TITLE PAGE

Effectiveness of Therapeutic Exercise for Children Undergoing Treatment for Cancer: A Systematic Review.

Therapeutic exercise children cancer

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Authors' contributions

ML-B revised the design, conducted the systematic search, conducted study selection, quality appraisal, acquired data from selected studies, developed statistical analysis and interpretation, and wrote the manuscript.

CG-C conducted study selection, reviewed quality appraisal, helped interpreting acquired data and co-wrote the manuscript.

LR-P reviewed study selection, quality appraisal and helped interpreting acquired data.

AC-V is guarantor, designed the study, supervised the methodology and interpretation, and made substantial contributions.

MT-F is guarantor, validated study selection, quality appraisal, acquired data from selected studies, reviewed interpretation, and drafted the manuscript.

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ABSTRACT

Purpose: To evaluate the effectiveness of therapeutic physical exercise (TPE) interventions on the physical functioning, psychosocial well-being and quality of life (QOL) of children undergoing treatment for cancer.

Method: Systematic Review. Databases were searched in April 2023. Selection criteria: Pediatric (<18 years old), undergoing treatment for cancer or a malignant neoplasm, randomized-controlled-trial (RCT) design, utilization of TPE and including physical and psychosocial outcomes. Internal validity was measured with PEDro scale.

Results: 7 RCTs were included. Most studies showed that strength (d = 1.30-0.14), fatigue (d = 1.00), and QOL improved (d = 0.9-0.23) after the intervention. Cardiorespiratory capacity through 6-minute walk test (6MWT) (d = 1.04-0.14) and physical activity levels (d = 1.24-1.09) were better in the experimental groups. No changes were noted in other variables.

Conclusions: This review reveals the importance of a TPE program during cancer treatment, with the aim of maintaining physical capacities and counteracting physical inactivity.

WHAT THIS EVIDENCE ADDS
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Current Evidence: Evidence from Developmental studies supports the concept that the adverse effects produced by both treatments and the disease itself can be reduced or attenuated with TPE[11]. Multiple studies have supported this relationship in adults with cancer, mostly research that evaluates cancer survivors outside of oncological treatment.[12]
Gap in the Evidence: There is a large amount of evidence on the effect of exercise in adults with cancer, however, systematic reviews analyzing the effects of exercise in children with cancer are

scarce. To the best of our knowledge, a similar systematic review exists, however, it excludes studies in which the main objective is correct physical fitness through aerobic, anaerobic, strength or combined exercise programs.
How did this study fill this evidence gap? We will evaluate the effects of EFT physical therapy intervention to promote physical activity, reduce fatigue, improve physical activity self-efficacy, muscle strength, and quality of life among children with cancer undergoing cancer treatment.
Implication of all the evidence to clinicians: The relevance of a regular, adapted, and supervised EFT program throughout cancer treatment, with the aim of maintaining children's autonomy and participation in clinical routine and counteracting physical inactivity and decreased motor performance. Pediatric oncology patients should have access to a structured exercise program early after diagnosis. Considering the difficult interaction of neuromotor, musculoskeletal and cognitive mechanisms involved in the performance of daily tasks, these patients could potentially benefit from intervention with exercise and specialized physiotherapy.

INTRODUCTION and PURPOSE

Cancer is one of the main causes of mortality in childhood and adolescence; it is estimated that each year about four hundred thousand children and adolescents under 18 years of age suffer from cancer.[1,2] The most typical types of cancer in pediatrics are leukemia, brain tumors, lymphomas, and solid tumors such as neuroblastoma and Wilms tumors.[1,2] In high-income countries, with access to comprehensive care services, more than 80% of affected children are cured, however, in low- or middle-income countries, less than 30% are cured.[1,2] Most childhood cancers can be cured with generic medications (antineoplastic treatments) or other types of treatments such as surgery.[3] Systemic and local antineoplastic treatments typically include similar treatment modalities, chemotherapeutic medications, and polypharmacy administered in different doses and combinations depending on the disease and severity, producing anticipated side effects that contribute to decreased fitness in children with cancer.[4]

