate.

Two studies analyzed endothelial function and structure through vascular ultrasound. Of these, one reported a decrease in intima-media thickness (IMT) and an increase in brachial artery flow-mediated dilation (FMD) at 40 s after the cuff release [11], whereas the other found an increase in FMD and delta diameter of the brachial artery [14].

Four studies analyzed blood pressure (BP) [10, 14, 16, 18]. One study found a reduction in diastolic BP [10] and one reported an increase in diastolic BP [16], but no changes were observed for BP or HR in the other two studies [14, 18].

3.4.3 Body weight and composition

Six studies analyzed the effects of exercise on body weight and composition [9, 10, 14, 16, 18, 20]. Only one [18] out of five studies found a reduction in body weight or BMI with exercise, with the remaining studies reporting no changes [10, 14, 16, 20]. Six studies analyzed fat mass or other markers of adiposity (such as peripheral and visceral adipose tissue) by means of skinfold thickness [10, 20] or dual-energy X-ray absorptiometry (DXA) [9, 14, 16, 18], with only three studies finding benefits on the percentage of fat mass [10], total fat mass [18], or trunk:limb fat mass ratio [16]. Two studies evaluated lean mass by DXA [9, 14], with one study finding an increase after exercise, but this was also reported in the non-exercising control group [9]. Only one study assessed bone health, finding an increase in total body bone mineral content and femoral neck bone mineral density [9]. Benefits in waist circumference and waist-to-hip ratio were also reported after the exercise interventions in one study [10].

3.4.4 Psychological status

Two studies analyzed health-related quality of life using the Pediatric Quality of Life Inventory 4.0 [9, 13], of which one study found an improvement in the school functioning subscale and in the total score [13], and the other found a decrease in total score after the exercise intervention [9]. No changes were reported in the two studies that analyzed the effects of exercise on mood [9] and fatigue [20]. One study evaluated psychological function using the Wechsler Abbreviated Scale of Intelligence (second edition) to examine cognitive function, the Adaptive Behavior Assessment Scale (second edition) for adaptive function, and the Achenbach System of Empirically Based Assessment for mental health, finding improvements in adaptive function [16].

3.4.5 Biochemical parameters

Two studies assessed the influence of exercise on biochemical parameters, reporting a reduction in plasma insulin levels and homeostatic model assessment for insulin resistance [10] or an increase in plasma insulin levels [16], but no changes in plasma glucose, HDL,LDL and total cholesterol, and triglyceride [10, 16] or in glycated hemoglobin and C-peptide [16] concentrations.

3.4.6 Brain volume and structure

Two studies in childhood brain tumor survivors, which shared the same sample, found benefits on white matter fractional anisotropy and hippocampal volume [17] and on cortical thickness and white matter volume [19].

3.4.7 Adverse events

The prevalence of adverse events associated with the exercise intervention was reported in five studies [13, 16–18, 20], and only two studies found adverse effects or problems regarding tolerance or safety [16, 20].

4 Discussion

This systematic review summarizes evidence on the effects of physical exercise in CCS who had been off treatment for at least 1 year before the beginning of the exercise intervention. Although controversial, there is evidence to suggest that exercise leads to improvements in endothelial function, PA levels, and markers of central adiposity (such as waist circumference and waist-to-hip ratio). Preliminary evidence also shows that

physical exercise might provide benefits on brain volume and structure. Also, exercise appears to be overall safe in this population, with only two studies having reported exercise-related adverse events, although more research is needed.

CCS have been reported to present with a high waist-to-hip ratio [3] and a high prevalence of abdominal obesity [21] as compared with their healthy peers with no previous history of cancer. The low PA levels commonly observed in the former, with > 50% of adult CCS not meeting the minimum PA guidelines [22, 23], could be an important contributor to these findings. Given that both central fat and physical inactivity are related to an increased morbimortality risk [24–26], the observed benefits of exercise interventions on these outcomes are potentially relevant. There is also strong evidence showing that CCS present with a worrying prevalence of cardiovascular risk factors [27, 28], and indeed, some anticancer treatments cause endothelial dysfunction [29–31], which increases the risk for cardiovascular disease [32–34]. Treatment-related cardiovascular events are indeed the leading non-malignant cause of death among CCS [35]. By contrast, exercise seems to provide benefits for the endothelium by decreasing the IMT and increasing the FMD, thereby improving cardiovascular health. For instance, for a difference of 0.1 mm in carotid IMT, the future risk of cardiovascular events changes by 10–18% [32], and Järvelä et al. [11] found a mean reduction of 0.02 mm after 16 weeks of exercise intervention. While these results are encouraging, further research is needed to confirm the effects of exercise on vascular function and structure.

The benefits observed on brain health in survivors treated for childhood brain tumors are also worth noting. These patients commonly experience brain injuries and cognitive deficits due to cancer and its treatment [36], which has been related to a reduction in white matter volume and hippocampal atrophy [37, 38]. Moreover, white matter fractional anisotropy has proven to be a clinically useful biomarker for the assessment of neurocognitive function in CCS (notably, in medulloblastoma survivors) [39, 40]. Thus, the observed benefits on white matter fractional anisotropy with exercise interventions might be clinically relevant in childhood brain tumor survivors.

Some limitations of the present systematic review include the low methodological quality and the small sample size of most included studies. It must be noted, however, that childhood cancer is a rare disease. Also, although ~ 80% of children diagnosed with cancer will survive the disease [1], studies on CCS experience enormous recruitment difficulties. Another limitation of the present work is the heterogeneity in the characteristics of the populations (different ages, cancer types, treatments, and times since diagnosis and since end of treatment) and exercise interventions (different frequencies, durations, and intensities) of the included studies. Finally, there is a lack of control of nutritional variables, which might exert a major influence on the effects of exercise on body composition.

5 Conclusions

Although no consistent benefits were observed in the present review, physical exercise interventions appear as a safe and, at least partly, effective option for the improvement of health-related markers in CCS who have been off treatment for at least 1 year before beginning the exercise intervention. More researches (especially randomized controlled trials) are, however, needed to validate these findings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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