CrossMark

Short and long-term impairments of cardiopulmonary fitness level in previous childhood cancer cases: a systematic review

Vesile Yildiz Kabak[1,2] · Patrick Calders[2] · Tulin Duger[1] · Jibril Mohammed[2,3] · Eric van Breda[2,4]

Abstract

Purpose To describe the impairments in physical fitness in individuals who were previously diagnosed and treated for childhood cancer.

Methods Using the PRISMA-guidelines, a systematic search was performed in PubMed, Web of Science, and Embase using a combination of the following predefined keywords: "exercise capacity" OR "aerobic capacity" OR "fitness" OR "cardiorespiratory fitness" OR "cardiopulmonary fitness" OR "physical fitness" OR "exercise testing" OR "exercise tolerance" OR "exercise" OR "oxygen consumption" AND "leukemia" OR "childhood cancer" OR "childhood cancer survivors (CCS)". Studies that met our inclusion criteria were reviewed on methodological quality, while the Newcastle-Ottawa Scale was used for evidence synthesis.

Results A total of 2644 articles were identified from the database search. After screening based on the eligibility (abstracts) and inclusion (full texts) criteria, 49 articles remained. Even though the risk-of-bias scores in the studies were generally low, yet the results from those with high-quality studies revealed that poor fitness levels were prevalent in individuals with acute lymphoblastic leukemia, brain tumor, and mixed cancer histories, compared to healthy controls.

Conclusions A global glance at CCS shows poor levels of fitness that is continuous and life-long even after active cancer treatment has ended. Nevertheless, the results presented in this review were based on a limited number of high-quality studies suggesting the need to for additional clinical trials in the topic area.

Keywords Childhood cancer survivor · Survivor · Physical fitness · Exercise capacity

Introduction

The 5-year survival rate has increased from 50 to over 80% during the last decade in childhood cancer [1–3]. This increased survival rates have led to an increased need to rehabilitation of treatment-related long-term side effects and comorbidities in this population. Moreover, it is well known that childhood cancer survivors (CCSs) represent a clinically heterogeneous group of patients that are dealing with multiple side effects of treatment protocols, lifestyle factors, and disease pathophysiology.

Specifically, about three-quarters of CCS develop a chronic illness; cardiovascular disease, pulmonary dysfunction, severe musculoskeletal problems, endocrine abnormalities, and secondary cancers are the most prevalent post-treatment [4, 5]. Again, it has been shown that these chronic side effects continued to increase over time in survivors [5]. As a result, fitness level can be affected negatively in CCS [6]. Poor fitness level leads to further increases in sedentary behavior which, in turn, is partly responsible for chronic fatigue, one of the most reported symptoms in cancer patients. Patients experiencing fatigue tend to be more inactive, and a self-sustaining vicious cycle develops [7]. Consequently, participation to daily activities and the overall quality of life level are affected negatively [8].

Just like in a healthy population, physical activity is an important as lifestyle ingredient in CCS, especially for those

✉ Vesile Yildiz Kabak
  vesile_yldz@hotmail.com; vesile.yildiz@hacettepe.edu.tr

1 Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Hacettepe University, Ankara, Turkey

2 Department of Rehabilitation Sciences and Physiotherapy, Ghent University, Ghent, Belgium

3 Department of Physiotherapy, Bayero University, Kano, Nigeria

4 Department of Physiotherapy, Research Group MOVANT, University of Antwerp, Antwerp, Belgium

{springer} Springer

having high risk for developing treatment-related chronic health derangements. In a recent Cochrane review, it was reported that within 5 years after diagnosis, participation in physical activity alone caused a positive impact on cardiopulmonary fitness, body composition, muscle strength, and quality of life [9]. However, this is not surprising because physical inactivity is associated with higher risk for osteoporosis, obesity, and metabolic syndrome [10, 11].

To date, literature regarding fitness levels in CCSs is scarce and inconclusive. The prior attempt at providing evidence by means of two earlier systematic reviews only focused on the maximum oxygen consumption (VO_2 max), as an outcome measure, to assess fitness levels [12, 13]. Moreover, one of these only focused on acute lymphoblastic leukemia (ALL) patients [12].

With the increasing number of CCS patients and also a possible concurrent increase in the rate of cancer-related morbidities in these patients, the evidence regarding fitness level in CCS is inadequately reflected in literature. Therefore, the present systematic review was conducted to assess both fitness levels and the different methods used in fitness assessment in all childhood cancers after active cancer treatment.

Methods

Design

This systematic review was registered within the PROSPERO system (registration number CRD42018082252). And, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement checklist was used as a guide in review process [14].

Search strategy

The PICOS (population, intervention, comparator, outcomes and study design) components were used to establish the research question, and the corresponding eligibility criteria are shown in Table 1. Thereafter, a structured search was conducted in three electronic databases: PubMed, Web of Science, and Embase. The last date of searching databases was on 1 March 2018. The search terms were ("leukemia" OR "childhood cancer" OR "childhood cancer survivors") AND ("exercise capacity" OR "aerobic capacity" OR "fitness" OR "cardiorespiratory fitness" OR "cardiopulmonary fitness" OR "physical fitness" OR "exercise testing" OR "exercise tolerance" OR "exercise" OR "oxygen consumption"). There were no restrictions regarding publication date. Duplicates were removed manually. In addition, we manually searched for relevant articles based on article citations and reference lists.

Study selection

The systematic screening of the articles was carried out in two different phases. First, all search results were screened based on title and abstract in a preliminary screening. The first and the fourth authors (VYK and JM) independently screened the titles and abstracts of all the articles based on the eligibility criteria. In the second phase, full text articles were evaluated for inclusion criteria. Similarly, VYK and JM independently screened full text of the articles. Thereafter, any disagreements were resolved through discussion to reach a consensus. If consensus could not be reached, a third opinion was given by the last author (EVB). The study selection and screening of articles were performed using the Covidence software (available online at www.covidence.org).

Data extraction

Two reviewers (VYK and JM) independently performed data extraction by selecting relevant data and integrating it into two separate columns in Covidence. Thereafter, the two columns were compared and integrated into a final extraction table. Again, disagreements were resolved through discussion between VYK and JM, and in case of disagreement, EVB was asked to make a final judgment. Specifically, the following data was extracted for each study: name of the first author, year of publication, study design, sample size, study population (demographic characteristics, diagnosis, treatment status, time after diagnosis), control group (demographic characteristics), and outcome measures (used fitness tests, reporting of the results) (Table 2).

Risk of bias

Two independent reviewers (VYK and JM) independently assessed risk of bias in all the included articles using the Newcastle-Ottawa scale [63]. Specific items checklist from this scale include suitability of randomization and concealment of allocation, blinding of patients, health care providers, data collectors, and outcome assessors and extent of loss to follow-up. This checklist has two different forms for randomized and non-randomized control studies, and it is recommended by the Cochrane Collaboration [64]. Maximum scores obtainable from each of the scales are 9 points, which represents the highest methodological quality. The included studies were defined as moderate or high-quality if they scored ≥ 6 points, whereas studies with < 6 were defined as low-quality studies [65].

Table 1 PICOS-based eligibility criteria

		Inclusion criteria	Exclusion criteria
P		Children	Adults (> 18 years) cancer patients
		Adolescents	Children with cancer (< 18 years) during cancer treatment
		Adults with completed childhood cancer treatment (surgery, chemotherapy, radiotherapy or hematopoietic stem cell transplantation)	
I		Fitness level based	/ Intervention study
		Tests for submaximal or maximal exercise capacity in numbers or percentages	
C		–	/
O		VO$_2$ max	
		6-min walking test	
		Shuttle run	
		12-min running test	
S		Case control study	Non-English, Dutch, French, or German, systematic review, meta-analysis
		Cohort study	
		Cross-sectional study	

Results

Study selection

According to our search terms, a total of 3688 articles were identified from the database search and screening of the reference lists yielded 6 eligible studies that were added. After duplicates ($n = 1048$) were removed, the titles and abstracts of total of 2646 articles were screened and 2520 articles were excluded for not meeting the eligibility criteria. The full text articles of the remaining 126 articles were retrieved for screening based on the inclusion criteria. Following the full text screening, 49 articles that fulfilled the included criteria were included in qualitative synthesis (Fig. 1).

Study characteristics

The characteristics of each eligible study were extracted and presented in Table 2. Of the 49 studies included, 19 studies reported on leukemia survivors [15–33], while 15 of them included ALL survivors [18–28, 30–33]. In two studies, physical fitness of lymphoma [34, 35], brain tumor [36, 37], and solid tumor [38, 39] survivors were reported. Twenty-four studies reported physical fitness level of individuals with mixed cancer diagnosis [6, 40–62], and five of them included individuals who had undergone hematopoietic stem cell transplantation (HSCT) [58–62]. The study characteristics in the included articles, ordered according to age (child or adult), time since active cancer treatment, and outcome measures are presented in Fig. 2.

Risk of bias analysis

Following the risk of bias analysis of the included studies, we found that methodological quality score of the case-control studies ($n = 43$) ranged from 2/9 to 8/9. While in the cohort studies ($n = 6$), the methodological quality score ranged between 4/9 and 6/9. The risk of bias analysis of the each eligible study is shown in Table 3.

Synthesis of the results

Leukemia

Three studies [15–17] with a total of 139 subjects reported physical fitness level of childhood leukemia. Of these, two studies compared the participants' scores with normative [15, 17], while the last study compared the participants scores with a healthy control group [16]. Although the age of the individual subjects and off-treatment period of 5 years were largely comparable, the mean time period from active treatment was variable. All the included studies assessed physical fitness using the VO$_2$ max. The results from two studies revealed that fitness level was significantly lower in leukemia survivors ($p < 0.05$) [16, 17]. In the last study, 25% of individuals had poor fitness levels measured at around 10 years after diagnosis [15]. All three studies regarding leukemia are of low-quality and high risk of bias (two to four out of nine).