Several studies have shown that variables such as strength, body composition, fatigue, and quality of life are affected during and after cancer treatment.[5] After diagnosis, most children with cancer experience a decrease in physical activity levels, which leads to muscle catabolism and atrophy that accentuates cancer-related fatigue and loss of strength.[6] Fatigue is the most

common symptom reported by children with cancer and negatively affects health-related quality of life (HRQoL).[7] Furthermore, corticosteroids and methotrexate (MTX) are known to cause a reduction in bone mineral density (BMD) and, according to several studies, BMD is already low at the time of diagnosis of some tumors such as acute lymphoblastic leukemia and decreases even more so during the treatment period.[8]

Therapeutic physical exercise (TPE) is considered an intervention strategy that seeks to improve or maintain the functional abilities of the subject.[9] Exercise is a useful and necessary tool for the physical and mental well-being of the general population, and is essential in patients who have a chronic pathology that affects the quality of life.[10] Exercise produces improvement at a systemic level; it produces cardiovascular, musculoskeletal, and endocrine benefits, among others.[10] In cancer, the adverse effects produced by both the treatments and the disease itself can be reduced or attenuated by TPE.[11] Exercise interventions can help improve physical fitness and reduce physical and psychosocial side effects during and after treatment and contribute to improved functional outcomes in this population.[12] Given that children with cancer are less physically active, it is important to further explore the improvement of variables such as cancer-related fatigue, quality of life, strength, or body composition, through increased physical activity.[13]

There is a large amount of evidence on the effect of exercise in adults with cancer, however, systematic reviews analyzing the effects of exercise in children with cancer are scarce. There is a previous systematic review, which analysed exercise effects in childhood cancer but it is outdated and they did not analyse exclusively children during treatment.[14] Therefore, based on the new medical paradigm of TPE, this review aims to evaluate the effects of physical therapy intervention with TPE to promote physical activity, reduce fatigue, improve physical activity self-efficacy, muscle strength and quality of life among children with cancer undergoing treatment for the disease. The hypothesis is that a specific TPE program may have positive

effects on quality of life, strength, cancer-related fatigue, depressive symptoms, etc. In pediatric patients undergoing cancer treatment.

METHODS

Design

This systematic review has been developed in accordance with the references to publish Systematic Reviews and Meta-analysis of The Prisma Declaration 2020[15] and registered in PROSPERO database (Registration: CRD42023442932).

Data Sources and Searches

A literature search has been carried out using the Pubmed, Embase and PEDro databases, selecting articles published until April 2023. The filter was applied exclusively to restrict the search to randomized clinical trials (RCTs) and patients where the age ranges from 0 to 18 years. The language of the articles or their publication date was not restricted. The terminology selected was based on Medical Subject Heading (MeSH) and Emtree by combining three broad concepts: (i) exercise therapy (MeSH) or kinesiotherapy (Emtree), (ii) neoplasm (MeSH) or cancer (Emtree), and (iii) pediatrics. Extended information about search strategies is provided in Supplemental File A.

Study Criteria

Randomized controlled trials (RCTs) meeting the previously established PICO (Population, Intervention, Comparison, Outcomes) were considered the framework of this review. The inclusion criteria were:

(i) Population: pediatric with an ongoing treatment for cancer or a malignant neoplasm.

(ii) Intervention: TPE

(iii) Comparison: any form of comparator, also in an isolated manner.

(iv) Outcomes: strength, fatigue, quality of life, body composition and/or psychosocial effects.

Duplicated studies were removed prior to the screening phase. This phase was performed by two researchers of this study independently. A third author was used to find consensus. Studies were excluded in the review if they met the following requirements during the title and abstract screening: (i) non-RCT studies and/or (ii) studies about pathologies other than cancer. The next step was the full-text reading where exclusion criteria were: (i) adult population in the interventions, (ii) cancer survivors not receiving treatment, and (iii) information not related to the PICO.

