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Exercise Interventions and Cardiovascular Health in Childhood Cancer: A Meta-analysis

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ABSTRACT

This study analyzed the effects of physical exercise interventions on cardiovascular endpoints in childhood cancer survivors. Relevant articles were systematically searched in PubMed, CINAHL, and Web of Science databases (since inception to 11th September 2019). We performed a meta-analysis (random effects) to determine the mean difference (expressed together with 95 % confidence intervals) between pre- and post-intervention values for those cardiovascular endpoints reported in more than three studies. Twenty-seven studies (of which 16 were controlled studies) comprising 697 participants were included. Only three studies reported adverse events related to exercise interventions. Exercise resulted in an increased performance on the 6-minute walk distance test (mean difference = 111 m, 95 % confidence interval = 39–183, p = 0.003) and a non-significant trend (mean difference = 1.97 ml·kg^{-1}·min^{-1}, 95 % confidence interval = − 0.12–4.06, p = 0.065) for improvement in peak oxygen uptake. Furthermore, left ventricular ejection fraction was preserved after exercise interventions (mean difference = 0.29 %, 95 % confidence interval = − 1.41–1.99, p = 0.738). In summary, exercise interventions might exert a cardioprotective effect in childhood cancer survivors by improving – or attenuating the decline of – physical capacity and cardiovascular function. Further studies, particularly randomized controlled trials, are needed to confirm these benefits.

Introduction

Despite treatment advances and improvements in 5-year survival rates, pediatric cancer survivors frequently experience adverse events related to the disease and its treatment [1]. Cardiovascular disease is the main cause of morbidity and mortality among childhood cancer survivors (CCS) [2, 3]. Anthracycline-induced cardiotoxicity is among the most frequent adverse effects observed in this patient population [4, 5], although CCS present with a lower left ventricular function (i. e., echocardiography-assessed ejection [LVEF] and fractional shortening [FS]) than their healthy peers irre-

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spective of the treatment received – that is, whether or not they had been treated with anthracyclines [6]. Thus, developing effective cardioprotective strategies is a clinical aspiration.

Dexrazoxane (ICRF-187) is arguably the most studied of the available cardioprotective agents and is associated with a statistically significant risk reduction for most cardiotoxic outcomes [7]. However, evidence suggests that in some contexts (e. g., when supplied concurrently with cancer therapies) this medication may increase the risk of developing second malignant neoplasms [7]. Exercise interventions have proven to be safe and to play a cardioprotective role by improving or at least mitigating cancer/treatment-related adverse effects on cardiovascular status. For instance, we recently found that in-hospital exercise interventions in CCS during treatment attenuated the impairment in LV function without increasing the risk of mortality, disease relapse, or metastasis [8]. Furthermore, there is meta-analytic evidence supporting the effectiveness of physical exercise for the improvement of cardiorespiratory fitness (CRF) in this population [9]. However, to our knowledge there is no meta-analytical evidence supporting the effectiveness of physical exercise interventions on the cardiovascular system in this patient population. Accordingly, in the present systematic review and meta-analysis, we aimed to summarize the evidence on the effects of exercise training intervention (duration ≥ 3 weeks) on cardiovascular endpoints in CCS.

Materials and Methods

The conduct and reporting of the current systematic review and meta-analysis conform to the Preferred Reporting Items for Systematic Reviews and Meta-analyses [10] as well as journal standards [11].

Systematic search

Two authors (J.S.M. and P.L.V.) independently performed the systematic search for relevant articles written in English and screened by title and abstract in the electronic databases PubMed, CINAHL, and Web of Science (from inception to September 11, 2019) using the following strategy: (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). The electronic search was supplemented with a manual review of reference lists from relevant publications to locate additional publications. Gray literature (e. g., abstracts, conference proceedings and editorials) and reviews were excluded. Disagreements were resolved through discussion with a third author (A.M.H.O.).

Study selection and data extraction

Studies were eligible for inclusion if they met all following criteria: a) assessing CCS during or after treatment, b) including an exercise intervention of ≥ 3 weeks composed of aerobic and/or strength exercises, and c) evaluating ≥ 1 endpoint related to cardiovascular health. Having a control group (i. e., a group performing no exercise) was not required for a study to be included. In those studies that included a control group of participants who were not CCS, only the results of the intervention group were considered in the analyses. Case studies (i. e., with one or two subjects) were excluded from the analysis.

Two authors (J.S.M. and P.L.V.) independently extracted 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 anti-cancer treatment received); interventions' characteristics; cardiovascular endpoints assessed; measurement methods; and main results. Main outcomes' data were extracted as mean and standard deviation (SD) or in a manner allowing their transformation into mean and SD. Two studies provided the median and interquartile range instead of the mean and SD [12, 13] and transformations were made with the formula proposed by Hozo et al [14]. Disagreements were resolved through discussion with a third reviewer (A.C.G.). We contacted the corresponding author of each study when necessary to clarify any uncertainty or to request additional data. In this regard, three authors provided the required specific data upon request: San Juan et al. [15], Long et al. [16], and Rath et al. [13].