Acute lymphoblastic leukemia

For childhood ALL survivors, 16 studies, totaling 1600 participants, were included in this review. In 10 studies, the ALL survivors were compared with healthy control group [21,

Table 2 Study characteristics

Author, year	Study design	Sample size (survivors, controls)	Controls	Subjects' mean/median age (years)	Mean/median length of time (years) after treatment	Treatment protocols CT/RT/HSCT	Fitness test protocol	Outcomes
Participants diagnosed with leukemia								
Black P et al., 1998 [15]	CC	56	Norm	16.75 (9–27.75)	10.5 (1.25–21.5)	CT: DR (10.7%), daunorubicin (19.6%) both (48.2%) RT: cranial (83.9%)	VO_2 max, ramp protocol, CE	25% of leukemia had abnormal VO_2 max
Jenney ME et al., 1995 [16]	CC	70/146	Age, sex matched C	14.6 (13.3–15.9)/14.6 (13.8–15.5)	4.21 [0.6–18.5]	CT: AC, VCR RT: Cranial (64.2%) Total body (20%)	VO_2 max, electronically braked CE	Leukemia < C (89.3 [84.5–94] vs 99.9 [97–102.8] lt/min, $p < 0.05$).
van Brussel M et al., 2006 [17]	CC	13	Norm	15.5 ± 5.8	61.9 ± 6.8 months	CT: VCR, MTX, 6-mercaptopurine, RT: None	VO_2 max, electronically braked CE	Leukemia < C (36.64 ± 18.3 vs 49.58 ± 21.22 ml/kg/min, $p = 0.001$)
Participants diagnosed with ALL								
Hartman A, et al., 2013 [18]	CC	34	Norm	12.3 [9.0–18.7]	5.2 [5–7.1]	CT: VCR, AC, Dexa	6 MWT	ALL < C (558.4 ± 43.3 m, mean SDS -2.05, $p < 0.001$)
Hung SH et al., 2017 [19]	CC	13	Norm	9.6 ± 1.4	5.1 ± 0.9	CT: AC	6 MWT	ALL < C (544.4 ± 95.4 vs 628.4 ± 29 m, 6-MWT↓in 85% of ALL)
Ness KK et al., 2012 [20]	CC	461	Norm	35.6 [21.9–52.3]	29.9 [13.7–46.5]	CT: MTX (92.8%) RT: cranial (73.5%)	6 MWT (limitation: ≤1.3 SD from norm)	46.5% had performance limitation
Ruble K et al., 2015 [21]	CC	16/16	Siblings with controlled medical conditions	12.9 ± 0.9/13.8 ± 0.9	3.6 ± 2.3	CT: AC (94%) RT: cranial (31%)	6 MWT	ALL = C (1825 ± 222 vs 1947 ± 265 ft, $p > 0.05$)
Shimomura Y et al., 2011 [22]	CC	61	Norm	5.7 ± 3.5	7.2 ± 2.8	CT: AC, Pirarubicin	6 MWT	ALL < C (563.4 ± 142.5 m $p < 0.05$)
Bär G et al., 2007 [23]	CC	19/29	Age matched pediatric and adult (trained/-untrained) HC	12 [9–15]/11 [9–14] for pediatric, 24 [20–28]/25 [19–29] for adults	4.9 [1–10] y for pediatric, 19.7 [10–28] y for adult	Adriamycin	VO_2 max, ramp protocol CE	Pediatric: ALL = C (31.15 vs 28 ml/kg/min, $p > 0.05$) Adult: ALL < trained C (24.4 vs 46.75 ml/kg/min, $p < 0.001$).
Bell W et al., 2006 [24]	CC	35/32	Healthy siblings	M 12.4 ± 3.4/12.8 ± 2.7 F 11.8 ± 3.7/12.2 ± 2.8	NR (at least 1.5 y)	AC + Cranial RT	VO_2 max, motorized treadmill	ALL < C (M 39.9 vs 47.6 ml/kg/min, $p < 0.05$; F 30.5 vs 41.3 ml/kg/min, $p < 0.05$)

Table 2 (continued)

Author, year	Study design	Sample size (survivors, controls)	Controls	Subjects' mean/median age (years)	Mean/median length of time (years) after treatment	Treatment protocols CT/RT/HSCT	Fitness test protocol	Outcomes
Christiansen JR et al., 2015 [25]	CC	133/1266	Age, body weight, SBP-matched HC	28.6 [18.6–46.5]/30.2 [19.4–45.2]	Age at diagnosis 5.3 [0.3–16]	CT:AC (78%), MTX (95%), VCR (100%) RT 15% HSCT 2%	VO_2 max, electrically braked CE	47% had poor fitness No AC < LD and M-HD AC (17 vs 48 and 67%, respectively $p < 0.001$)
Hauser M et al., 2001 [26]	CC	38/38	Age, body surface area matched HC	69.3 ± 27.1/72.4 ± 22.3 months	At least 6 months	CT: DR	VO_2 max, Bruce protocol, treadmill	ALL with normal stress-echo = C (49.5 ± 10.9 vs 50.2 ± 12.6 ml/kg/min); ALL with abnormal stress-echo < C (35.4 ± 11.6 ml/kg/min, $p < 0.05$)
Hrstkova H et al., 2006 [27]	CC	19/19	Age matched HC	16.2 ± 2.2/16.2 ± 2.2	8.3 ± 3.2	CT:AC + CP	VO_2 max, on ergometer	ALL = C (38.2 ± 13.3 vs 42.9 ± 9.3 ml/kg/min, $p > 0.05$)
Jarvela LS et al., 2010 [28]	CC	21/21	Non-athletic HC	22.07 [16.7–30.3]/NR	15.9 [11.3–21.4]	CT: AC (100%) RT 23.8%	VO_2 max, electronically braked BE	ALL < C (34.8 ± 9.3 vs 40.5 ± 8.8; −5.7 ml/kg/min, $p = 0.01$)
Mrydal OH et al., 2018 [29]	CC	116	Norm	28.5 [18.6–46.5]	Age at diagnosis: 5.4 [0.3–16]	CT: VCR (100%) MTX (95%) AC (77%)	VO_2 max, CE	42% of had poor fitness Mean 35 ± 8.5 ml/kg/min
Ness KK et al., 2007 [30]	CC	75	Norm	30.2 ± 7.1	24.6 ± 4.8	CT: MTX and VCR (100%) RT 69.3%	VO_2 max, Duke Activity Status Index	ALL < C (M 32.4 ± 4.68 vs 41 ± 5.68; F 29.18 ± 7.12 vs 33.8 ± 4.89 ml/kg/min; $p < 0.001$)
Ness K et al., 2015 [31]	CC	365/365	Age, sex, and race matched C	28.6 ± 5.9/28.9 ± 7.5	21.9 [11.0–30.7]	CT: MTX + VCR (100%) L-Asp (98.9%) RT: cranial (40.8%)	VO_2 max, submaximal CPET	ALL < C; treated with cranial RT < without RT (22.1 ± 5.5 vs 25.5 ± 6.2 ml/kg/min, $p < 0.001$)
Tonorezos ES et al., 2013 [32]	CC	115/570	Age, sex, race matched C	24.3 ± 4.9/NR 18–24 y: 63.5%/62.3% 25–38 y: 36.5%/37.7%	4–9 y: 10.4% 10–14 y: 24.4% ≥ 15 y: 65.2%	CT: AC (72.2%) CP (40.9%) RT: cranial (33.9%)	VO_2 max, graded maximal exercise test, treadmill	ALL < C (30.7 vs 39.9 ml/kg/min, $p < 0.001$); treated with cranial RT < without (F 23.5 vs 27.3 ml/kg/min, $p = 0.01$; M 31.6 vs 38.9 ml/kg/min, $p < 0.01$)
Taskinen MH et al., 2013 [33]	Retro CC	45 (without HSCT), 34	HC	13.3 (9.2–20.1)/12.0 (9.0–30.0)/12	6.8 [2.8–13.4]/5.2 [3.5–11.6]	CT: L-Asp, DR, Dexa, VCR, MTX	10 × 5 m shuttle run	Patients without HSCT = C ($p > 0.05$), patients

Table 2 (continued)

Author, year	Study design	Sample size (survivors, controls)	Controls	Subjects' mean/median age (years)	Mean/median length of time (years) after treatment	Treatment protocols CT/RT/HSCT	Fitness test protocol	Outcomes
		(with HSC-T)/522						without HSCT > with HSCT (SDS −0.5 ±1.9 vs −1.3 ±1.8, $p < 0.001$)
Participants diagnosed with lymphoma								
Adams MJ et al., 2004 [34]	Cohort	43	NA	31.9 [18.7–49.5]	14.3 [5.9–27.5]	CT 48.8% RT 100%	VO_2 max (VO_2 max↓: ≤ 20 ml/kg/m²)	VO_2 max↓ (30% of HD, 25.8 ±7.20 ml/kg/m²)
Ehrhardt MJ et al., 2016 [35]	Cohort	200	Norm	10 [1–19]	34 [20–58]	CT: Anti-metabolite (91.5%), Alkylating agent (90.5%), RT 44%	6 MWT (impairment: <10th percentile)	32% had fitness impairment
Participants diagnosed with brain tumor								
Ness KK et al., 2010 [36]	CC	78/78	Age, sex, zip code matched C	22 [18.4–58.3]/25 [18–54]	5–9 y: 15.4% 10–14 y: 38.5% 15–19 y: 28.2% ≥20 y: 17.9%	CT: any (30.8%) RT: CNS (96.2%) S 87.2%	VO_2 max, Duke Activity Status Index	BT <C (M 24.6 ±9.5 vs 33.2 ±3.4 ml/kg/min; F 25.1 ±8.8 vs 31.1 ±5.1 ml/kg/min, $p < 0.001$)
Wolfe KR et al., 2012 [37]	CC	14	Chronic illnesses and HC	14.41 ±1.86/NR	Age at diagnosis 5.59 ±2.89	Adjuvant CT (78.5%) RT + S 100%	VO_2 max, stationary CE	BT <C and BT <patients with cystic fibrosis (31.8 ±7.2 vs 49.3 ±7.9, 42.5 ±6.8 ml/kg/min respectively; $p < 0.001$).
Participants diagnosed with solid tumor								
Fernandez-Pineda et al., 2017 [38]	CC	206/206	Age, sex, race matched C	Bone 38.0 ±9.7, soft tissue 34.7 ±9.1/ 33.1 ±7.2	Age at diagnosis: Bone 13.1 ±4.2, soft tissue 11.4 ±5.2	CT: AC (80%) Platinum (56.7%) RT 28.1% S 84%	6 MWT	CES <C (525.0 ±109.3 vs 610.4 ±94.7 m, $p < 0.001$)
Ness KK et al., 2013 [39]	Cohort	531	NA	31.6 [18.7–63.8]	25.2 [10.7–48.2]	CT: Vinca-alkaloid (54%)	6 MWT (poor endurance: <500 m)	14% had poor endurance
Participants with mix childhood cancer histories								
Armstrong GT et al., 2015 [40]	Cohort	1807	NA	31 [18–65]	22.6 [10.4–48.3]	AC and/or chest-RT	6 MWT (poor distance <490 m)	Poor distance 17.6%; 14.9% of AC, 27.4% of chest RT, 17.3% of AC + chest RT
Chemaitilly W et al., 2015 [41]	Retro cohort	748	NA	34.2 (19.4–59.6)	27.3 (10.8–47.7)	Cranial RT	6 MWT (poor distance <400 m)	Poor distance 5.7% of patients without GHD, 11.8% of patients with GHD (OR 2.11, $p = 0.01$)
Beulertz J et al., 2016 [42]	CC	13/13	Age, sex matched HC	11.14 ±3.53/11.29 ± 3.42	2.13 ±1.18	CT ($n = 11$) RT ($n = 4$) S ($n = 9$)	6 MWT	Percentage rank: CCS <C (12.05 ±11.92 vs 26.22 ±21.92, $p < 0.05$)