Quality Assessment

The RCTs were evaluated for methodological quality using the Evidence-Based Physiotherapy (PEDro) database.[16] It consists of 11 items, in which the first section has been omitted (specified inclusion/exclusion criteria) and each section that is answered with a "yes" is scored with 1 point and 0 points with a "no". The closer to 10 points, the better the quality of the study.

The sections to analyze were: (i) Random assignment, (ii) Blinded assignment, (iii) Baseline comparability, (iv) Blinded subjects, (v) Blinded therapists, (vi) Blinded raters, (vii) Adequate follow-up, (viii) "Intention-to-treat" analysis, (ix) Comparisons between groups, (x) Point estimates and variability.

Quality assessments were independently conducted by two researchers and discrepancies were solved with a third reviewer.

Data Extraction and Data Synthesis

A narrative synthesis from the TPE intervention in children with cancer was conducted. The characteristics of the participants in each study (participants in each group, mean age, gender, type of cancer, treatment, and inclusion criteria), the characteristics of each study (number of participants, objective, intervention, clinical variables, and preclinical variables) and the statistical results (mean, standard deviation, median, range or p statistic) were extracted from the included RCTs. The variables related to physical capacities were strength, endurance, cardiorespiratory fitness, range of joint motion, motor performance, activity levels, and fatigue. The psychosocial variables were dimensions based on depression and self-perception. In addition, bone mineral density and quality of life were also extracted. For the comparison between groups, priority was given to the group-time interaction if the authors of the study had calculated it.

The statistical results are presented in the results section (table 4), through Cohen's d value or partial N^2 (N^2_p), a main outcome calculated to interpret the "effect size" based on the differences between two means (control group and intervention group). This data is reflected in the results section if there was a significant difference in the inferential analysis. The authors calculated the Cohen's d value if it was not shown in the study. The effect size was classified into four categories according to Cohen's suggestions: $d < 0.2$ = trivial effect size; d between 0.2 and 0.5 = small effect size; d between 0.5 and 0.8 = medium effect size; $d \geq 0.8$ = large effect size. The significance level was set at 0.05.

RESULTS

Study selection

Firstly, a total of 598 articles were obtained; after eliminating duplicates, 504 articles were obtained, of which 429 were not RCTs and 24 did not discuss the pediatric oncology population. The final studies were selected based on a reading of the information contained in the full text

of the remaining 51 documents. 25 of them were excluded because they did not offer conclusive information for carrying out the review. 14 of them spoke about the survivor population and 5 studies were about adults with cancer. Finally, 7 RCTs met the established inclusion criteria. The methodological quality of these studies ranges from 5 to 7 on the PEDro Scale. More information about the quality appraisal is described in Table 1. All of RCTs were included in the systematic review.[6,17–22]

The number of studies selected from each database and the number of studies excluded in each screening phase are shown in a flow chart in Figure 1. The studies, characteristics, and statistical results of each one is found in the tables 2-4.

Characteristics of the samples

The population chosen for the trials of this systematic review has a series of characteristics that are detailed in Table 2. All studies include both female and male populations between 5 and 14 years old who are undergoing treatment against acute lymphoblastic leukemia or another type of malignant neoplasm such as a brain or bone tumor. Treatments are based, above all, on cycles of chemotherapy and/or radiotherapy and on surgical processes to extract tumor cells. The participants of the 7 RCTs selected to carry out this review exhaustively meet the inclusion criteria established by the selectors.

Characteristics of the intervention

All the selected studies pursue the objective of carrying out a TPE program that produces positive effects on physical capacities and psychosocial effects in pediatric oncology patients. To do this, an intervention with a TPE program is carried out on an intervention group and the results are compared with a control group of participants who follow a standard cancer treatment process. In two of the studies, the results of the effects of TPE in children with cancer are compared to the expected normative values by age, sex, and race.

