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Clinical exercise interventions in pediatric oncology: a systematic review

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Studies in pediatric oncology have shown a positive effect of physical activity on disease- and treatment-related side effects. Although several reviews have approved the benefits of therapeutic exercise for adult cancer patients, no systematic review exists summarizing the evidence of physical activity in pediatric oncology. We identified a total of 17 studies using the PubMed database and Cochrane library. To evaluate the evidence, we used the evaluation system of the Oxford Center for Evidence-Based Medicine 2001. The findings confirm that clinical exercise interventions are feasible and safe, especially with acute lymphoblastic leukemia (ALL) patients and during medical treatment. No adverse effects have been reported. Positive effects were found on fatigue, strength, and quality of life. Single studies present positive effects on the immune system, body composition, sleep, activity levels, and various aspects of physical functioning. Child-specific aspects such as cognitive abilities, growth, adolescence, and reintegration into peer-groups, school, and sports have barely been taken into consideration. The evidence for exercise interventions in pediatric oncology is rated level "3." Although the results are very promising, future research of high methodological quality and focusing on child-specific aspects is needed to establish evidence-based exercise recommendations, particularly for childhood cancer patients.

As a result of improved treatment regimes in pediatric oncology, the survival rates of children with cancer have risen to ~80% for 5-y survival (1–4). Therefore, the population of childhood cancer survivors is constantly growing. Despite these positive developments, childhood cancer is associated with a wide spectrum of various disease- and treatment-related side effects that may develop into chronic diseases and therefore result in long-term consequences. A negative impact on social, psychological, and physiological levels can be observed. Inactivity (5–7), impaired cardiopulmonary and musculoskeletal function, as well as reduced motor performance levels (8,9) and cognitive abilities (10) have been detected. Current studies also examined a negative impact on psychological well-being, satisfaction, and social functioning (11). Taken together, an impaired quality of life can thus be determined (8,12).

During the past few years, several studies have generated first hints describing holistic, positive effects of clinical exercise interventions in pediatric oncology. First results present an association between increased physical activity levels in childhood cancer patients and an improvement in quality of life (13). In particular, physical functioning is increased, anxiety is reduced, and social integration is encouraged (14). Considering the fact that physical activity plays a vital role in the physiological and psychosocial development of children, therapeutic exercise in pediatric oncology is particularly important. However, there is still a lack of comprehensive and evidence-based data in the field of exercise interventions in pediatric oncology. Therefore, evidence-based exercise recommendations for childhood cancer patients are still missing (15,16).

By contrast, systematic reviews in adult oncology have already been available for some years (17) and have even focused on specific entities such as prostate cancer (18). In pediatric oncology, three reviews (3,15,16) provided an overview of current research with promising results, but to our knowledge, no systematic review on exercise interventions including evidence levels has yet been published. However, this information would be important to establish evidence-based exercise recommendations particularly for childhood cancer patients.

Because multiple studies on clinical exercise interventions in pediatric oncology have recently been published, it seems to be appropriate and necessary to conduct a systematic review, including levels of evidence and quality of trials. Therefore, the objective of the following review is to compile and structure current investigations examining the effects of exercise interventions in pediatric oncology and to evaluate the evidence of these studies for the first time.

RESULTS

According to the defined inclusion and exclusion criteria, 17 studies investigating clinical exercise interventions in pediatric oncology with a total of 282 participating children were included (**Table 1**). Of all the study participants, 257 children were diagnosed with cancer. Six of the identified studies did not enroll a control group (19–26). Ten studies did include 10 or

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Table 1. Evidence levels of clinical exercise interventions in pediatric oncology based on the evidence levels of the Oxford Centre for Evidence-Based Medicine