Table 2 (continued)

Author, year	Study design	Sample size (survivors, controls)	Controls	Subjects' mean/median age (years)	Mean/median length of time (years) after treatment	Treatment protocols CT/RT/HSCT	Fitness test protocol	Outcomes
Hartman A et al., 2018 [43]	CC	71/75	Age matched C	AML-NBL-WT 31.5 [22.5–62.6]–29.1 [20.4–43.3]–28.2 [18.8–47.9]/26.9 [17.9–61.7]	Age at diagnosis: AML-NBL-WT 9.1 [0.07–14.6]–0.74 [0.04–11.7]–4.2 [0.01–12.3]	S 100% in NBL and WT CT: AML-NBL-WT 94.1%–76.9%–85.7%	6 MWT	CCS<C (588±6.1 vs 611±6 m, $p=0.008$)
Hoffman MC et al., 2013 [6]	CC	183/147	Age, sex matched siblings	13.5±2.5/13.4±2.4	9.3±3.0	CT: MTX, AC, VCR	6 MWT	CCS<C (567.8±7.0 vs 594.1±8.3 m, $p<0.05$). CNS tumor<C (533.3±15.6 m, $p<0.001$).
Smith WA et al., 2014 [44]	CC	1778	Norm	18–29 y: 37.1% 30–39 y: 40.8% 40–49 y: 18.8% 50–60 y: 3.3%	24.9 [10.9–48.2]	NR	6 MWT (physical performance↓: distance ≤300 m	Physical performance↓: bone and CNS tumors (15.6 and 9.2%)
Ahomäki R et al., 2017 [45]	CC	1300 (ST=564, BT=324, HC=412)/7209	Age, sex matched C	During the age of 18 in the military service	Age at diagnosis: <7 y: 39.7% 7–12 y: 27.8% >12 y: 32.5%	RT: BT 10% Leukemia 39%	12 min running test E: >3000 m G: >2600 m F: >2200 m P: <2000 m	BT and HC<C ($p<0.05$), ST=C ST: E 7%, G 32%, F 39%, P 22% BT: E 7%, G 25%, F 33%, P 35% HC: E 5%, G 27%, F 50%, P 18%
Braam KI et al., 2016 [46]	CC	60	Age and sex based norm	12.6±3.1	Within the first year	CT 61.6% CT+RT 11.6% CT+S 13.3% CT+RT+S 13.3%	VO2 max, electronically braked CE	CC<C (31.7±9.2 vs 45.1±3.6, −13.4±9.2 ml/kg/min $p<0.001$)
De Caro E et al., 2006 [47]	CC	84/79	HC, non-athletic but active with normal ECG	7–13 y of age: 10.2±1.4/10.1±1.6 14–21 y of age: 16.5±2.2/16.2±2.5	6.4±3.4	CT: AC (98.8%) RT: chest (38%)	VO2 max, treadmill, modified Bruce protocol	CCS=C (36.5±7.7 vs 38.2±8.2 ml/kg/min $p≥0.05$) CCS age of ≤13 y<C (34.0±5.7 vs 38.9±6.7 ml/kg/min, $p<0.001$)
De Caro E et al., 2011 [48]	CC	55/63	Non-athletic gender and age matched HC	13.5±2.9/13.8±2.6	6.2±3.3	CT: AC (100%) RT: chest (38.1%) HSCT 27.2%	VO2 max, treadmill, modified Bruce protocol	CCS<C (41.4±7.7 vs 45.7±4.3 ml/kg/min $p<0.05$)
Johnson D et al., 1997 [49]	CC	13/15	Age matched C	13±4/14±2	4.5±1.9	CT: AC	VO2 max, progressive maximal exercise test, CE	CCS<C (32.0±6.31 vs. 41.3±8.4 ml/kg/min, $p<0.001$)

Table 2 (continued)

| Author, year	Study design	Sample size (survivors, controls)	Controls	Subjects' mean/median age (years)	Mean/median length of time (years) after treatment	Treatment protocols CT/RT/HSCT	Fitness test protocol	Outcomes
Kaneko S et al., 2016 [50]	CC	22/10	HC	16 [8–19]/14 [8–19]	6 [2–16]	CT: AC (100%) RT: chest (14.2%)	VO$_2$ max, incremental exercise test, CE	CCS<C (35 [28–60] vs 45 [44–53] ml/kg/min, $p=0.005$)
Matthys D et al., 1993 [51]	CC	35/50	Age matched HC	M 14.3±2.3/14.3±1.4 F 13.9±2.7/14±1.1	M 6.6±3.4 F 6.7±3.5	CT: AC (M=11, F=11) RT: cranial (M=5, F=9)	VO$_2$ max, CE	F: CCS<C (29±3 vs 37.5 ml/kg/min, $p<0.001$) M: CCS=C (41±4 vs 44±5 ml/kg/min, $p≥0.05$)
Miller AM et al., 2013 [52]	CC	72/32	Healthy siblings	M 21.39±1.36/20.97±2.14 F 22.29±1.19/19.15±1.73	M 14.94±1.09 F 12.63±0.95	CT: VCR (M 84.2%, F 82.4%), AC (M 44.7%, F 67.7%)	VO$_2$ max, treadmill, Bruce protocol	CCS<C (M 28.53±0.81 vs 30.90±1.13 ml/kg/min, $p=0.08$; F 19.81±0.87 vs 23.40±1.42, $p=0.03$)
Pihkala J et al., 1995 [53]	CC	30	Norm	17 [8–25]	7 [2–13]	CT: AC (93.3%) RT 100% HSCT 16.6%	VO$_2$ max, CE	Exercise tolerance↓ (35.4±9.7 ml/kg/min, median 14% lower than norm)
Sato T et al., 2001 [54]	CC	29/41	C referred to hospital without heart disease	12.3±3.0/13.1±2.9	24±10 months	CT: AC	VO$_2$ max, CE	CC<C (22.0±3.7 vs 28.5±7.1 ml/kg/min, $p<0.01$)
Tham EB et al., 2013 [55]	CC	30/30	Age and gender matched HC	15.2±2.7/13.8±3.4	7.6±4.5	CT: AC (100%) RT: chest (17%)	VO$_2$ max, CE	35±10 ml/kg/min (17%↓ than norm)
Warner JT et al., 1997 [56]	CC	56/32	Healthy siblings	M 12.4±3.4/12.8±2.7 F 11.8±3.7/12.2±2.8	At least 1.5 y	CT: AC (78.5%) RT: cranial (62.5%)	VO$_2$ max, motorized treadmill	CCS<C (M 39.9 vs 47.6 ml/kg/min, $p<0.05$; F 30.5 vs 41.3 ml/kg/min, $p<0.05$).
Braam KI et al., 2015 [57]	Feasi-bility	61	NA	12.9±3	NR	NR	VO$_2$ max, steep ramp test and CPET	VO$_2$ max according to steep ramp test/CPET 26.6 [22.2–34]/29.8 [24.2–36.4] ml/kg/min
Participants treated with HSCT								
Hogarty AN et al., 2000 [58]	CC/ follow-up	33	Age, sex matched norm	Age at last follow-up 17.4 (7.8–33.9)	Initial test 1.6 [0.3–9]	Allo 57.5% Auto 42.4%	VO$_2$ max, ramp cycle protocol, CE	Initial test: HSCT <norm (24.7±5.1 ml/kg/min; 61.6% of norm, $p<0.05$). VO$_2$ max↑ at the end of 5 y: HSCT <norm (69.3% of norm, $p<0.001$)

Table 2 (continued)

Author, year	Study design	Sample size (survivors, controls)	Controls	Subjects' mean/median age (years)	Mean/median length of time (years) after treatment	Treatment protocols CT/RT/HSCT	Fitness test protocol	Outcomes
Larsen RL et al., 1992 [59]	CC	31/70	Nonathletic HC	$15.8 \pm 7.5/12.2 \pm 3.2$	3.9 ± 3.3	Allo 61.2%, Auto 35.4%, Syn 3%	VO_2 max, incremental ptorocol, CE	HSCT survivors $< C$ (24 ± 6 vs 34 ± 7 ml/kg/min, $p < 0.05$)
Slater ME et al., 2015 [60]	CC	119/66	Age, sex matched siblings	$27.4 \pm 0.7/25.0 \pm 1.0$	Age at HSCT 12.7 ± 0.6	Allo 73.1% Auto 26.9%	6 MWT	HSCT survivors $= C$ (583.1 ± 29.8 vs 591.9 ± 39.1 m, $p > 0.05$)
Bianco et al., 2014 [61]	CC	18/40	Non-athletic HC	$7.55 \pm 2.43/7.92 \pm 1.78$	10–24 months	Auto	4×10 m shuttle run test	HSCT $< C$ (16.04 ± 2.20 s vs 14.28 ± 1.5 s, $p < 0.05$)
Hovi L et al., 2010 [62]	CC	94/522	Age, sex matched C	Early test 11 (6–20) Late test 13 (7–30)	Early test (1–2 y after HSCT) 58 Late test (≥ 4 y after HSCT) 36	Allo	10×5 m shuttle run test	HSCT $< C$ both at early and late tests (SDS: $- 1.2$ (1.8) and $- 1.2$ (1.9), respectively; $p < 0.001$).