Quality assessment of the included studies

The methodological quality of the included studies was assessed with the PEDro scale, which is based on the Delphi list [17]. Two authors (J.S.M and A.C.G.) independently scored the studies, and disagreements were resolved through discussion with a third author (A.M.H.O.). A total score of 0–10 was determined by counting the number of criteria satisfied by each study (see footnote in ▶ **Table 1** for a brief description of criteria). Study quality was rated as poor (PEDro score ≤ 3), fair (4–5), or high (> 5).

Statistical analysis

We performed a meta-analysis using a random effects model to compute the mean difference (MD, expressed along with the 95 % confidence interval [CI]) between pre- and post-intervention data for those endpoints assessed in ≥ 3 studies and using the same assessment method. When possible, we performed a sub-analysis based on whether participants were still under treatment or not. The weight assigned to each study in the meta-analysis was defined by the SD of the endpoints and the sample size. Begg's test was used to determine the presence of publication bias, and the Q and I^2 statistics were used to assess heterogeneity across studies. The level of significance was set at 0.05. All statistical analyses were performed using the statistical software package MIX 2.0 Pro for Excel software [18].

Results

Study selection

From the retrieved articles, 27 studies [8, 12, 13, 15, 16, 19–40] were finally included in the systematic review (▶ **Fig. 1**). The characteristics of the included studies are summarized in ▶ **Tables 2** and ▶ **3**. Sixteen studies included a non-exercising control group [8, 12, 15, 16, 19–21, 23, 25, 27, 31, 34–36, 38, 39], of which seven were randomized controlled trials [20, 21, 25, 27, 31, 34, 36], five used a parallel design [8, 12, 15, 19, 35], three used a crossover design [16, 38, 39], two used a control group composed of participants who were not CCS [15, 19], and one used a 'historical' control group whose medical conditions were comparable with those

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▶ **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** *
Beulertz et al. [19]	+	–	?	–	?	?	–	+	?	+	+	3
Braam et al. [20]	+	+	+	+	?	?	+	+	+	+	+	8
Braam et al. [21]	+	+	+	+	?	?	+	+	+	+	+	8
Chamorro-Viña et al. [23]	+	N/A	N/A	+	N/A	N/A	+	+	?	+	+	5
Cox et al. [25]	+	+	+	+	?	+	?	+	?	+	+	7
Dubnov-Raz et al. [12]	+	–	N/A	+	–	–	–	+	?	+	+	4
Esbenshade et al. [26]	+	N/A	N/A	N/A	N/A	N/A	N/A	–	?	N/A	–	0
Fiuza-Luces et al. [27]	+	+	+	+	?	?	+	+	+	+	+	8
Järvelä et al. [28]	+	N/A	N/A	N/A	N/A	N/A	N/A	+	?	N/A	+	2
Järvelä et al. [29]	+	N/A	N/A	N/A	N/A	N/A	N/A	+	?	N/A	+	2
Järvelä et al. [30]	+	N/A	N/A	N/A	N/A	N/A	N/A	+	?	N/A	+	2
Keats & Culos-Reed et al. [32]	+	N/A	N/A	N/A	N/A	N/A	N/A	+	?	N/A	+	2
Kim & Park [33]	+	N/A	N/A	N/A	N/A	N/A	N/A	+	?	N/A	+	2
Long et al. [16]	+	–	?	–	–	–	–	+	?	+	+	3
Marchese et al. [31]	+	+	?	+	?	?	?	+	?	+	+	6
Morales et al. [8]	+	–	–	+	–	–	–	+	+	+	+	5
Moyer-Mileur et al. [34]	+	+	?	+	?	?	?	+	?	+	+	5
Piscione et al. [38]	+	+	+	–	–	–	–	+	?	+	+	5
Rath et al. [13]	+	–	?	N/A	–	–	–	–	?	N/A	+	1
Riggs et al. [39]	+	+	+	–	–	–	–	+	?	+	+	5
San Juan et al. [24]	+	N/A	N/A	N/A	N/A	N/A	N/A	+	?	N/A	+	2
San Juan et al. [15]	+	N/A	N/A	N/A	N/A	N/A	N/A	+	?	+	+	3
Shore & Shepard [35]	+	N/A	N/A	N/A	N/A	N/A	N/A	+	?	+	+	3
Smith et al. [40]	+	N/A	N/A	N/A	N/A	N/A	N/A	+	?	N/A	–	1
Su et al. [37]	+	N/A	N/A	N/A	N/A	N/A	N/A	–	+	N/A	+	2
Takken et al. [22]	+	N/A	N/A	N/A	N/A	N/A	N/A	–	?	N/A	–	0
Tanir & Kuguoglu [36]	+	+	?	+	?	?	?	+	?	+	+	5

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 the 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 indicates that it was not applicable.

of the intervention group [23]. The remaining studies were non-controlled trials [13, 22, 24, 26, 28–30, 32, 33, 37, 40].

Quality assessment and publication bias

The quality of the included studies was overall fair (median PEDro score = 4, range 0–8; ▶ **Table 1**). Fifteen studies were deemed to have poor methodological quality [13, 15, 16, 19, 22, 24, 26, 28–30, 32, 33, 35, 37, 40], seven had fair quality [8, 12, 23, 34, 36, 38, 39], and the remainder were considered to present a high quality [20, 21, 25, 27, 31].