In table, the outcome measures are separated into Clinical Variables, such as scales and tests that are used to assess different competencies at a functional level, and Preclinical Variables, such as vital signs and other neurophysiological parameters involved in physical conditioning performance and health. All the studies performed an intention-to-treat analysis.

Results of the outcomes after the TPE intervention

Outcomes for strength, cardiorespiratory fitness, physical activity levels and motor performance, fatigue and psychological effects are shown in Table 4.

Strength

Overall, the TPE intervention showed statistically significant effects on the strength, however the results were not homogeneous according to the muscle groups analyzed. One study found a large effect (1.28-1.30) of the TPE in hand grip strength [6] accompanied by a significant decrease in the strength of the control group during the intervention.[21] On the other hand, Gaser et al. did not find any important difference in the hand grip strength after the intervention.[20] Regarding the lower limbs, two studies gave significant differences with a small effect in the lower limb strength with a dynamometer in favor of the TPE (0.18-0.22).[18,22] However, the sit-to-stand test did not show differences between the TPE and the control group.[20] Finally, the strength of upper limbs was greater in the intervention group according to the dynamometer and the explosive strength performance (d = 0.14)[18,20] but other authors did not find any differences in this variable.[22]

Cardiorespiratory fitness

The cardiorespiratory fitness was analyzed using different parameters. According to the 6MWT performance, the TPE showed good and solid results due to the improvement in the distance during the test. The intervention group had a small to good effect over the control group in two different studies.[21,22] Regarding the VO2 peak, there is no change between groups [18] but both

were reduced in one study.[21] Finally, the endurance measured by a sports physical test was better in the TPE group after the intervention.[19]

Physical activity levels and motor performance

Three studies confirmed improvement in the physical activity levels after the TPE program over the control group with a large effect (d = 1.24) using different scales or questionnaires.[6,19,22] Additionally, a pedometer showed more steps in the intervention group against the control group.[19] No differences were found in the motor performance tests.[17,20]

Fatigue

Analysis of the effect of TPE on cancer-related fatigue revealed statistically significant main effects between interventions. One study found a large effect on fatigue using a TPE intervention instead of the control group (d = 1.00).[6] Furthermore, fatigue levels improved only in the experimental group after the intervention in another study.[22] On the other hand, no differences were shown regarding fatigue in the Braam et al. study.[18]

Psychosocial effects and HRQoL

Only two studies analyzed the changes in the psychosocial effects during the TPE program. There were no differences in the self-esteem and competence dimensions.[18] Depression according to a scale was reduced in the control group in one study.[18] However, self-efficacy was better in the intervention group with a large effect size in other studies (d = 1.09).[6]

According to the included studies in this systematic review, two studies confirmed the improvement in the HRQoL in favor of TPE program.[6,18] The effects of these improvements in the intervention groups were from small to large (d = 0.23-0.91). One of these studies found a better HRQoL in the control group.[18] Nevertheless, another study showed a worse quality of life in both groups, although the decrease in the TPE group was less than in the

control group. Some specific subscales showed different results in both groups according to one study.[22]

Bone mineral density

The results about the TPE in the bone mineral density were different according to each study. There were improvements in both groups in the pre-post analysis in the density of the total body.[17] Regarding the bone mineral density in the lumbar spine, opposite results were found in two studies. Braam et al. proved significant differences in favor of the TPE group with a small effect (0.23). Other studies did not present differences between groups in the pre-post analysis.[17]

DISCUSSION

Our review focused on the effectiveness of the application of a TPE program to improve physical capacities and reduce psychosocial effects among children with cancer undergoing treatment for the disease. The importance of this systematic review of RCTs is to explore the quality and results of these studies in relevant outcomes such as physical activity, fatigue, or depression. As hypothesized, there was a general improvement in TPE group, but the effectiveness differed among studies. Regarding the quality of the studies, all of them obtained 5/10 as a minimum. The main issue was the difficult blinding process that is predominant in exercise intervention.