Data are expressed as mean ± standard deviation, mean (range), median [range], or number (*n* or %)

CC case control, *Retro* retrospective, *ALL* acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *CCS* childhood cancer survivor, *ST* solid tumor, *BT* brain tumor, *HC* hematologic cancer, *HSCT* hematopoietic stem cell transplantation, *CES* childhood extremity sarcomas, *NBL* neuroblastoma, *HD* Hodgkin's disease, *WT* Wilms tumor, *M* male, *F* female, *C* control group, *HC* healthy control, *NA* not applicable, *NR* not reported, *CNS* central nervous system, *CT* chemotherapy, *RT* radiotherapy, *S* surgery, *AC* anthracyclines, *VCR* vincristine, *MTX* methotrexate, *CP* cyclophosphamide, *L-Asp* L-asparaginase, *Dexa* dexamethasone, *DR* doxorubicin, *LD* low dose, *M-HD* moderate–high dose, *allo* allogeneic, *auto* autologus, *syn* syngeneic, *CPET* cardiopulmonary exercise test, *VO₂ max* maximum oxygen consumption, *6 MWT* 6-min walk test, *m* meter, *CE* cycle ergometer, *E* excellent, *G* good, *F* fair, *P* poor, *SBP* systolic blood pressure, *ECG* electro cardiograph, *BMI* body mass index, *GHD* growth hormone deficiency, *ATS* American Thoracic Society, *y* year, *SDS* standard difference score, *ml* milliliter, *ll* liter, *kg* kilogram, *min* minute, *sec* second

Fig. 1 Study selection process
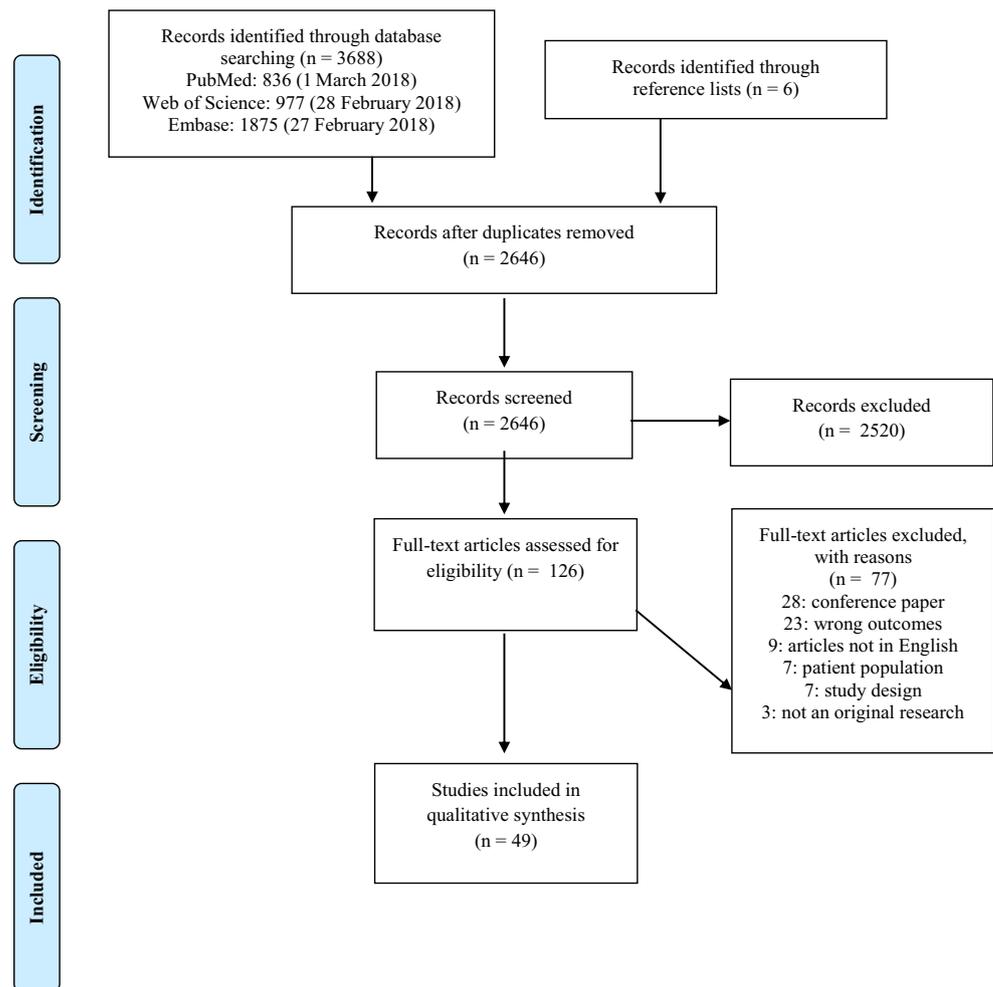
23–28, 31–33], while normative data was used as comparator in the remaining 5 studies [18–20, 22, 29, 30]. To assess physical fitness, VO_2 max was utilized in 10 studies [23–32], 6-min walk test (6-MWT) was used in 5 studies [18–22], and shuttle run test was used in one study [33]. In addition, one study utilized VO_2 max as a predictor for physical fitness level using the Duke Activity Status Index (DASI) [30].

Results from the risk of bias indicated that four studies with high-quality study design investigated fitness level by means of VO_2 max [23, 28, 31, 32]. Of these, three studies revealed that ALL survivors had a significantly poorer fitness level compared to controls ($p < 0.05$) [28, 31, 32]. Participants were also compared whether they received cranial radiotherapy (RT) treatment, and results indicated that individuals treated with cranial RT had lower fitness level than individuals treated without cranial RT ($p < 0.05$) [31, 32]. In addition, Ness et al. consisting of 365 ALL survivors who had long period after treatments (≥ 10 years) indicated that survivors participating in a moderate to vigorous physical activity for a minimum of 30 min per day had higher VO_2 max than controls [31]. Furthermore, one high-quality study, which assessed fitness levels in mix population (pediatric and adult) reported similar

results with controls for the pediatric population ($p > 0.05$), while adult population had lower fitness level compared with the controls ($p < 0.05$) [23]. Similarly, results from two studies with low-quality design that assess VO_2 max values were indicated lower fitness in ALL survivors regardless of gender than those of the controls [24, 30].

There is only one study with high-quality, used 6-MWT as outcome measure and found about 46.5% of ALL survivors had performance limitation (≤ 1.3 SD from normative) [20]. One study reported that 6-MWT distance covered in feet was similar between ALL subjects with siblings who had controlled medical condition [21], whereas in three studies that reported distance following 6-MWT found a comparatively lower score for ALL survivors compared with controls [18, 19, 22]. In these studies, participants treated only with chemotherapy (CT) and mean duration after treatment were less than 10 years. All of these four studies using 6-MWT had low-quality level and high risk of bias. The only study with low quality that reported physical fitness using shuttle run test indicated that ALL survivors treated without HSCT had similar fitness level with controls ($p > 0.05$); on the other hand, their fitness level was higher than ALL survivors who treated with HSCT [33].
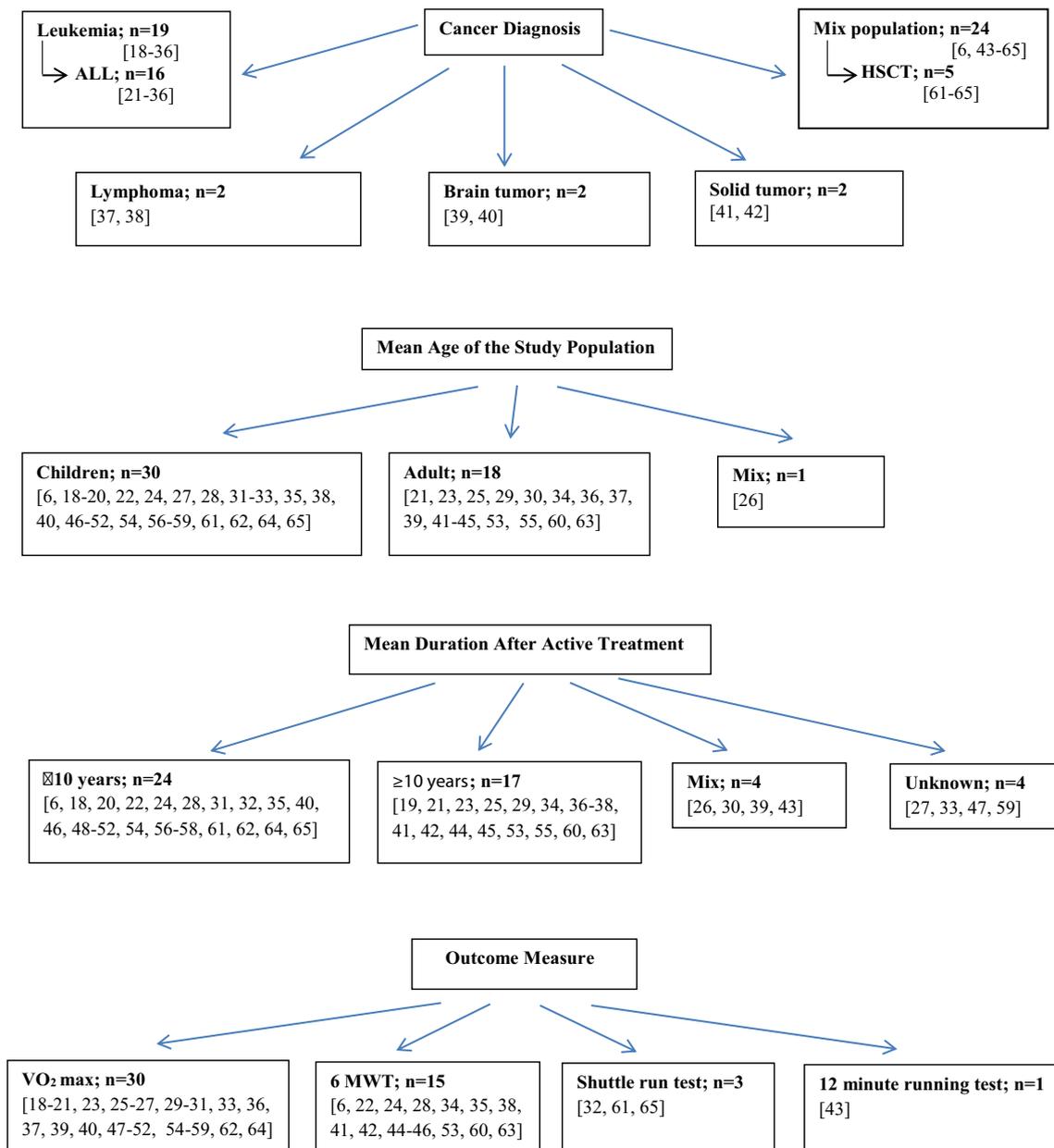
Fig. 2 Flow chart of streaming of included studies by diagnosis, study population, time since active cancer treatment, and outcome variables. ALL acute lymphoblastic leukemia, HSCT hematopoietic stem cell transplantation, 6 MWT 6-min walk test