Characteristics of participants and interventions

The retrieved studies included a total of 697 participants (range 4–169), of which 669 were CCS and 28 were healthy children. Two participants from two studies were excluded because they had non-cancer-related hematological disorders [12, 33]. Some studies analyzed the same sample (Braam et al. [20, 21], Järvela et al. [28–30], Riggs et al. [39], and Piscione et al. [38]), 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 (average age range 5–38 years) with different types of childhood cancer (the most common being leukemias) during or after treatment completion. Sixteen studies [8, 15, 19–21, 23–27, 31, 32, 34–37] analyzed the effects of physical exercise interventions in CCS during treatment (or at least 50 % of the included CCS were in active treatment) and 11 studies [12, 13, 16, 22, 28–30, 33, 38–40] analyzed CCS who had already finished anti-cancer therapy. The age at diagnosis ranged from zero to 15 years, the time since diagnosis from one to 22 years, and the time since the end of treatment of those CCS who had already finished treatment from zero to 21 years. Three of the included studies did not report

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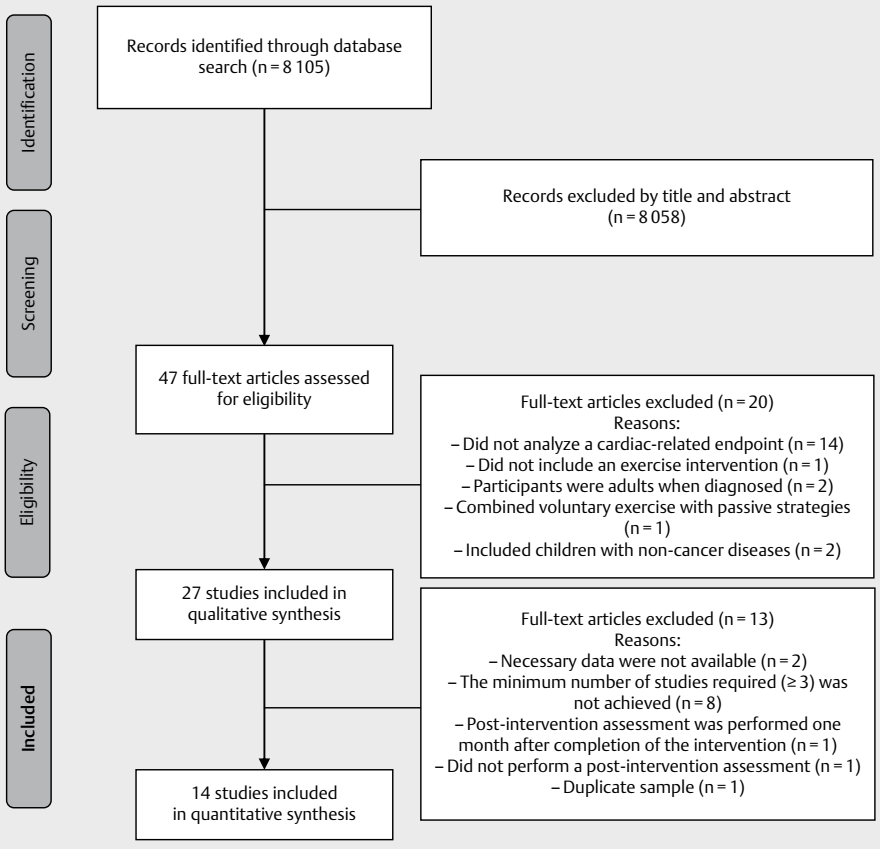

▶ **Fig. 1** Flow chart of literature search.

the age at diagnosis, four did not report the time since diagnosis, and four did not report the time since the end of treatment.

Exercise interventions were supervised in 16 studies [8, 12, 13, 15, 16, 19–24, 27, 32, 33, 38, 39] and mixed in four [25, 31, 35, 37]. The remainder were not supervised [26, 28–30, 34, 36, 40]. Exercise interventions consisted of aerobic exercise [35, 37–39] or a combination of both aerobic and resistance exercise [8, 12, 13, 15, 16, 19–34, 36, 40], lasted 3 weeks to 2.5 years, and were performed 1–6 days per week. Exercise intensity ranged from 50 to 60 % of one-repetition maximum for resistance exercise, and between 50 and > 90 % heart rate peak for aerobic exercise. Fourteen out of the 27 studies did not register exercise intensity.

The prevalence of adverse events associated with the exercise intervention was reported in 16 studies [8, 13, 15, 19–24, 27, 31–33, 37, 39, 40], and only three of them found adverse events [13, 19, 22]: in the study of Beulertz et al. [19] a participant dislocated his patella, Rath et al. [13] reported a fall during an exercise session, and Takken et al. [22] reported headache, muscle soreness, fatigue, and hyperventilation during the exercise interventions.