The summary of the results confirms the improvements due to exercise in children undergoing treatment for cancer [14,23,24], proving that this therapeutic tool is safe, effective and feasible.[25] Positive effects of exercise interventions during childhood cancer treatment have been demonstrated on activity level, muscle strength, cardiorespiratory fitness, HRQoL, and decreased levels of cancer-related fatigue. In addition, physical impairments, primarily muscle weakness, are associated with early reports of poor HRQoL, both among parents and among

the children themselves.[23] On the contrary, the effects of TPE on psychosocial outcomes were not clear because there were several discrepancies between studies, however, we can highlight positive effects mentioned in other articles such as the decrease in stress levels.[26] The highlights of this study can help clinicians and other health professional support exercise intervention in children undergoing chemotherapy or radiotherapy.

Physical capacities

Thanks to this systematic review, many physical abilities that are sensitive to exercise have been reviewed. Overall, there is an improvement in these with the programs, but there are data that are more strongly contrasted than others depending on the capacity. According to the results of this review, strength is a parameter that is generally improved with TPE intervention but there are some results that are contradictory. Across the selected studies, most of them demonstrated an improvement or a maintenance of strength in the TPE group compared to the control group.[6,18,20,22] The lower limb strength, which is the most affected part of the body in these patients, improved during the post-intervention dynamometer assessment.[27] In addition, a loss of strength in hand grip in the control group was demonstrated during treatment.[21] Although the two studies did not find differences between groups and measurements, it is relevant to comment that muscle weakness, active motion, and hand grip are reduced with the administration of chemotherapy treatment, such as vincristine and intrathecal methotrexate, which are neurotoxic.[28] Another important point is the duration of the intervention. Braam et al. shared the message that this great improvements in strength appeared in the long-term or during the last doses of treatment.[18] Nevertheless, other studies found short-term effects on lower limb strength thanks to a TPE.[19,29] Thus, the treatment doses can be important to determining the success of the exercise program, although the benefits of it seem to be clear during and after the treatment.[24]

Fatigue is a common feature during and after oncology treatment and can become chronic, having a negative impact on daily life.[30] Overall, participants in the experimental group reported significantly lower levels of fatigue than the control group after the program.[6,22] This may be explained by increased physical activity levels among participating children, which improved cancer-related fatigue as shown in other studies with childhood cancer patients.[31] On the other hand, Braam et al. did not prove any differences in both groups regarding fatigue.[18] There are several reasons exposed in the literature to consider that can change the intervention effect on fatigue. Depending on the condition grade and treatment, fatigue is a common symptom in these patients as well as dyspnea or cough.[32] Besides the sequalae, a good physical fitness level prior to diagnosis is related to the risk of fatigue.[31] We cannot forget that it is necessary to rethink new forms of evaluation to detect the degree of fatigue related to cancer.[33] On the other hand, the cardiorespiratory fitness improvement was found clearly in two studies assessing the performance with two different functional tests.[21,22] The use of the 6-MWT has been shown as a good reference in the evaluation of childhood cancer survivors [34], so the inclusion of this test while undergoing cancer treatment is necessary too. According to other cardiorespiratory outcomes, VO_2 maximum peak did not change positively in any study.[18,21] It was very noticeable how the peak decreased significantly in both groups in the Senn-Malashonak et al study.[21] Some authors point to the cardiotoxic effects of the ongoing treatment.[35] This fact makes sense with the significant improvement shown by childhood cancer survivors in the VO_2 maximum peak.[36,37]

Nielsen et al. showed significant differences over time in the same value in the intervention group.[38] Specifically, the peak was reduced during the 3-months follow up but improved in the 6-months follow up more than the baseline peak.[38] For this reason, engaging children with cancer in physical activity through an integrated program can positively affect cancer-related

fatigue and cardiorespiratory fitness, but health professionals should design better TPE according to the treatment dose.