Reference/type of study	Demographics	Diagnosis	Setting	Form of exercise and exercise control	Measuring point	Main outcomes	Level of evidence
(32)/Case–control study	IG: $n = 10$ (15.3 ± 3.7 y)	IG/CG: stem cell transplanted patients	Supervised in-hospital endurance/strength training (during isolation phase of PBSCT)	IG: 34.1 ± 94 d; 3×/wk, 50 min; cycle ergometer (25 min at 0.6 watt/kg) and additional strength/coordination exercises	t1: day 1 t2: day 14	Acceptance: positive opinion; approved exercise	3b
	CG: $n = 10$ (13.6 ± 4.0 y)			CG: no sports therapy	t3: discharge	Feasibility: grip strength ↑ (NS); QoL ↑ (NS); fatigue ↑ (NS) in IG from t1–t3	
(34)/Case–control study	IG: $n = 12$ (11.01 ± 3.56 y)	IG/CG: ALL	Home-based endurance exercise program (during maintenance chemotherapy)	IG: 6 wk; 3×/wk, 30 min; endurance exercise at 40–60% of HRR (depending on patient's physical functioning) with exercise video	t1: before exercise intervention t2–t7: once weekly during exercise intervention	Feasibility: adherence 67–83%	3b
	CG: $n = 10$ (12.48 ± 3.86 y)			CG: standard care	t8: 1-mo follow-up	Fatigue: general fatigue score ↑ ($P = 0.06$ for ITT and $P = 0.02$ for PP) in IG vs. CG at t8	
(20)/Case series	$n = 9$ (2–14 y)	ALL	Supervised, in-hospital and individual home-based physical therapy program (during medical treatment)	~6–7 mo; initial physical therapy and exercise program (stretching, strengthening, aerobic exercise)	t1: study entry (within 2 wk of diagnosis) t2–t5: after each of the first four phases of chemotherapy	Feasibility: 98%; gross motor function: ↑ from t1–t5; QoL: ↑ from t1–t5, slight ↓ from t4–t5	4
(19)/Case series	$n = 6$ (5–19 y)	Mixed cancer types	Supervised, in-hospital yoga sessions (after induction phase during medical treatment)	2 mo; 5 yoga sessions	t1: before first yoga class t2: after yoga intervention	QoL: physical function (child report) ↑ ($P = 0.016$); all other dimensions (child/parent report) ↑ (NS)	4
(22–24)/Case series	$n = 7$ (5.1 ± 1.2 y)	ALL	Supervised, in-hospital endurance/strength training (during maintenance therapy) and a 20-wk detraining period	16 wk; 3×/wk, 90–120 min. aerobic: 30 min. at 50–70% HR_{max} resistance: one set, 8–15 repetitions, 11 exercises	t1: before exercise intervention	Immune status: no significant changes in IGF-1 and IGF-2, GH, IGFB-2, IGFB-3 from t1–t3; IGFB-1 ↓ from t1–t2 ($P = 0.014$) Adherence: > 85% VO_{2peak}: ↑ ($P < 0.05$) from t1–t2 VT ↑ ($P < 0.05$) from t1–t2 Strength ↑ from t1–t2 ($P < 0.05$) and t1–t3 ($P < 0.05$) Functional mobility ↑ ($P < 0.05$) from t1–t2;	4
					t2: after exercise intervention	Passive DF-ROM ↓ ($P < 0.01$) from t1–t3	
					t3: after detraining period	QoL: no differences	
(33)/Randomized, controlled trial (two-sequence, four-period crossover study)	$n = 30$ (13.6 ± 2.9 y)	Mixed cancer types	Supervised, in-hospital APA (during medical treatment)	IG: >3×/wk; 30 min individualized, supervised training during hospitalization CG: no APA	t1–t4: last day of each hospitalization phase	QoL: IG vs. CG ↑ in physical functioning ($P < 0.0001$), role/social–physical ($P = 0.0011$), self-esteem ($P < 0.0001$), mental health ($P < 0.0001$) in child and parent report; behavior ($P = 0.01$) in child report; bodily pain ($P = 0.0004$) in parent report	2b

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Table 1. (Continued)