Endpoints

Cardiorespiratory fitness

Twelve studies [12, 15, 16, 20–22, 24, 27, 28, 35, 38, 40] analyzed CRF through the measurement of peak oxygen uptake (VO_{2peak}). Of these, nine could be meta-analyzed, showing a non-significant trend towards an improvement in VO_{2peak} (n = 118, MD = 1.97 ml·kg^{-1}·min^{-1}, 95 %CI = 0.12–4.06, p = 0.065, ▶ **Fig. 2a**), with no signs of heterogeneity (Q = 4.633, I^2 = 0 %) and no signs of publication bias (p = 0.602). Three studies [20, 35, 38] could not be meta-analyzed because post-intervention assessment was performed one month after completion of the exercise intervention [20], data could not be obtained because the authors could not be contacted [35], and the authors could not analyze the data because of participants' refusal and difficulties performing the necessary procedures [38]. In the latter case, Piscione et al. [38] used pro-rated work rate as a proxy measure of CRF, finding a significant improvement after the exercise intervention. Sub-analyses revealed no differences for VO_{2peak} in CCS who were still under treatment (n = 69, MD = 2.26 ml·kg^{-1}·min^{-1}, 95 %CI = –0.54–5.07, p = 0.114) or who had already finished anti-cancer therapy (n = 49, MD = 1.62 ml·kg^{-1}·min^{-1}, 95 %CI = –2.62–5.86, p = 0.453).

Ten studies [19, 25, 26, 31–34, 36, 37, 39] analyzed the effects of exercise on CRF assessed with submaximal tests. Four studies [25, 26, 37, 39] evaluated CRF using the 6-minute walk distance (6MWD) test, although data from one [39] study could not be obtained despite contacting the authors. From the three studies meta-analyzed, a significant increase in 6MWD performance was found (n = 66, MD = 111 m, 95 %CI = 39–183, p = 0.003, ▶ **Fig. 2b**) with no evidence of publication bias (p = 1) but with heterogeneity between

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▶ **Table 2** Studies analyzing the effects of exercise interventions on CCS during treatment

Study	Study design	Sample size by group (sex), age (mean ± SD; range)	Primary Cancer	Intervention	Endpoints	Main results
Beulertz et al. [19]	Non-randomized controlled trial	- EXP: n = 20 (9 female), 9 ± 5 years (5–13) - CT: n = 13 (8 female), 10 ± 4 years (6–14) - Healthy group: n = 20 (9 female), 9 ± 4 years (5–13)	Different types of cancer (during outpatient medical phase – i. e., maintenance treatment –)	*Type*: aerobic and resistance exercise *Frequency*: 1 day/week *Duration*: 6 months *Intensity*: 13–15 on RPE scale *Supervised*: yes *Setting*: in hospital	- CRF (DMT 6–18)	- No changes
Braam et al. [20]	Randomized controlled trial	- EXP: n = 30 (14 female), 13 ± 3 years - CT: n = 38 (17 female), 13 ± 3 years	Different types of cancer (during or within the first year of post-cancer treatment)	*Type*: aerobic and resistance exercise *Frequency*: 2 days/week *Duration*: 12 weeks *Intensity*: N/R *Supervised*: yes *Setting:* physical therapy center Included psychosocial training	- CRF (VO_{2peak})	- No changes
Braam et al. [21]	Randomized controlled trial	- EXP: n = 30 (14 female), 13 ± 3 years - CT: n = 38 (17 female), 13 ± 3 years	Different types of cancer (during or within the first year of post-cancer treatment)	*Type*: aerobic and resistance exercise *Frequency*: 2 days/week *Duration*: 12 weeks *Intensity*: 66–100 % HR_{peak} *Supervised*: yes *Setting:* physical therapy center Included psychosocial training	- CRF (VO_{2peak})	- No changes
Chamorro-Viña et al. [23]	Non-randomized controlled trial	- EXP: n = 7 (2 female), 8 ± 4 years - CT: n = 13 * (4 female), 7 ± 3 years	ALL, AML, rhabdomyosarcoma and neuroblastoma (during HSCT hospitalization)	*Type*: aerobic and resistance exercise *Frequency*: 5 days/week *Duration*: ~21 days *Intensity*: 50–70 % HR_{peak} (aerobic exercise) and color of therabands (resistance exercise) *Supervised:* yes *Setting*: in hospital	- RHR	- ↓ RHR
Cox et al. [25]	Randomized controlled trial	- EXP: n = 36 (19 female), 4–18 years - CT: n = 41 (18 female), 4–18 years	ALL (during treatment – participants had started ALL therapy within the past 10 days –)	*Type*: aerobic and resistance exercise *Frequency*: 5 days/week *Duration*: 2.5 years *Intensity*: N/R *Supervised:* mixed[a] *Setting*: in hospital and home Included behavioral training	- CRF (6MWD)	- No changes
Esbenshade et al. [26]	Non-controlled trial	- EXP: n = 12 (2 female), 7 ± 2 years - No CT	ALL (during maintenance treatment)	*Type*: aerobic and resistance exercise *Frequency*: 6 days/week *Duration*: 6 months *Intensity*: N/R *Supervised*: no *Setting*: home	- CRF (6MWD)	- ↑ distance walked in 6MWD