The physical activity levels were measured also in three studies and they proved the importance of the TPE in an active lifestyle.[6,19,22] These authors used scales and pedometers to show how the TPE groups became significantly more active according to the self-perception of the patient and the achieved steps/distances. Implementation programs to improve physical activity levels are mandatory in young people due to the risk of multimorbidity in survivors [39] so, its monitorization must be a priority during the ongoing treatment. The beneficial effect of exercise in this clinical population agrees with other systematic reviews focused on physical activity levels.[40] Health providers should use the TPE intervention to promote a change in the patients, setting… a long-term goal that these patients exercise after treatment and during their lifespan. For this aim, researchers must increase the body of literature with homogenous assessment tools and with a higher degree of accuracy, validity, and specificity which will ultimately contribute to the generation of formal recommendations or guidance on appropriate physical activity levels for researchers, healthcare providers, and policymakers.[41]

Psychosocial effects and HRQoL

The process that leads to the disease, directly affects the quality of life and the development of depressive and anxious symptoms. There is a significant association between the symptomatology of depression and HRQoL.[18] Psychosocial effects outcomes were measured only in two studies.[6,18] Surprisingly, there was an improvement in depression only in the control group after the intervention in the study by Braam et al.[18] The authors themselves do not provide a justification for this finding. Despite this, other studies also reported similar changes.[42,43] A theory to explain this may be the different way of perceiving the uncertain future from the earliest stages of cancer compared to the final ones, and it seems that exercise does not influence

this according to the few studies carried out on the subject.[42] Psychosocial features were assessed briefly such as self-steem, competence, and self-efficacy. Only self-efficacy improved significantly in the intervention group compared with the control group.[6] It is very relevant to improve self-efficacy because this allows the patient to better confront the barriers that may exist to exercise and continue with the practice, obtaining all the possible benefits of an active lifestyle.[44]

Regarding quality of life, participants in studies that received an TPE program showed an increase in HRQoL from the start of the intervention.[6,18,22] The improvement in quality of life among participants in the experimental group can be attributed to improved fatigue, which is the most prevalent symptom in children with cancer.[6] Nonetheless, other authors found a worse HRQoL after the intervention in both groups where the decrease in TPE group was less.[21] Authors justified the finding with the possible isolation and lack of social support that children could have during the treatment.[21] The significant associations between psychosocial factors and HRQoL indicate that psychosocial factors may be important intervention targets to improve HRQoL.[18] Furthermore, physical capacities at diagnosis may negatively affect HRQoL.[45] Future studies should find more effective strategies to improve psychosocial function in order to improve the HRQoL of these patients [18] and should include muscle strengthening and physical fitness components to address presenting skeletal and motor deficits.[45]

Limitations of the systematic review

The results of our review should be considered in the context of certain potential limitations. Although there are possible benefits on physical capacities and HRQoL, longer studies are required to achieve solid new results. In addition to the longer intervention, the long-term effects, and benefits of an integrated training program in children with cancer remain uncertain, having potential to influence thanks to the active lifestyle change. Another important issue

identified was incomplete physical fitness assessments to examine the effect of the training program, as they typically only assess hand grip strength and/or lower limb extension strength. More evidence is needed about other parameters that can provide reliable information about the TPE program such as bone mineral density, fractures, body composition, and motor performance.

CONCLUSIONS

The results of this review reveal the relevance of a regular, adapted, and supervised TPE program throughout cancer treatment, with the aim of maintaining the autonomy of children, increasing participation in the clinical routine, and counteracting physical inactivity. There is increasing evidence about the effectiveness of physical activity treatment in decreasing cancer-related fatigue and improving muscle strength, cardiorespiratory fitness, activity level, and HRQoL among children with cancer. In conclusion, the positive association between physical activity and quality of life, and the many other health benefits of an active lifestyle, are important to encourage physical activity in childhood cancer patients. The current findings may be useful for future studies to define the training content, duration, and intensity of exercise interventions.