Reference/type of study	Demographics	Diagnosis	Setting	Form of exercise and exercise control	Measuring point	Main outcomes	Level of evidence
(27)/Case–control study	IG: $n = 7$ (8 ± 4 y)	IG/CG: high-risk pediatric cancer patients undergoing allogeneic HSCT	Supervised, in-hospital endurance/ strength training (during isolation phase of HSCT)	IG: ~3 wk; 5x/wk, ~50 min aerobic: 50–70% of age-predicted HR_{max} resistance: one set, 8 exercises, 12–15 repetitions	t1: before HSCT	Transplant outcomes: no differences in IG vs. CG from t1–t3	3b
					t2: day 15	Training: adherence (>90%); no adverse effects; aerobic fitness ↑ ($P = 0.034$); muscle strength ↑ ($P = 0.018$) in IG from t1–t3	
	CG: $n = 13$ (7 ± 3 y)			CG: standard care	t3: day 30	Immune cell recovery: dendritic cell count ↓ from t1–t2 and remained stable up to t3 in IG/CG; decrease more abrupt in CG ($P = 0.045$) from t1–t2	
(28)/Randomized, controlled trial	IG: $n = 20$ (1.3–15.6 y)	IG/CG: ALL	Supervised and home-based exercise (during medical treatment)	IG: 2-y exercise program (supervised every 6 wk)	t1: at diagnosis	Motor performance: ↑ (NS) in IG/CG from t1–t4	2b
						BMD_{TB}: ↓ (IG: $P = 0.03$; CG: $P = 0.003$) in IG/CG from t1–t4 and ↑ (IG: $P = 0.004$; CG: $P = 0.002$) in IG/CG from t4–t5	
						Passive ankle dorsiflexion: ↓ (NS) in IG/CG from t1–t4	
						BMI: ↓ (NS) in IG/CG from t1–t4 and ↑ (NS) in IG/CG from t4-t5; ↑ in IG vs. CG ($P = 0.026$) from t4–t5	
					t2–t4: 32 wk, 1 y, and 2 y after diagnosis	body fat: ↑ in IG/CG (NS) from t1–t4 and ↓ in IG vs. CG ($P = 0.013$) from t4–t5	
	CG: $n = 21$ (1.7–17.1 y)			CG: standard care	t5: 3 y after diagnosis (1 y after cessation of treatment)	Unsatisfactory adherence	
(31)/Randomized, controlled trial	IG: $n = 6$ (7.2 ± 0.7 y)	IG/CG: ALL	Home-based nutrition and exercise program (during maintenance therapy)	IG: 12 mo; >3×/wk; 15–20 min moderate to vigorous physical activity and educational nutrition material/activities	t1: beginning of maintenance therapy t2: after 3 mo	Pedometer steps: ↑ ($P = 0.06$) in IG vs. CG at t3; ↑ ($P = 0.02$) in IG vs. CG from t1–t3 and t2–t3; pos. correlation with muscle mass (t2–t3) and BMI (t1–t2)	2b
					t3: after 6 mo	Activity: IG vs. CG ↑ ($P = 0.10$) from t1–t2 and ↑ ($P = 0.14$) from t1–t3; pos. correlation with height (t2–t3), neg. correlation with muscle mass (t1–t2) and BMI/weight (t1–t3)	
					t4: after 9 mo	PACER laps: IG vs. CG ↑ ($P = 0.05$) at t3 and ↑ ($P = 0.09$) from t2–t3; positive correlation with muscle mass (t1–t3)	
	CG: $n = 7$ (5.9 ± 0.7 y)			CG: standard nutrition and exercise recommendations	t5: after 12 mo	Nutrition intake: IG vs. CG no differences from t1–t3	
(26)/Case series	$n = 9$ (9.3 ± 3.2 y)	ALL	Supervised (local physiotherapist) and home-based exercise program (at least 6 mo after last chemotherapeutic treatment)	12 wk; 2×/wk, 45 min, supervised (at 66–>90% of HR_{max}) and 2×/wk home-based exercise	t1: before exercise intervention	Feasibility: can be appreciated	4
					t2: after exercise intervention	Efficacy: no significant changes in muscle strength, exercise capacity, functional mobility, fatigue	

Table 1 (Continued on next page)

Table 1. (Continued)