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▶ **Table 2** Continued

Study	Study design	Sample size by group (sex), age (mean ± SD; range)	Primary Cancer	Intervention	Endpoints	Main results
Fiuza-Luces et al. [27]	Randomized controlled trial	- EXP: n = 24 (7 female), 10 ± 1 years (4–16) - CT: n = 25 (7 female), 11 ± 1 years (5–17)	Solid tumors (during neoadjuvant chemotherapy)	*Type*: aerobic and resistance exercise *Frequency*: 3 days/week *Duration*: 19 ± 2 weeks (9–41) *Intensity*: 60–70 % HR_{peak} (aerobic exercise) and N/R (resistance exercise) *Supervised*: yes *Setting*: in hospital	- CRF (VO_{2peak})	- No changes
Keats & Culos-Reed [32]	Non-controlled trial	- EXP: n = 12 (8 female), 16 ± 2 years (14–18) - No CT	Different types of cancer (having completed the treatment or on active treatment)	*Type*: aerobic and resistance exercise *Frequency*: 1 day/week *Duration*: 16 weeks *Intensity*: N/R *Supervised*: yes *Setting*: University Included educational intervention	- CRF (Fitness-gram)	- ↑ performance in Fitnessgram at week 8 (mid-program), but no changes at the end of the program (week 16)
Marchese et al. [31]	Randomized controlled trial	- EXP: n = 13 (5 female), 7 years (4–11) - CT: n = 15 (12 female), 8 years (5–16)	ALL (during maintenance treatment)	*Type*: aerobic and resistance exercise *Frequency*: resistance exercise: 3 days/week and aerobic exercise: 7 day/weeks *Duration*: 4 months *Intensity*: N/R *Supervised*: mixed[a] *Setting*: in hospital and home	- CRF (9MWD)	- No changes
Morales et al. [8]	Non-randomized controlled trial	- EXP: n = 68 (27 female), 11 ± 4 years (4–18) - CT: n = 101 (63 female), 11 ± 3 years (4–18)	Different types of cancer (during the neoadjuvant treatment for solid tumors or during intensive chemotherapy treatment for leukemias)	*Type*: aerobic and resistance exercise *Frequency*: 2–3 days/week *Duration*: 22 weeks (14–28) *Intensity*: 65–80 % HR reserve (aerobic exercise) and gradual increments of 5–10 % (resistance exercise) *Supervised*: yes *Setting*: in hospital	- LV function (echocardiogra-phy)	- Preserved LVEF and FS (compared to control group)
Moyer-Mileur et al. [34]	Randomized controlled trial	- EXP: n = 6 (3 female), 7 ± 1 years (4–10) - CT: n = 7 (3 female), 6 ± 1 years (4–10)	ALL (during maintenance treatment)	*Type*: aerobic and resistance exercise *Frequency*: ≥ 3 day/weeks *Duration*: 12 months *Intensity*: N/R *Supervised*: no *Setting*: home Included nutrition intervention	- CRF (20-meter shuttle run test)	- ↑ performance in 20-meter shuttle run test
San Juan et al. [24]	Non-controlled trial	- EXP: n = 7 (3 female), 5 ± 1 years (4–7) - No CT	ALL (during maintenance treatment)	*Type*: aerobic and resistance exercise *Frequency*: 3 days/week *Duration*: 16 weeks *Intensity*: 50– ≥ 70 % HR_{peak} (aerobic exercise) and N/R (resistance exercise) *Supervised*: yes *Setting*: in hospital	- CRF (VO_{2peak} and VO_{2peak} at VT)	- ↑ VO_{2peak}

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▶ **Table 2** Continued

Study	Study design	Sample size by group (sex), age (mean ± SD; range)	Primary Cancer	Intervention	Endpoints	Main results
San Juan et al. [15]	Non-randomized controlled trial	- EXP: n = 8 (4 female), 11 ± 3 years (8–16) - Healthy group: n = 8 (4 female), 11 ± 3 years	ALL and AML (participants had undergone HSCT within the last 12 months)	*Type*: aerobic and resistance exercise *Frequency*: 3 days/week *Duration*: 8 weeks *Intensity*: 50– ≥ 70 % HR_{peak} (aerobic exercise) and N/R (resistance exercise) *Supervised*: yes *Setting*: in hospital	- CRF (VO_{2peak}, VT and HR_{peak})	- ↑ VO_{2peak} - No changes in VT and HR_{peak}
Shore & Shepard [35]	Non-randomized controlled trial	- EXP: n = 3 (N/R female), 14 ± 1 years - CT: n = 3 (N/R female), 13 ± 3 years	ALL and other types of cancer (having completed the treatment or under active treatment)	*Type*: aerobic exercise *Frequency*: 3 days/week *Duration*: 12 weeks *Intensity*: 70–85 % HR_{peak} *Supervised*: mixed[a] *Setting*: N/R	- CRF (VO_{2peak})	- No changes
Su et al. [37]	Non-controlled trial	- EXP: n = 18 (11 female), 12 ± 5 years - No CT	ALL, AML and solid tumors (having completed the treatment or under active treatment)	*Type*: aerobic exercise *Frequency*: ≥ 5 days/week *Duration*: 6 weeks *Intensity*: N/R *Supervised*: mixed[a] *Setting*: in hospital and home Included behavioral training	- CRF (6MWD)	- ↑ distance walked in 6MWD
Tanir & Kuguoglu [36]	Randomized controlled trial	- EXP: n = 19 (4 female), 10 ± 2 years (8–12) - CT: n = 21 (9 female), 11 ± 2 years (8–12)	ALL (on remission after 1 + year of diagnosis)	*Type*: aerobic and resistance exercise *Frequency*: 3 days/week *Duration*: 3 months *Intensity*: N/R *Supervised*: no *Setting*: home	- CRF (9MWD)	- ↑ distance walked in 9MWD