Lymphoma

Only two studies comprising 243 investigated fitness levels of individuals diagnosed with lymphoma [34, 35]. One study that included adults who had experienced childhood cancer found that 30% of the participants had poor fitness levels (VO_2 max < 20 ml/kg/m^2). Lymphoma patients in this study were previously treated with chest RT and mean duration after treatments was 15 years [34]. The second study by Ehrhardt et al. [35] included 200 adults who were ≥ 20 years post-treatment. Expectedly, results showed that 32% of the participants had fitness impairments, which is about 22% higher than

expected values of the general population [35]. To summarize, both of these two studies, those were of low-quality revealed that around 30% of lymphoma survivors had poor physical fitness even after long post-treatment period.

Brain tumor

Two studies consisting of 93 participants assessed physical fitness in survivors of childhood brain tumor [36, 37]. Both of these studies used VO_2 max as outcome measure. One of the studies, which had a high-quality included adults 10–20 years post-treatment, found that there is low level of

Table 3 Risk of bias analysis of the included studies

Author, year

Case-control studies		1	2	3	4	5	6	7	8	NOS for case-control studies Total score (0–9)
1	Black P et al., 1998 [15]	+	+	−	−	−	−	−	−	2
2	Jenney MEM et al., 1995 [16]	+	+	+	−	−	−	+	−	4
3	van Brussel M et al., 2006 [17]	+	+	−	−	−	−	+	−	3
4	Hartman A et al., 2013 [18]	+	+	−	−	−	−	−	−	2
5	Hung SH et al., 2017 [19]	+	+	−	+	−	−	−	−	3
6	Ness KK et al., 2012 [20]	+	+	−	+	++	−	−	+	6
7	Ruble K et al., 2015 [21]	+	−	+	+	−	−	+	−	4
8	Shimomura Y et al., 2011 [22]	+	+	−	−	−	−	−	−	2
9	Bar G et al., 2007 [23]	+	+	+	+	+	−	+	−	6
10	Bell W et al., 2006 [24]	+	−	+	−	−	−	+	−	3
11	Christiansen JR et al., 2015 [25]	+	+	+	+	−	−	+	−	5
12	Hauser M et al., 2001 [26]	+	−	−	+	++	−	−	−	4
13	Hrstkova H et al., 2006 [27]	+	−	+	−	+	−	+	−	4
14	Jarvela LS et al., 2010 [28]	+	+	+	−	++	+	+	−	7
15	Mrydal OH et al., 2018 [29]	+	+	−	−	++	−	−	−	4
16	Ness KK et al., 2007 [30]	+	+	−	−	−	−	−	−	2
17	Ness K et al., 2015 [31]	+	+	+	+	++	−	+	−	7
18	Taskinen MH et al., 2013 [33]	+	+	+	+	−	−	+	−	5
19	Tonorezos ES et al., 2013 [32]	+	+	+	+	++	−	−	−	6
20	Ness KK et al., 2010 [36]	+	+	+	+	++	−	+	−	7
21	Wolfe KR et al., 2012 [37]	+	+	−	−	−	−	−	−	2
22	Fernandez-Pineda et al., 2017 [38]	−	+	+	−	++	−	−	+	5
23	Beulertz J et al., 2016 [42]	+	+	+	−	++	−	+	−	6
24	Hartman A et al., 2018 [43]	+	−	+	−	+	−	+	−	4
25	Hoffman MC et al., 2013 [6]	+	+	+	+	++	−	+	+	8
26	Smith WA et al., 2014 [44]	+	+	+	−	−	−	−	−	3
27	Ahomaki R et al., 2017 [45]	+	+	+	−	++	−	+	−	6
28	Braam KI et al., 2016 [46]	+	+	−	−	−	−	−	−	2
29	De Caro E et al., 2006 [47]	+	+	+	+	−	−	+	−	5
30	De Caro E et al., 2011 [48]	+	+	+	+	−	−	+	−	5
31	Johnson D et al., 1997 [49]	+	−	+	+	−	−	+	−	4
32	Kaneko S et al., 2016 [50]	+	−	+	+	−	−	+	−	4
33	Matthys D et al., 1993 [51]	+	−	+	−	+	−	+	−	4
34	Miller AM et al., 2013 [52]	+	+	+	+	−	−	+	−	5
35	Pihkala J et al., 1995 [53]	+	−	+	+	−	−	+	−	4
36	Sato et al., 2001 [54]	+	−	−	+	−	−	−	+	3
37	Tham EB et al., 2013 [55]	+	−	+	−	++	−	+	−	5
38	Warner JT et al., 1997 [56]	+	+	+	−	−	−	+	−	4
39	Bianco et al., 2014 [61]	+	−	+	+	−	−	+	−	4
40	Hogarty AN et al., 2000 [58]	+	+	+	−	−	−	+	−	4
41	Hovi L et al., 2010 [62]	+	+	+	+	−	−	+	−	5
42	Larsen RL et al., 1992 [59]	+	+	+	−	−	−	+	−	4
43	Slater ME et al., 2015 [60]	+	+	+	−	++	−	+	−	6
Cohort studies		1	2	3	4	5	6	7	8	NOS for cohort studies Total score (0–9)
44	Adams MJ et al., 2004 [34]	+	NA	+	+	NA	+	+	NA	5

Table 3 (continued)

Author, year		1	2	3	4	5	6	7	8	NOS
45	Armstrong GT et al., 2015 [40]	−	NA	+	−	NA	+	+	+	4
46	Chemaitilly W et el, 2015 [41]	+	+	+	−	−	+	+	+	6
47	Ehrhardt MJ et al., 2017 [35]	+	+	+	−	−	−	+	NA	4
48	Ness KK et al., 2013 [39]	+	NA	−	−	NA	+	+	+	4
49	Braam KI et al., 2015 [57] Feasibility study[a]	+	NA	NA	NA	NA	−	NA	NA	

Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies; 1-Case Definition: Is the case definition adequate? (Independent validation, record linkage or self-reported), 2-Case Description: Representativeness of cases (Random sample: description of area, hospital and clinic), 3-Selection of Controls: Selection of controls (Community controls with no history of disease), 4-Control Definition: Controls with no history of disease (endpoint), 5-Comparability: Controlled for the most important confounders (age or other factors), 6-Blindness: Researchers were blinded for participant's status, 7-Same method used for controls and cases, 8: Non-Response Rate: same rate for both groups

Newcastle-Ottawa Quality Assessment Scale for Cohort Studies; 1-Representativeness of exposed cohort (truly representative average in the community), 2-Selection of the non-exposed cohorts: Drawn from the same community, 3-Ascertainment of exposure: Independent validation or self-reported; 4-Demonstration that outcome of interest was not present at start of study; 5-Comparability of cohorts on the basis of the design or analysis (age or other factors); 6-Assessment of outcome: Independent or blind assessment or record linkage, 7-Enough follow-up time for disease 8-Adequacy of follow up of cohort

+ = score fulfilled, − = score not fulfilled, *NOS* Newcastle-Ottawa Quality Assessment Scale, *NA* not applicable

[a] As our knowledge, there is no bias analysis method for feasibility studies. Because of this, the risk of bias analysis of this study could not be performed comprehensively

physical fitness in survivors compared to controls ($p < 0.001$) [36]. The second study included a small sample ($n = 14$) and was of low quality. The results showed that there is a reduction in physical fitness for pediatric survivors with a posterior fossa tumor who are in their early (< 2 years) post-treatment phase ($p < 0.001$). Significant reduction was also found when these results are compared to that of children diagnosed with other types of cancer ($p < 0.001$) [37]. Impairments in physical fitness were reported in these two studies both at early and late post-treatment period.

Solid tumors

Two studies were found concerning solid tumors used 6-MWT as outcome measure, totaling 737 participants [38, 39]. In one study, Fernandez-Pineda et al. included survivors who were diagnosed with bone or soft tissue sarcoma mostly treated with surgery and CT and reported that they had lower fitness levels in comparison to controls ($p < 0.001$) [38]. In the second study, 531 adult survivors who were ≥ 10 years post-diagnosis were included, and a few proportion (14%) of the participants who walked less than 500 m were classified as poor endurance performers [39]. Both of these studies were conducted at least 10 years post-treatments and yet were of low-quality study design.