Reference/type of study	Demographics	Diagnosis	Setting	Form of exercise and exercise control	Measuring point	Main outcomes	Level of evidence
(21)/ Case series	$n = 10$ (16.2 ± 1.6 y)	Mixed cancer types	Supervised group exercise and educational intervention (~62.5 mo postdiagnosis)	16 wk;1×/wk, 90 min; education, endurance, strength, flexibility	t1: before exercise intervention	Attendance: 81.5%	4
					t2: week 8	During exercise program: QoL: emotional health ↑ ($P < 0.05$)/ social health ↑ ($P = 0.05$) from t1–t2; physical health ↑ ($P = 0.01$)/ psychological health ↑ ($P < 0.05$)/ overall QoL ↑ ($P = 0.01$) from t1–t3	
					t3: after exercise intervention	Fatigue: general fatigue ↑ ($P =$ 0.01) from t1–t3	
					t4: 3-mo follow-up	Activity: PA ↑ ($P = 0.02$) from t1–t2 Fitness: endurance ↑ from t1–t2; upper body strength ↑ ($P = 0.04$)/ flexibility ↑ ($P < 0.05$) from t1–t3 Follow-up effects: QoL: physical health ↑ ($P = 0.003$)/emotional health ↑ ($P = 0.01$)/psychological health ↑ ($P = 0.03$)/overall QoL ↑ ($P = 0.02$) from t1–t5	
					t5: 12-mo follow-up	Fatigue: general fatigue ↑ ($P =$ 0.02) from t1–t4; total fatigue ↑ ($P = 0.01$), sleep/rest fatigue ↑ ($P = 0.01$) from t1–t5 Activity: PA ↓ ($P = 0.05$) from t1–t4 Fitness: upper body strength ↑ ($P = 0.05$) from t1–t4; flexibility ↑ ($P = 0.03$) from t1–t5; endurance ↓ ($P = 0.04$) from t1–t5	
(8)/Case–control study	IG: $n = 8$ (10.9 ± 2.8 y)	IG: leukemia (BMT)	Supervised endurance/strength training (~8.9 ± 4.5 mo post-BMT)	8 wk; 3x/wk, 90–120 min endurance and strength training	t1: before exercise intervention	Adherence: 70% Functional mobility: ↑ TUDS in IG vs. CG from t1–t2 ($P < 0.05$); TUG-3m/TUG-10m ↑ in IG from t1–t2 ($P < 0.05$) Strength: strength ↑ in IG from t1–t2 ($P < 0.05$)	3b
				Endurance: 10–30 min at 50–70% HR_{max}	t2: after exercise intervention	Endurance: VO_2 peak in ↑ IG vs. CG from t1–t2 ($P < 0.05$)	
	CG: $n = 8$	CG: healthy matched controls		Strength: 1 set, 11 exercises, 8–15 repetitions		QoL: comfort and resilience (self-report) ↑ in IG vs. CG from t1–t2 ($P < 0.05$); satisfaction and achievement (parent report) ↑ in IG vs. CG from t1–t2 ($P < 0.05$)	

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Table 1. (Continued)