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BP, blood pressure; CCS, childhood cancer survivors; CRF, cardiorespiratory fitness; CT, control group; DMT 6–18, *Deutscher Motoriktest* 6–18; EXP, experimental group; FS, fractional shortening; HR, heart rate; HR_{peak}, peak heart rate; HSCT, hematopoietic stem cell transplant; IMT, intima media thickness; LVEF, left ventricular ejection fraction; MWD, minute walk distance N/R: not reported; RHR, resting heart rate; RPE, rating of perceived exertion; VO_{2peak}, peak oxygen uptake; VT, ventilatory threshold. Symbols: [a]Supervised + non-supervised; * HR was measured only in EXP.

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▶ **Table 3** Studies analyzing the effects of exercise intervention on childhood cancer survivors after treatment

Study	Study design	Sample size by group (sex), age (mean ± SD; range)	Main cancer characteristics	Intervention	Endpoints	Main results
Dubnov-Raz et al. [12]	Non-randomized controlled trial	– EXP: n = 10 (6 female), 11 years (8–14) – CT: n = 10 * (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})	– No changes
Järvelä et al. [28]	Non-controlled trial	– EXP: n = 17 (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) – BP	– ↑ VO_{2peak} – No changes in LVEF and FS – ↓ diastolic BP
Järvelä et al. [29]	Non-controlled trial	– EXP: n = 17 (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. [30]	Non-controlled trial	– EXP: n = 17 (3 female), 23 years (17–30) – No CT	*Type of cancer*: ALL *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	*Type*: aerobic and resistance exercise *Frequency*: 3–4 days/week *Duration*: 16 weeks *Intensity*: N/R *Supervised*: no	– LV structure and function (echocardiography)	– No changes in LVEF and FS – No changes in LV end-systolic and end-diastolic dimensions and volumes, intraventricular septum thickness, and LV 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 & Park [33]	Non-controlled trial	– EXP: n = 4 * (2 female), 12 years (11–12) – No CT	*Type of cancer*: ALL and AML *Age at diagnosis*: N/R *Time since diagnosis*: N/R *Time since treatment*: 1 year (0–3) *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	– CRF (PAPS)	– No changes
Long et al. [16]	Crossover controlled trial	– EXP: n = 13 (7 female), 19 years (16–23) – CT: n = 13 (7 female), 19 years (16–23)	*Type of cancer*: brain tumor, ALL and rhabdomyosarcoma *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	– CRF (submaximal and VO_{2peak}) – RHR and BP – FMD and delta diameter of the brachial artery (vascular ultrasound)	– ↑ V_E, RER and relative VO_{2peak} and ↓ absolute and relative VO_{2peak} – No changes in RHR and BP – ↑ delta diameter and FMD

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▶ **Table 3** Continued

Study	Study design	Sample size by group (sex), age (mean ± SD; range)	Main cancer characteristics	Intervention	Endpoints	Main results
Piscione et al. [38]	Crossover controlled trial	– EXP: n = 28 (12 female), 12 years (8–17) – CT: n = 28 (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 (VO_{2peak} and pro-rated work rate)	– ↑ pro-rated work rate
Rath et al. [13]	Non-controlled trial	– EXP: n = 20 (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	– ↑ diastolic BP
Riggs et al. [39]	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)	– No differences
Smith et al. [40]	Non-controlled trial	– EXP: n = 5 (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}) – LV function (echocardiography) – BP and HR_{max}	– ↑ VO_{2peak} – No changes in RER – ↑ LVEF – No changes in BP and HR_{max}
Takken et al. [22]	Non-controlled trial	– EXP: n = 4 (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	– CRF (VO_{2peak})	– No changes

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BP, blood pressure; CCS, childhood cancer survivors; CRF, cardiorespiratory fitness; CRT, cranial radiation therapy; CT, control group; EXP, experimental group; FMD40, flow mediation dilation at 40 s after the cuff release; FMDauc, flow mediation dilation area under curve; FS, fractional shortening; HR, heart rate; HR_{max}, maximum heart rate; HSCT, hematopoietic stem cell transplantation; IMT, intima media thickness; LV, left ventricleLVEF, left ventricular ejection fraction; MWD, minute walk distance; N/R: not reported; PAPS, physical activity promotion system; RER, respiratory exchange ratio; RHR, resting heart rate; V_E, minute ventilation; VO_{2peak}, peak oxygen uptake. * Two participants were excluded because they had hematological disorders that were not cancers [12, 33].