CCS with a mixed histories

Most of the studies in literature, aimed at assessing fitness of cancer survivors, have been performed on a population with a mixed history of cancer. The results from the reviewed studies, presented either as percentiles or numeric values, tend to suggest that most of the studies used the VO_2 max test [46–57]. The 6-MWT was used in six studies [6, 40–44], while one study utilized a 12-min running test [45].

Of these studies mentioned above, four studies were of high quality and low risk of bias [6, 41, 42, 45]. The 6-MWT used in three of these studies [6, 41, 42] and the last study used 12-min running test as outcome measure [45]. In this study, participants with brain tumor and hematologic cancer had poor distance covered in 12-min running test (35% and 18%, respectively), whereas those with a solid tumor had similar fitness level compared to the control subjects during the age of 18 in military service [45]. In another high-quality study, 11.8% of survivors with growth hormone deficiency who treated with cranial RT had poor distance covered in 6-MWT (< 400 m), whereas only 5.7% of those without hormone deficiency had poor distance ($p < 0.05$) [41]. Hoffman et al. also reported that all CCS treated with CT and mean duration after CT was less than 10 years had lower fitness level than controls ($p < 0.05$), according to diagnosis low level of fitness determined in only individuals diagnosed with central nervous system tumor ($p < 0.001$) [6].

Based on the VO_2 max in CCS, results in all studies with low-quality design have reported impaired VO_2 max for overall CCS population [46–49, 53–55]. Four of these studies stated that VO_2 max was lower among CCS within the first 10 years after treatment than in controls [46, 48, 49, 54]. In one study, 17% of CCS had a lower fitness level than normative [55], while in the other, the median value was found to be 14% lower than the predicted value [53]. In both studies, CCS mostly treated with anthracyclines and mean duration after

treatments was around 7 years [53, 55]. Only one study found similar VO_2 max level when compared with controls in CCSs mostly treated with anthracyclines who were within the first 10 years after treatments [47]. In three other studies, results were presented according to gender; apart from one study, it was found that fitness levels were lower in both male and female CCS compared to their controls group counterparts [51, 52, 56]. Only one study reported that there is a similar fitness level between male survivors and controls, while female survivors had lower scores than controls [51]. Similarly, results from the feasibility study, in which steep ramp test and was used, showed that 1 min step protocol can be used to assess VO_2 max [57].

Furthermore, Smith et al. reported that performance limitation was the most prevalent among bone and central nervous system tumor survivors (15.6 and 9.2%, respectively) [44]. Moreover, performance limitation was most prevalent in CCS older than 50 years (13.8%) and whose BMI lower than 18.5 kg/m^2 (12.5%) or higher than 40 kg/m^2 (11.2%) [44]. In another study, rate of fitness impairment was 17.6% for all CCSs and participants treated with chest RT were found to have the highest rate of impairment, which was 27.4% [40]. Both of these studies were of low-quality design and survivors who were in 10 to 50 years after treatments.

Hematopoietic stem cell transplantation survivors

Physical fitness levels of CCS who had undergone HSCT were reported in five studies [58–62]. In one study that is of high quality, reported similar results in 6-MWT in CCS mostly undergone allogeneic HSCT and after more than 10 years from transplantation ($p > 0.05$) [60]. Contrastingly, one study by Larsen et al. that used VO_2 max as outcome measure found lower fitness levels among HSCT patients compared to controls after less than 10 years from transplantation [59]. Poor fitness levels were also reported in two studies that used shuttle run test as outcome measure [61, 62]. In one study, participants were tested during early (1–2 years) and late (≥ 4 years) period after HSCT, and in both groups, lower level of fitness was reported [62]. In the other study, participants were evaluated longitudinally. The VO_2 max was lower in HSCT survivors both at the initial and later tests and increased by 4% per year; it was 69.3% of predicted at the end of 5 years. Still, fitness level was lower in comparison with normative ($p < 0.001$) [58].

Discussion

The aim of the present review was to summarize and provide a more detailed insight in the scientific literature concerning the level of physical fitness in CCS after active cancer treatment. To the best of our knowledge, this is the first systematic

review to analyze and review all available literature on fitness tests during post-treatment period for all type of childhood cancers. Altogether, CCS show poor physical fitness levels in comparison with their healthy counterparts. In addition, impairments in fitness level seem to be present for long even in CCS. Our results also showed that there is a poor level of evidence regarding impairment of physical fitness in leukemia, solid tumor, and lymphoma survivors. Moreover, a significant proportion of the studies reviewed were of low quality, and only 11 (22.4%) of studies had moderate to high quality. Hence, the need for high-quality studies with better study designs and large sample sizes was sought for the future.

Summary of evidence

It is well known that good level of physical fitness in CCS is associated with a higher quality of life and overall survival rates [8]. Physical fitness is one of the most important aspects that are directly related to mortality in general population. Such an association has been shown among earlier studies conducted in adult cancer patients and has been supported by systematic reviews and meta-analysis [65, 66]. According to these studies, adult cancer survivors who engage in high and moderate levels of physical fitness have a decreased mortality risk in comparison with those who have a low level of fitness (RR 0.55, 95% CI 0.47–0.65; and RR 0.80, 95% CI 0.67–0.97, respectively). Even though this is not yet proven among children with cancers or CCS, assessment of physical fitness in general, and in CCSs in particular, should not be underestimated and should become the standard care in the clinical setting of CCSs. Unfortunately, no such practice is currently performed either during hospitalization or during long-term follow-up that is routinely been performed in children with cancer.

Acute lymphoblastic leukemia

In studies with high-evidence score and based on the extracted information from CCS with a history of ALL, it can be inferred that serious impairments in fitness levels are prevalent in this population [20, 28, 31, 32]. In contrast, however, the latter findings of Bar et al. reported no difference in cardiopulmonary fitness levels between former ALL patients and age-matched untrained control [23]. A major drawback of the latter study is the small number of included patients ($n = 19$) and the moderate level of evidence (see Table 3) [23]. In addition, when we looked at the different fitness tests, the VO_2 max was the major test utilized in studies with high quality [23, 28, 31, 32]; only in one study 6-MWT scores were recorded, yet results were presented in percentage; nearly half of the ALL survivors had performance limitation [20]. Nevertheless, the evidence appears to be also scanty. Hence, based on these results, it was concluded that there is limited or

conflicting evidence regarding fitness levels in childhood ALL survivors.

Brain tumor

Because of the aggressiveness of this type of cancer, it is a big challenge to find sufficient brain tumor survivors that can be incorporated in any high-quality studies. Incidentally, this review found that one high-quality study in brain tumor survivors reported poor level of fitness. We must, however, take into account that fitness level was assessed according to the DASI, a patient-reported questionnaire [36]. Therefore, there is a possibility that patient self-reporting proof of fitness is questionable and should be regarded as inadequate. It seems also that for future brain tumor survivor studies, high-quality design and objective measurement of physical fitness should be emphasized as not only important and valuable, but necessary.

CCSs with mixed cancer histories

According to the results of four studies with high quality, poor fitness level was found in CCS with mixed histories of cancer [6, 41, 42, 45]. Among these studies, only 6-MWT was scarcely used results in standardized numeric data (mean ± SD) [6]. In the remaining studies, the results were expressed as percentage and the rate of impairment of physical fitness ranged from 5.7 to 35% [41, 42, 45]. Also, there were no high-quality studies that used VO_2 max in CCSs. In survivors of HSCT, there was only one study with high-quality and similar fitness level was reported between the groups [60]. There was some statistically differences between the groups in this study such as age, height, and weight. Hence, these results should be interpreted carefully. To conclude more precisely, there is great need to further investigate fitness level in HSCT survivors. Furthermore, despite the fact that there were relatively more studies conducted on CCSs diagnosed with different cancer types, quality level of the studies was not satisfactory. In addition, presentation of the results in existing studies is usually not presented in standardized forms, making comparison of results difficult. For these reasons, it is important for future studies to perform studies with higher level of quality with standardized data.

Outcome measures for cardiopulmonary fitness

Exercise testing of cardiorespiratory fitness in post-cancer treatment in adults has become an important part of clinical diagnosis in adult cancer survivors [67, 68]. According to the guidelines of the American Thoracic Society, both the 6-MWT and cardiopulmonary exercise testing (CPET) can be used for functional assessment of physical fitness [69]. In this present review, the outcomes of the 6-MWT and CPET, i.e.,

distance covered and VO_2 max, respectively, are being considered as important outcome measures. Nevertheless, since the shuttle run test and the 12-min running test have been used as well, it is important to suggest a gold standard for adequate classification. Moreover, these tests can be used as a complementary assessment tool, except for the differences in terms of information, which makes comparison among the studies difficult. In addition, there is presently no consensus regarding the best test protocol in assessing physical fitness at present as well. Presently, ergometer or treadmill tests, as in the case of CPET, are mostly used utilized in existing studies; however, there is a need to adequately explore protocols used to determine VO_2 max level in CCS. Moreover, increase in the use of higher number of muscle mass that is involved during treadmill testing may cause a higher values of VO_2 max in comparison to ergometer testing, indicating another limitation in our study and the need for care in interpreting this results [69, 70]. Another different CPET ergometer protocol is the steep ramp test that was used in one study, and they reported that such a test is feasible and valid in CCSs [57]. In two studies, indirect patient-reported inventory, DASI was used to predict VO_2 max. The use of questionnaire that is validated against the cardiopulmonary exercise test in healthy and sick populations; however, because it is a patient-reported inventory, the results could be overestimated [71, 72].

Around one third of all studies in the present review used the 6-MWT to measure physical fitness level in CSSs. The major advantage of this test is inexpensive and can be performed easily in clinical setting [73, 74]. This test has also been accepted as an important prognostic factor for survival in adult cancer patients [75, 76]. However, there are inconclusive results in the eligible studies. For instance, it was discovered that different cut-off points were used to determine poor fitness level in different studies. Therefore, we suggest that there is a need for more studies using the 6-MWT to adequately and conclusively determine the presence of impairment in physical fitness in CCS.