Reference/type of study	Demographics	Diagnosis	Setting	Form of exercise and exercise control	Measuring point	Main outcomes	Level of evidence
(29)/Randomized, controlled trial	IG: $n = 14$ (13.08 ± 2.55 y) CG: 15 (11.92 ± 3.24 y)	IG/CG: solid tumor, AML	Supervised, in-hospital endurance training (during medical treatment)	2–4d, 2x/d, 30 min; endurance training on stationary bike	t1: d 0 t2–t4: d 1–3	Adherence: 85.4% Sleep: sleep efficiency ↑ ($P =$ 0.053)/sleep duration ($P = 0.05$) in IG vs. CG in daily differences from t0 Fatigue: no effect Fatigue intensity scores are related to sleep duration ($P = 0.05$) and negatively related to sleep efficiency ($P = 0.048$)	2b
(35)/Case–control study	IG: $n = 4$ (11.5 ± 5.3 y) CG: $n = 6$ (10.8 ± 4.6 y)	IG: ALL CG: healthy matched controls	Acute, supervised exercise intervention (during maintenance therapy)	30 min, intermittent run-walk on a treadmill at 70–85% of VO_2 peak	t1: fasting t2: preexercise t3: postexercise t4: 1 h postexercise t5: 2 h postexercise	CBC: WBCs ↑ ($P = 0.002$)/ANC ↑ ($P = 0.006$)/ ALC ↑ ($P = 0.003$)/ eosinophil ↓ ($P = 0.003$) in IG from t1–t2; ANC ↓ ($P < 0.100$) from t2–t3; WBCs ↓ / ALC ↓ / eosinophil ↓ ($P < 0.100$) from t2–t4 ALC ↓ ($P =$ 0.000)/ eosinophil ↓ ($P = 0.003$) in IG vs. CG. Neutrophil function: ratio of active neutrophils to resting neutrophils ↑ ($P = 0.048$; 0.074; 0.050) in IG vs. CG at 5, 10, and 15 min	3b
(30)/Randomized, controlled trial	IG: $n = 13$ (4.3–10.6 y) CG: $n = 15$ (5.1–15.8 y)	IG/CG: ALL	Supervised physical therapy and home-based exercise program (during maintenance therapy)	IG: 5 physical therapy sessions and home-based exercises within 4 mo; CG: no exercise recommendations	t1: before exercise intervention t2: after exercise intervention	Active DF-ROM: IG vs. CG ↑ ($P <$ 0.01) from t1–t2 Knee extension strength: IG vs. CG ↑ ($P < 0.01$) from t1–t2	2b
(36)/Case–control study	IG: $n = 6$ (9.11–14.6 y) CG: $n = 11$	IG: mixed cancer types CG: healthy children	Supervised and home-based exercise program (after induction therapy had been completed for at least 4 wk)	IG^1 ($n = 3$): assessments only; IG^2 and CG ($n = 3$): training: 12 wk; 3x/wk, 30 min, 70–85% HR_{max} (1x/wk supervised and 2x/wk home-based); acute exercise: 30-min exercise at anaerobic threshold 7 d after t1 and t2	t1: before exercise intervention t2: after exercise intervention	Immune response to acute exercise: IG^2 vs. CG similar overall leukocytosis and lymphocytosis immune response to training: $CD3^+$, $CD4^+$, $CD8^+$ ↓ in IG^2 from t1–t2	3b
(25)/Case series	$n = 10$ (19 ± 3 y)	Mixed cancer types (>100 mg/m^2 anthracyclines)	Supervised and home-based exercise program (after medical treatment)	12 wk; supervised: 2x/wk, 45–60 min, 60–80% HR_{max} (wk 1–12) and additional home-based exercises: 1x/wk, 60 min, 70–80% HR_{max} (wk 7–12)	t1: before exercise intervention t2: after exercise intervention	Activity: total exercise time ↑ ($P <$ 0.05) from t1–t2	4

ALC, absolute lymphocyte count; ALL, acute lymphoblastic leukemia; ANC, absolute neutrophil count; APA, adapted physical activity; BMD, bone mineral density; CBC, complete blood count; CG, control group; DF-ROM, dorsiflexion range of motion; HRR, heart rate range; HR_{max}, maximum heart rate; HSCT, hematopoietic stem cell transplant; IG, intervention group; IG vs. CG, comparison between cohorts; IGF, insulin-like growth factor; ITT, intention-to-treat analyses; *n*, sample size; NS, not significant; *P*, level of significance; PA, physical activity; PACER, progressive aerobic cardiovascular endurance run; PBSCT, peripheral blood stem cell transplant; PP, per-protocol analyses; QoL, quality of life; t, measuring point; TUDS, timed up and down stairs test; TUG, time up and go test; VT, ventilator threshold; WBC, white blood cells.

↑, improved/better; ↓, deteriorated/worse.

more patients (21,25,27–34). Five randomized, controlled trials have been identified (28–31,33) and were ranked with evidence level "2b." Six studies reached level "3b" as they included a control group but were not randomized (8,27,32,34–36). Six studies were classified level "4" (19–26) because they did not enroll a control group. Only two of all included studies calculated and published confidence intervals (8,31).