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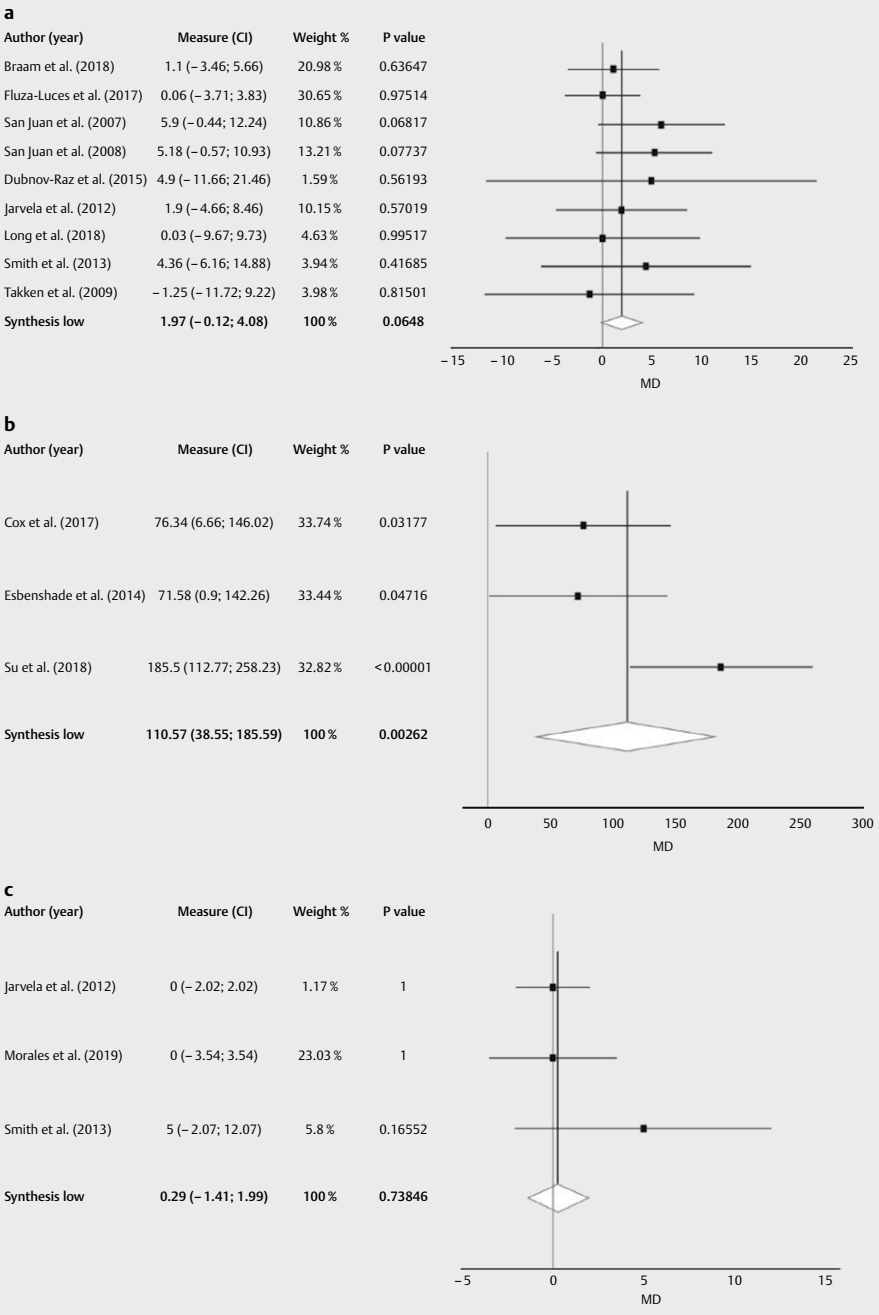

▶ **Fig. 2** Effects (mean difference [MD] between pre-and post-intervention, expressed along with 95 % confidence intervals [CI]) of exercise interventions in childhood cancer survivors on peak oxygen uptake (panel **a**, in $ml \cdot kg^{-1} \cdot min^{-1}$), on the distance walked in the 6-minute walk distance test (panel **b**, in meters), and on left ventricular ejection fraction (panel **c**, in %).

studies ($Q = 6.17$, $I^2 = 67.58$ %). No sub-analysis could be performed because the three meta-analyzed studies included CCS who were under treatment. Two studies [31, 36] used the 9-minute walk distance, with one [36] reporting an increased performance after exercise and the other study [31] finding no changes. One study [33] reported an improvement in overall physical fitness – but not in CRF – as measured through the physical activity promotion system, a standardized measurement table for primary school children in Korea that measures CRF, flexibility, muscle strength, quickness, and body mass index. No changes were found for CRF in the only study [19] that applied the Deutscher Motoriktest 6–18, a battery test that assesses endurance, strength, coordination, and flexibility. Another study [32] measured CRF using the fitnessgram, a physical fitness testing protocol that evaluates CRF, muscle strength, muscular endurance, flexibility, and body composition, finding that CRF increased at week 8 (mid-program) of the exercise interven-

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tion, but with no changes at week 16 (end of the intervention). One study [34] found an increase in CRF measured through the 20-meter shuttle run test after the exercise intervention.

Cardiovascular function and structure

Four studies assessed echocardiography-determined LV systolic function [8, 28, 30, 40]. Järvelä et al. [28, 30] used the same sample, and thus we could only meta-analyze three studies. Overall, LVEF was maintained with the exercise intervention (n = 44, MD = 0.29 %, 95 %CI = –1.41–1.99, $p = 0.738$, ▶ **Fig. 2c**) with no signs of heterogeneity ($Q = 1.811$, $I^2 = 0$ %) and no signs of publication bias ($p = 0.296$). Only one study [8] included a non-exercising control group, in which LVEF was significantly impaired in the control group compared with baseline at the end of the study. No sub-analyses could be performed. Although the effects on FS were analyzed in three studies, two of them [28, 30] shared the same sample, and thus we could not meta-analyze this endpoint. One study [8] reported that FS was preserved and reduced in the exercise and control groups, respectively, whereas in the studies by Järvelä et al. [28, 30], in which no control group was included, the FS was also preserved after exercise. One study [30] analyzed LV structure, finding an increase in early diastolic mitral inflow velocity and peak circumferential strain rate and diastolic strain rate after exercise.