Finally, among the studies that were included in the present study, shuttle run test and 12-min running test were used as well. In the literature, there is no consensus on the data concerning feasibility and validity of these two test protocols in cancer patients in general and in CCS in particular. Taken together, these results in the current literature suggest that there is discrepancy in the test methods for physical fitness in childhood cancer, thereby warranting more studies in CCS. Also, the development of consensus and recommendations on exercise testing and results analyses for CCSs is important in future research.

In conclusion, physical fitness in CCSs is hampered by either tumor growth or medication of long-term side effects that can occur during and post-cancer treatment. According to results of the high-quality studies, poor fitness level is described in ALL, brain tumors, and individuals with mixed

cancer histories. However, these results should be interpreted with care since of the small number of studies with high evidence. Because of the latter phenomenon, there is great need to study physical fitness level within a better designed study in larger populations. In addition, there is a need for more information about implementation of fitness tests and interpretation of the results of these tests for CCS. To date, it is difficult to interpret and compare results according to diagnosis. Although a reason is not easy to provide, a lack of consensus should be put aside and focus should be directed towards the beneficial effects for future studies. To uncover impairments of physical fitness in CCSs will contribute to treatment protocols and to design exercise programs for this population in the future. As a result, physical fitness level of previous childhood cancer cases should be carefully examined even after long period from treatment.

Compliance with ethical standards

Ethical approval   This article does not contain any studies with human participants or animals performed by any of the authors.

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

References

1. Howlader N, Krapcho M, Miller D, Bishop K, Altekruse S, Kosary C, et al (2016) SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD; November 2015.[updated April 2016]

2. Winther JF, Kenborg L, Byrne J, Hjorth L, Kaatsch P, Kremer LC et al (2015) Childhood cancer survivor cohorts in Europe. Acta Oncol 54(5):655–668

3. Fidler MM, Soerjomataram I, Bray F (2016) A global view on cancer incidence and national levels of the human development index. Int J Cancer 139(11):2436–2446

4. Mertens AC, Yasui Y, Neglia JP, Potter JD, Nesbit ME Jr, Ruccione K et al (2001) Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. J Clin Oncol 19(13):3163–3172

5. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, Friedman DL, Marina N, Hobbie W, Kadan-Lottick NS, Schwartz CL, Leisenring W, Robison LL, Childhood Cancer Survivor Study (2006) Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 355(15):1572–1582

6. Hoffman MC, Mulrooney DA, Steinberger J, Lee J, Baker KS, Ness KK (2013) Deficits in physical function among young childhood cancer survivors. J Clin Oncol 31(22):2799–2805

7. Lucía A, Earnest C, Pérez M (2003) Cancer–related fatigue: can exercise physiology assist oncologists? Lancet Oncol 4(10):616–625

8. Badr H, Chandra J, Paxton RJ, Ater JL, Urbauer D, Cruz CS, Demark-Wahnefried W (2013) Health-related quality of life,

9. Braam KI, van der Torre P, Takken T, Veening MA, van Dulmen-den Broeder E, Kaspers GJ (2016) Physical exercise training interventions for children and young adults during and after treatment for childhood cancer. Cochrane Database Syst Rev 31(3): CD008796

10. van der Sluis IM, van den Heuvel-Eibrink MM (2008) Osteoporosis in children with cancer. Pediatr Blood Cancer 50(S2):474–478

11. Tillmann V, Darlington A, Eiser C, Bishop N, Davies H (2002) Male sex and low physical activity are associated with reduced spine bone mineral density in survivors of childhood acute lymphoblastic leukemia. J Bone Min Res 17(6):1073–1080

12. van Brussel M, Takken T, Lucia A, van der Net J, Helders PJ (2005) Is physical fitness decreased in survivors of childhood leukemia? A systematic review. Leukemia 19(1):13–17

13. Berkman AM, Lakoski SG (2016) A review of cardiorespiratory fitness in adolescent and young adult survivors of childhood cancer: factors that affect its decline and opportunities for intervention. J Adolesc Young Adult Oncol 5(1):8–15

14. Moher D, Liberati A, Tetzlaff J, Altman DG (2010) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 8(5):336–341

15. Black P, Gutjahr P, Stopfkuchen H (1998) Physical performance in long-term survivors of acute leukaemia in childhood. E J Pediatr 157(6):464–467

16. Jenney ME, Faragher EB, Jones PH, Woodcock A (1995) Lung function and exercise capacity in survivors of childhood leukaemia. Med Pediatr Oncol 24(4):222–230

17. van Brussel M, Takken T, van der Net J, Engelbert RH, Bierings M, Schoenmakers MA et al (2006) Physical function and fitness in long-term survivors of childhood leukaemia. Pediatr Rehabil 9(3): 267–274

18. Hartman A, Hop W, Takken T, Pieters R, Van Den Heuvel-Eibrink M (2013) Motor performance and functional exercise capacity in survivors of pediatric acute lymphoblastic leukemia. Pediatr Blood Cancer 60(3):494–499

19. Hung SH, Rankin A, Virji-Babul N, Pritchard S, Fryer C, Campbell KL (2017) Associating physical activity levels with motor performance and physical function in childhood survivors of acute lymphoblastic leukemia. Physiother Can 69(1):57–64

20. Ness KK, Hudson MM, Pui CH, Green DM, Krull KR, Huang TT, Robison LL, Morris EB (2012) Neuromuscular impairments in adult survivors of childhood acute lymphoblastic leukemia. Cancer 118(3):828–838

21. Ruble K, Davis CL, Han HR (2015) Endothelial health in childhood acute lymphoid leukemia survivors: pilot evaluation with peripheral artery tonometry. J Pediatr Hematol Oncol 37(2):117–120

22. Shimomura Y, Baba R, Watanabe A, Horikoshi Y, Asami K, Hyakuna N, Iwai A, Matsushita T, Yamaji K, Hori T, Tsurusawa M, for The Japanese Childhood Cancer and Leukemia Study Group (JCCLSG) (2011) Assessment of late cardiotoxicity of Pirarubicin (THP) in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 57(3):461–466

23. Bar G, Black PC, Gutjahr P, Stopfkuchen H (2007) Recovery kinetics of heart rate and oxygen uptake in long-term survivors of acute leukemia in childhood. Eur J Pediatr 166(11):1135–1142

24. Bell W, Warner JT, Evans WD, Webb DK, Mullen RH, Gregory JW (2006) Perception of effort at low and moderate intensity exercise in survivors of childhood acute lymphoblastic leukaemia. Ann Hum Biol 33(3):357–371

25. Christiansen JR, Kanellopoulos A, Lund MB, Massey R, Dalen H, Kiserud CE, Ruud E, Aakhus S (2015) Impaired exercise capacity and left ventricular function in long-term adult survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 62(8): 1437–1443

26. Hauser M, Gibson BS, Wilson N (2001) Diagnosis of anthracycline-induced late cardiomyopathy by exercise-spiroergometry and stress-echocardiography. Eur J Pediatr 160(10):607–610

27. Hrstková H, Elbl L, Nováková Z, Honzíková N, Fišer B, Závodnáe E et al (2006) Exercise testing in children and adolescents after completing anthracycline antitumour therapy. Scr Med (Brno) 79(5–6):271–278

28. Jarvela LS, Niinikoski H, Lahteenmaki PM, Heinonen OJ, Kapanen J, Arola M et al (2010) Physical activity and fitness in adolescent and young adult long-term survivors of childhood acute lymphoblastic leukaemia. J Cancer Surviv 4(4):339–345

29. Mrydal OH, Kanellopoulos A, Christensen JR, Ruud E, Edvardsen E, Kongerud J et al (2018) Risk factors for impaired pulmonary function and cardiorespiratory fitness in very long-term adult survivors of childhood acute lymphoblastic leukemia after treatment with chemotherapy only. Acta Oncol 57:658–664. https://doi.org/10.1080/0284186X.2017.1423177

30. Ness KK, Baker KS, Dengel DR, Youngren N, Sibley S, Mertens AC, Gurney JG (2007) Body composition, muscle strength deficits and mobility limitations in adult survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 49(7):975–981

31. Ness KK, DeLany JP, Kaste SC, Mulrooney DA, Pui CH, Chemaitilly W et al (2015) Energy balance and fitness in adult survivors of childhood acute lymphoblastic leukemia. Blood 125(22):3411–3419

32. Tonorezos ES, Snell PG, Moskowitz CS, Eshelman-Kent DA, Liu JE, Chou JF, Smith SM, Dunn AL, Church TS, Oeffinger KC (2013) Reduced cardiorespiratory fitness in adult survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 60(8):1358–1364

33. Taskinen MH, Kurimo M, Kanerva J, Hovi L (2013) Physical performance of nontransplanted childhood ALL survivors is comparable to healthy controls. J Pediatr Hematol Oncol 35(4):276–280

34. Adams MJ, Lipsitz SR, Colan SD, Tarbell NJ, Treves ST, Diller L, Greenbaum N, Mauch P, Lipshultz SE (2004) Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. J Clin Oncol 22(15):3139–3148

35. Ehrhardt MJ, Sandlund JT, Zhang N, Liu W, Ness KK, Bhakta N, Chemaitilly W, Krull KR, Brinkman TM, Crom DB, Kun L, Kaste SC, Armstrong GT, Green DM, Srivastava K, Robison LL, Hudson MM, Mulrooney DA (2017) Late outcomes of adult survivors of childhood non-Hodgkin lymphoma: a report from the St. Jude lifetime cohort study. Pediatr Blood Cancer 64(6):e26338

36. Ness KK, Morris EB, Nolan VG, Howell CR, Gilchrist LS, Stovall M, Cox CL, Klosky JL, Gajjar A, Neglia JP (2010) Physical performance limitations among adult survivors of childhood brain tumors. Cancer 116(12):3034–3044

37. Wolfe KR, Hunter GR, Madan-Swain A, Reddy AT, Baños J, Kana RK (2012) Cardiorespiratory fitness in survivors of pediatric posterior fossa tumor. J Pediatr Hematol Oncol 34(6):e222–e2e7