Although eight studies were conducted with acute lymphoblastic leukemia (ALL) patients (20,22–24,26,28,30,31,34,35), study cohorts including mixed cancer types have also been examined (19,21,25,29,33,36). The settings differ from supervised exercise intervention (8,19,21–24,27,29,32,33,35) to home-based exercise programs (31,34). Six studies included a combination of a supervised and an additional home-based exercise intervention (20,25,26,28,30,36). Exercise interventions within the hospital were always supervised. Most studies were conducted during medical treatment, but four studies included patients exclusively after cessation of treatment (8,21,25,26). One study included patients during medical treatment, as well as during survivorship (36). Only two studies conducted a home-based exercise intervention during medical treatment (maintenance therapy) (31,34). The duration varies from a short term 2–4-d intervention (29) to a 2-y program (28). One study even investigated the effects of an acute exercise intervention of 30 min on immune parameters (35). However, most studies covered an 8–16-wk training period. Regarding the form of exercise, a combined exercise program including strength, endurance, and coordination was performed in most studies. Three studies analyzed the effect of an isolated endurance training (29,34,35), and one study examined the effects of a yoga intervention (19).

First, the results of all included studies confirm that exercise interventions with childhood cancer patients are feasible and safe. No adverse effects or complications related to the exercise intervention were reported in any of these 17 studies. Within four studies, "feasibility" was one of the main outcomes, and all authors present positive results within this context (20,26,32,35). Adherence has been examined within eight studies and ranges between 67 and 98% (8,21,23,24,27–29,32,35). Only one study with a duration of 2 y reported an unsatisfactory adherence to the exercise program (28). Next to feasibility, all studies included some parameter of physical functioning (i.e., strength, motor function, and endurance) as one of the main outcomes. Fatigue has been evaluated within five of the included studies (21,26,29,32,34) and quality of life within seven studies (8,19–21,23,24,32,33). However, the examination of psychological parameters focused only on quality of life, and a specific psychological analysis has not been conducted yet.

Most studies investigating fatigue as one of the main outcomes present a positive impact of clinical exercise during medical treatment (32,34), as well as during survivorship (21). However, these findings are not confirmed by all authors (26,29). Positive effects were also found on health-related quality of life (8,19,20,32,33) and muscle strength (8,22–24,27,30) during medical treatment and during survivorship (21). Furthermore, clinical exercise interventions have a positive impact on BMI and body fat (28), sleep efficiency and duration (29), and activity levels (21,25,31), as well as ankle dorsiflexion (30), motor function (20), endurance (8,22–24,27), functional mobility (8,22–24), and flexibility (21). In contrast to these positive effects, Hartman *et al.* (28) reported that their exercise program was not more beneficial than standard care in terms of bone mineral density, motor performance, and ankle dorsiflexion. However, this might be due to the unsatisfactory adherence within this study. Takken *et al.* (26) reported no significant changes in muscle strength, exercise capacity, functional mobility, and fatigue during their 12-wk exercise program. However, their program was described as being too demanding.

The effects of clinical exercise on the immune system suggest that physical activity in pediatric oncology can be safely undertaken (22–24,27,35,36). None of these studies focusing on immune parameters found any negative effects that argue against exercise with childhood cancer patients. However, Shore and Shepard (36) recommend a careful monitoring of the immune response.

DISCUSSION

Taken together, the findings of this, possibly first, systematic review on exercise interventions in pediatric oncology confirm that engaging childhood cancer patients in physical activity is feasible and safe. None of the included studies described any adverse effects. In addition, the results present positive effects of supervised physical activity during medical treatment. Although Huang and Ness (15) found evidence primarily in terms of positive effects on muscle strength, flexibility, and cardiopulmonary fitness, we found positive evidence mainly in terms of feasibility, fatigue, muscle strength, and quality of life. Only single studies examined a positive impact on the immune system (22–24,27,35,36), body composition (28), sleep (29), activity levels (21,25,31), and various aspects of physical functioning (8,20–24,27,30). Therefore, it is hardly possible to provide any precise statements about these parameters.