Two studies analyzed endothelial function and structure through vascular ultrasound. Of these, one reported a decrease in intima media thickness and an increase in brachial artery flow-mediated dilation [29], whereas the other found an increase in this parameter and also in the delta diameter of the brachial artery [16].

Three studies [16, 23, 40] analyzed the effects of exercise on different markers of heart rate. Chamorro-Viña et al. [23] found a reduction in resting heart rate after the exercise intervention in children during allogeneic hematopoietic stem cell transplant. The remaining studies found no changes in heart rate peak [40] or resting heart rate [16].

Four studies analyzed blood pressure [13, 16, 28, 40]. All of them measured systolic (SBP) and diastolic blood pressure (DBP) in the sitting [13, 28, 40] or supine [16, 28] position. No differences were observed for SBP (n = 59, MD = 1 mmHg, 95 %CI = –3–6, $p = 0.605$) or for DBP (n = 59, MD = 1 mmHg, 95 %CI = –6–8, $p = 0.709$). No sub-analysis could be performed because the four meta-analyzed studies included CCS who had finished treatment.

Discussion

The main finding of this systematic review and meta-analysis is that exercise interventions increased CRF in CCS, as reflected by increased performance on the 6MWD test and a trend towards improvement in VO_{2peak}. Additionally, our results suggest that LV systolic function (i. e., LVEF) is preserved after exercise, and only three studies found any adverse event related to the exercise intervention. Therefore, exercise appears to exert a cardioprotective effect in CCS by improving – or at least attenuating the decline of – physical capacity and cardiovascular function.

Our findings show that exercise interventions increase VO_{2peak} and performance on the 6MWD test (specifically, 1.97 $ml \cdot kg^{-1} \cdot min^{-1}$ and 111 m from baseline to post-intervention, respectively). To our knowledge, the minimal detectable change or minimal clinically important difference for this test in this patient population is unknown. However, the observed improvement in the 6MWD test was well above the minimal detectable change reported for children and adolescents with other conditions such as cystic fibrosis (i. e., 57–71 m) [41]. Cancer treatments are cardiotoxic, especially if they include anthracyclines [4, 5]. In turn, CRF, which seems to be enhanced with exercise, is a valid predictor of overall mortality and cardiovascular risk [42]. Further, there is meta-analytical evidence showing that the VO_{2peak} of survivors of childhood acute lymphoblastic leukemia is 13 % lower than in healthy controls [43]. Thus, the observed exercise benefits on CRF are clinically relevant. It must be noted that a previous meta-analysis reported that aerobic exercise can have beneficial effect on CRF in CCS [9], although this meta-analysis included only studies that performed an aerobic exercise intervention.

Treatment-related cardiac death is the leading non-malignant cause of death among CCS [44]. Data from preclinical models have demonstrated the cardioprotective effects of exercise against anthracycline-induced cardiotoxicity [45–47], but the evidence in humans after cancer diagnosis remains sparse [48]. Thus, another important finding of our study is that exercise interventions seem to exert a cardioprotective effect, maintaining LVEF with respect to baseline values. In this regard, a preserved LVEF and FS were observed after a supervised in-hospital exercise intervention performed during the acute phase of treatment in CCS (neoadjuvant for solid tumors and intensive chemotherapy treatment period for leukemias), whereas both parameters were decreased during the same time period in a control group that performed no exercise [8]. Therefore, although LV function did not improve in the present meta-analysis, the fact that exercise interventions attenuated its decline is also worth noting because CCS frequently experience impaired LV function (i. e., LVEF and FS) even after treatment has ended [6]. It should be noted that in the study by Morales et al. [8], exercise-associated benefits on LV function were not maintained at 1 year of follow-up or thereafter, suggesting that exercise should be ideally maintained after treatment has ended.

Some limitations of the present systematic review include the fair methodological quality and the small sample size of most included studies (with only one out of the 27 studies including > 100 participants). Another limitation of the present work is the heterogeneity found across studies in terms of sample characteristics (different ages, cancer types, treatments and time since diagnosis and since end of treatment), and exercise interventions (different frequency, duration, and intensity). Further research is needed to elucidate how these individual factors influence exercise benefits on CCS. Further, one of the greatest limitations we found was that some data were not available in the original studies, and although we contacted the authors to solve this problem, not all of them responded.

Conclusions

Physical exercise interventions appear to exert a cardioprotective effect in CCS by improving – or at least attenuating the decline of – physical capacity (i. e., increased performance on the 6MWD test and a trend towards an increase in VO_{2peak}) and cardiovascular function (i. e., preserved LVEF). However, more research (especially ran-

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domized controlled trials with larger sample sizes) is needed to confirm these findings.

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Conflict of Interest

The authors declare no conflicts of interest.

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