38. Fernandez-Pineda I, Hudson M, Pappo A, Bishop M, Klosky J, Brinkman T et al (2017) Long-term functional outcomes and quality of life in adult survivors of childhood extremity sarcomas: a report from the St. Jude lifetime cohort study. J Cancer Surviv 11(1):1–12

39. Ness KK, Jones KE, Smith WA, Spunt SL, Wilson CL, Armstrong GT, Srivastava DK, Robison LL, Hudson MM, Gurney JG (2013) Chemotherapy-related neuropathic symptoms and functional impairment in adult survivors of extracranial solid tumors of childhood: results from the St. Jude lifetime cohort study. Arch Phys Med Rehabil 94(8):1451–1457

40. Armstrong GT, Joshi V, Ness KK, Zhang N, Srivastava D, Griffin B et al (2014) Myocardial strain for detection of treatment-related cardiac dysfunction in adult survivors of childhood cancer: results from the St. Jude lifetime cohort study. J Clin Oncol 32(15)

41. Chemaitilly W, Li Z, Huang S, Ness KK, Clark KL, Green DM, Barnes N, Armstrong GT, Krasin MJ, Srivastava DK, Pui CH, Merchant TE, Kun LE, Gajjar A, Hudson MM, Robison LL, Sklar CA (2015) Anterior hypopituitarism in adult survivors of childhood cancers treated with cranial radiotherapy: a report from the St Jude lifetime cohort study. J Clin Oncol 33(5):492–500

42. Beulertz J, Bloch W, Prokop A, Rustler V, Fitzen C, Herich L, Streckmann F, Baumann FT (2016) Limitations in ankle dorsiflexion range of motion, gait, and walking efficiency in childhood cancer survivors. Cancer Nurs 39(2):117–124

43. Hartman A, Pluijm SMF, Wijnen M, Neggers SJCMM, Clemens E, Pieters R, van den Heuvel-Eibrink MM (2018) Health-related fitness in very long-term survivors of childhood cancer: a cross-sectional study. Pediatr Blood Cancer 65. https://doi.org/10.1002/pbc.26907

44. Smith WA, Li Z, Loftin M, Carlyle BE, Hudson MM, Robison LL et al (2014) Measured versus self-reported physical function in adult survivors of childhood cancer. Med Sci Sports Exerc 46(2):211–218

45. Ahomäki R, Harila-Saari A, Parkkola K, Matomäki J, Lähteenmäki PM (2017) Compulsory military service as a measure of later physical and cognitive performance in male survivors of childhood cancer. Acta Oncol:1–8

46. Braam KI, van Dijk-Lokkart EM, Kaspers GJL, Takken T, Huisman J, Bierings MB, Merks JHM, van de Heuvel-Eibrink MM, van Dulmen–den Broeder E, Veening MA (2016) Cardiorespiratory fitness and physical activity in children with cancer. Support Care Cancer 24(5):2259–2268

47. De Caro E, Fioredda F, Calevo MG, Smeraldi A, Saitta M, Hanau G et al (2006) Exercise capacity in apparently healthy survivors of cancer. Arch Dis Child 91(1):47–51

48. De Caro E, Smeraldi A, Trocchio G, Calevo M, Hanau G, Pongiglione G (2011) Subclinical cardiac dysfunction and exercise performance in childhood Cancer survivors. Pediatr Blood Cancer 56(1):122–126

49. Johnson D, Perrault H, Fournier A, Leclerc JM, Bigras JL, Davignon A (1997) Cardiovascular responses to dynamic submaximal exercise in children previously treated with anthracycline. Am Heart J 133(2):169–173

50. Kaneko S, Tham EB, Haykowsky MJ, Spavor M, Khoo NS, Mackie AS, Smallhorn JF, Thompson RB, Nelson MD (2016) Impaired left ventricular reserve in childhood cancer survivors treated with anthracycline therapy. Pediatr Blood Cancer 63(6):1086–1090

51. Matthys D, Verhaaren H, Benoit Y, Laureys G, Denaeyer A, Craen M (1993) Gender difference in aerobic capacity in adolescents after cure from malignant disease in childhood. Acta Paediatr 82(5):459–462

52. Miller AM, Lopez-Mitnik G, Somarriba G, Lipsitz SR, Hinkle AS, Constine LS, Lipshultz SE, Miller TL (2013) Exercise capacity in long-term survivors of pediatric cancer: an analysis from the cardiac risk factors in childhood cancer survivors study. Pediatr Blood Cancer 60(4):663–668

53. Pihkala J, Happonen JM, Virtanen K, Sovijarvi A, Siimes MA, Pesonen E et al (1995) Cardiopulmonary evaluation of exercise tolerance after chest irradiation and anticancer chemotherapy in children and adolescents. Pediatrics 95(5):722–726

54. Sato T, Harada K, Tamura M, Watanabe A, Ishii M, Takada G (2001) Cardiorespiratory exercise capacity and its relation to a new Doppler index in children previously treated with anthracycline. J Am Soc Echocardiogr 14(4):256–263

55. Tham EB, Haykowsky MJ, Chow K, Spavor M, Kaneko S, Khoo NS, Pagano JJ, Mackie AS, Thompson RB (2013) Diffuse myocardial fibrosis by T-1-mapping in children with subclinical anthracycline cardiotoxicity: relationship to exercise capacity, cumulative dose and remodeling. J Cardiovasc Magn Reson 15:48

56. Warner JT, Bell W, Webb DKH, Gregory JW (1997) Relationship between cardiopulmonary response to exercise and adiposity in survivors of childhood malignancy. Arch Dis Child 76(4):298–303

57. Braam KI, Van Dulmen-Den Broeder E, Veening MA, JHM M, Van Den Heuvel-Eibrink MM, Kaspers GJL et al (2015) Application of the steep ramp test for aerobic fitness testing in children with cancer. Eur J Phys Rehabil Med 51(5):547–555

58. Hogarty AN, Leahey A, Zhao HQ, Hogarty MD, Bunin N, Cnaan A, Paridon SM (2000) Longitudinal evaluation of cardiopulmonary performance during exercise after bone marrow transplantation in children. J Pediatr 136(3):311–317

59. Larsen RL, Barber G, Heise CT, August CS (1992) Exercise assessment of cardiac function in children and young adults before and after bone marrow transplantation. Pediatrics 89(4 SUPPL):722–729

60. Slater ME, Steinberger J, Ross JA, Kelly AS, Chow EJ, Koves IH, Hoffmeister P, Sinaiko AR, Petryk A, Moran A, Lee J, Chow LS, Baker KS (2015) Physical activity, fitness, and cardiometabolic risk factors in adult survivors of childhood cancer with a history of hematopoietic cell transplantation. Biol Blood Marrow Transplant 21(7):1278–1283

61. Bianco A, Patti A, Thomas E, Palma R, Maggio MC, Paoli A, Palma A (2014) Evaluation of fitness levels of children with a diagnosis of acute leukemia and lymphoma after completion of chemotherapy and autologous hematopoietic stem cell transplantation. Cancer Med 3(2):385–389

62. Hovi L, Kurimo M, Taskinen M, Vettenranta J, Vettenranta K, Saarinen-Pihkala UM (2010) Suboptimal long-term physical performance in children and young adults after pediatric allo-SCT. Bone Marrow Transplant 45(4):738–745

63. Wells G, Shea B, O'connell D, Peterson J, Welch V, Losos M et al (2009) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute, Ottawa

64. Zeng X, Zhang Y, Kwong JS, Zhang C, Li S, Sun F et al (2015) The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med 8(1):2–10

65. Schmid D, Leitzmann M (2014) Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis. Ann Oncol 26(2):272–278

66. Jensen MT, Holtermann A, Bay H, Gyntelberg F (2016) Cardiorespiratory fitness and death from cancer: a 42-year follow-up from the Copenhagen male study. Br J Sports Med 51: 1364–1369. https://doi.org/10.1136/bjsports-2016-096860

67. Jones LW, Eves ND, Haykowsky M, Joy AA, Douglas PS (2008) Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. Lancet Oncol 9(8):757–765

68. De Backer IC, Schep G, Hoogeveen A, Vreugdenhil G, Kester AD, van Breda E (2007) Exercise testing and training in a cancer rehabilitation program: the advantage of the steep ramp test. Arch Phys Med Rehabil 88:610–616

69. Society AT (2003) ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 167(2):211

70. Hermansen L, Saltin B (1969) Oxygen uptake during maximal treadmill and bicycle exercise. J Appl Physiol 26(1):31–37

71. Alonso J, Permanyer-Miralda G, Cascant P, Brotons C, Prieto L, Soler-Soler J (1997) Measuring functional status of chronic coronary patients: reliability, validity and responsiveness to clinical change of the reduced version of the Duke Activity Status Index (DASI). Eur Heart J 18(3):414–419

72. Carter R, Holiday DB, Grothues C, Nwasuruba C, Stocks J, Tiep B (2002) Criterion validity of the Duke Activity Status Index for assessing functional capacity in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil Prev 22(4):298–308

73. Schmidt K, Vogt L, Thiel C, Jäger E, Banzer W (2013) Validity of the six-minute walk test in cancer patients. Int J Sports Med 34(07): 631–636

74. Laboratories ACPSCPF (2002) Statement AT: guidelines for the six-minute walking-test. Am J Respir Crit Care Med 166:111–117

75. Jones LW, Hornsby WE, Goetzinger A, Forbes LM, Sherrard EL, Quist M, Lane AT, West M, Eves ND, Gradison M, Coan A, Herndon JE, Abernethy AP (2012) Prognostic significance of functional capacity and exercise behavior in patients with metastatic non-small cell lung cancer. Lung Cancer 76(2):248–252

76. Kasymjanova G, Correa JA, Kreisman H, Dajczman E, Pepe C, Dobson S, Lajeunesse L, Sharma R, Small D (2009) Prognostic value of the six-minute walk in advanced non-small cell lung cancer. J Thorac Oncol 4(5):602–607