By contrast, the current study situation on exercise interventions with adult cancer patients is considerably better. There is good evidence that exercise has a positive impact on fatigue, physical fitness, quality of life, and strength in adult breast cancer, prostate cancer, leukemia, and lymphoma patients (37).

In addition, it needs to be noted that the main outcomes in all included studies are comparable with those in adult oncology. Fatigue and quality-of-life questionnaires have been specifically developed for children, but the effects of therapeutic exercise on child-specific parameters such as cognitive abilities, motor development, growth, and adolescence have hardly been evaluated. Moreover, the reintegration into peer groups, school, and sport has not been examined, as well. To develop specific exercise interventions for childhood cancer patients, future research must therefore focus on child-specific aspects. In addition, psychopathological aspects such as anxiety, depression, and self-esteem were barely taken into consideration.

The comprehensive evaluation of the identified studies is very challenging because they all differ substantially in terms of study design, outcomes, assessments, duration, and setting. Regarding the study designs, six studies did not enroll a control group (19–26), only 10 studies included a sample of 10 or more patients (21,25,27–34), and only five randomized, controlled trials have been conducted (28–31,33).

In terms of duration and setting, the exercise interventions differ as well. Whereas most studies were conducted within a 6–16-wk period, long-term trials of 1–2 y could be found. Furthermore, most exercise interventions have been conducted within a study cohort of ALL patients and were carried out during medical treatment. Except two (31,34), all studies were supervised programs that present a higher adherence as compared with home-based programs. To date, this large heterogeneity in terms of study design, duration, and setting makes it impossible to define evidence-based exercise recommendations. However, practical experience reveals that therapeutic exercise programs for childhood cancer patients are partly integrated into the therapeutic care structure of some childhood cancer centers. For the main part, these programs differ substantially. Future research must focus on exercise intervention studies that are not only feasible and safe but also realistic and transferable so that childhood cancer patients and their families are able to integrate them into their everyday lives. Research must focus on cancer diagnosis other than ALL, as well as on patients during survivorship and child-specific outcomes.

The overall study situation on exercise interventions in pediatric oncology is considered to be limited. Current literature includes primarily explorative, descriptive pilot studies. In summary, the evidence for clinical exercise interventions with childhood cancer patients is rated evidence level "3." However, it must be noted that the ranking of all studies according to the Oxford Levels of Evidence-Based Medicine has been conducted without considering confidence intervals, because only two studies reported those. Therefore, studies might be under- or overrated. In addition, certain subjectivity might exist, although all evaluation systems are associated with some restrictions (38–40). Another unavoidable limitation of this systematic review is the literature research. Although a systematic and comprehensive research has been performed, possibly not all relevant studies were identified.

Taken together, this systematic review provides evidence that clinical exercise interventions in pediatric oncology are feasible and safe. Relatively good evidence is given in terms of positive effects of supervised exercise programs during medical treatment on fatigue, muscle strength, and quality of life. However, because most studies were conducted within a study cohort of ALL patients, this review provides the best evidence only within this patient group. Future research must therefore focus on cancer diagnosis other than ALL, as well as on patients during survivorship. Exercise intervention studies must be designed to be realizable and transferable into the everyday life of childhood cancer patients. In addition, relevant child-specific outcomes and appropriate assessments must be determined to evaluate the holistic effects of therapeutic exercise specifically on childhood cancer patients. Consequently, as presented in other reviews, the current literature not only provides promising results but also reveals challenges to be faced in the future (3,12,13,15,16).

METHODS

This review focuses on clinical exercise interventions among pediatric cancer patients. Throughout August 2012, two independent researchers identified studies by searching the PubMed database and Cochrane library. The search terms listed in **Table 2** were entered in different

Table 2. Search terms involving physical activity and childhood cancer used in different combinations

Category	Search term
Indication	"cancer" OR "oncology"
Population	"pediatr*" OR "child*" OR "adolescent"
Physical activity	"exercise" OR "motor performance" OR "physical activity" OR "sport* therapy" OR "physical functioning" OR "fitness"

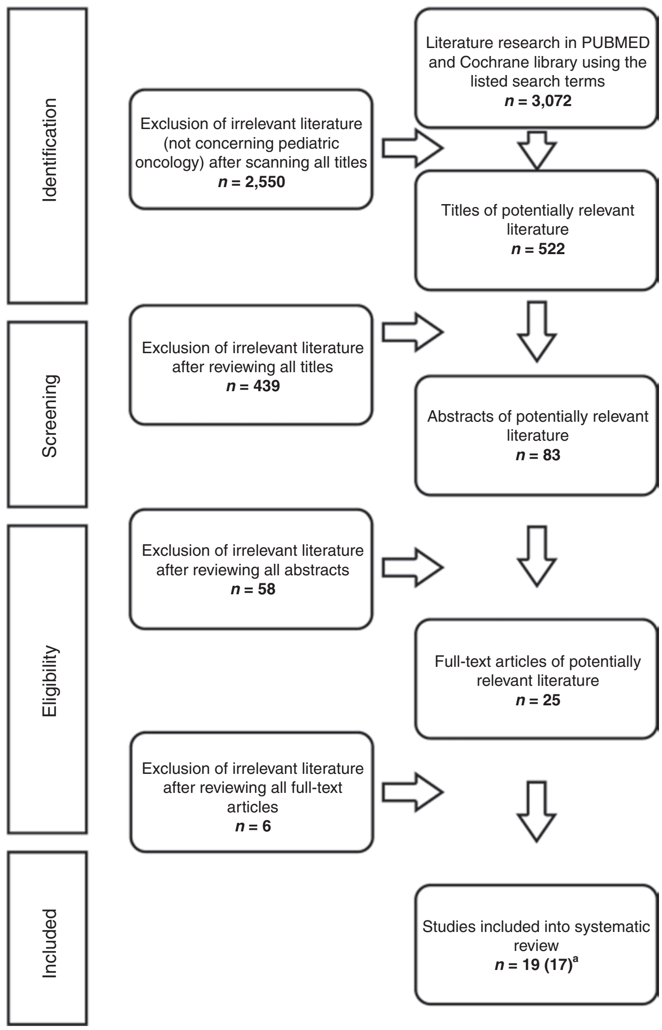

Figure 1. Course of literature research and study design. *n*, number of included papers. [a]Although 19 full-text articles were included in this review, only 17 studies are presented because the results of one study have been published in three articles.

combinations. Reference lists of selected papers were also tracked to find additional studies related to our topic. Related reviews were scanned to find further relevant information. According to defined inclusion and exclusion criteria, only studies investigating exercise interventions with pediatric cancer patients (0–21 y of age), published in the English language, were included. Studies published before 1990 or focusing on physical activity behavior or motivation were excluded.

To evaluate the evidence of the included studies, the evaluation system of the Oxford Center for Evidence-Based Medicine 2001 was used because it has been specially developed to evaluate the evidence of therapeutic interventions (40,41). This evaluation system contains five levels of evidence ranked from 1 (least potential bias) to 5 (most potential bias) and is primarily based on the study design. The best evidence (level "1a") is given by systematic reviews of randomized controlled trials. Randomized controlled trials with narrow confidence intervals are ranked level "1b," whereas individual cohort studies or low-quality randomized controlled trials are ranked level "2b." Individual case–control studies reach level "3b," and case series or poor-quality cohort and case–control studies are ranked level "4." Therefore, the quality of the study and the reported results are considered likewise, as well (40,41). Ranking studies according to these defined levels of evidence enable the determination of a lack of evidence within a specific field of research. This might help future researchers to generate specific studies aiming to improve therapeutic exercise in pediatric oncology.

As shown in **Figure 1**, titles, abstracts, and full-text articles were viewed considering the inclusion and exclusion criteria. Finally, 19 full-text articles focusing on clinical exercise interventions in pediatric oncology were included in the following systematic review. However, only 17 studies are described within this review because the results of one study have been published within three different articles. All included studies examined some of the following parameters: acceptance and feasibility, quality of life, physical function/functional mobility, immune status, fatigue, bone mineral density, ankle dorsiflexion, body composition, activity, and/or sleep.

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