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Table 1 R5

Table 1. PEDro SCALE ASSESSMENT

Study	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*TOTAL*
Lam et al. 2018[6]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7/10
Braam et al. 2018[18]	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7/10
Gaser et al. 2022[20]	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6/10
Senn-Malashonak et al. 2019[21]	Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	5/10
Stossel et al. 2020[22]	Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	5/10
Moyer-Mileur et al. 2009[19]	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5/10
Hartman et al. 2009[17]	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	5/10

PEDro scale items: 1. Random assignment, 2. Blinded assignment, 3. Baseline comparability, 4. Blinded subjects, 5. Blinded therapists, 6. Blinded raters, 7. Adequate follow-up, 8. “Intention-to-treat” analysis, 9. Comparisons between groups, 10. Point estimates and variability.

Table 2. DESCRIPTION OF THE PARTICIPANTS OF EACH RCT.

	N		*MIDDLE AGES*		*GENDER*		*TYPE OF CANCER*		*TREATMENT*	*INCLUSION CRITERIA*
	IG	**CG**	**IG**	**CG**	**IG**	**CG**	**IG**	**CG**		
Hartman et al. 2009[17]	25	26	5.3	6.2	56% children. 44% girls.	62% children. 38% girls.	84% type B lineage ALL 16% T-lineage ALL	77% type B lineage ALL 23% T-lineage ALL	Dutch Children's Oncology Group (DCOG) ALL-9 protocol: 1. Induction therapy with dexamethasone and vincristine. 2. High doses of MTX. 3. Maintenance therapy with pulses of 6-mercaptopurine/MTX + vincristine/dexamethasone. Patients with high-risk ALL: - 1st + anticyclines. - Higher doses of MTX. - Two additional intensification courses. Patients did not receive CNS irradiation.	▪ Patients with ALL. ▪ Age 1-18 years. ▪ Correct cognitive development. ▪ Correct command of the Dutch language.
Lam et al. 2018[6]	37	33	12.8	12.5	54% children. 46% girls .	45% children. 55% girls .	43% leukemia. 19% lymphoma. 16% brain tumor. 11% germ cell and gonadal tumors. 5% bone tumor. 6% others.	43% leukemia. 24% lymphoma. 15% brain tumor. 6% germ cell and gonadal tumors. 6% bone tumor. 6% others.	▪ 70% chemotherapy. ▪ 7% surgery. ▪ 23% mixed method.	▪ Diagnosed with cancer sometime in the previous month and currently undergoing active treatment. ▪ Age 9-18 years. ▪ Correct cognitive development. ▪ Correct command of Cantonese and Chinese.

Braam et al. 2018[18]	30	38	13.4	13.1	53% children. 27% girls.	55% children. 55% girls.	40% AML, NS, NHL, CML, Burkitt. 3% CNS brain tumor. 30% solid tumor. 27% others.	34% AML, NS, non-HL, CML, Burkitt. 16% brain tumor. 18% solid tumor. 12% others.	Chemotherapy and/ or radiotherapy .	▪ They were currently receiving or were within the first year after cancer treatment. ▪ The remaining treatment period did not include planned hospitalization. ▪ Age 8-18 years. ▪ The clinical condition made exercise possible.
Moyer-Mileur et al. 2009[19]	6	7	7.2	5.9	50% children. 50% girls.	60% children. 40% girls.	Standard risk ALL.	Standard risk ALL.	Treatment with chemotherapy and/or radiotherapy. Treatment phases: 1. Induction phase with vincristine and dexamethasone. 2. Consolidation phase with vincristine, mercaptopurine, methotrexate. 3. Interim maintenance phase.	▪ Patients with standard risk ALL. ▪ Age 4-10 years. ▪ Not treated with cranial irradiation.
Gaser et al. 2022[20]	21	20	10.1	9.2	71% children. 29% girls.	60% children. 40% girls.	52% ALL. 5%AML 43%NHL.	70% ALL. 15% AML. 15% NHL.	Treatment with chemotherapy or radiotherapy.	▪ Primary or secondary diagnosis of ALL, AML or NHL. ▪ Age 4-18 years. ▪ Correct command of English.

Senn-Malashonak et al. 2019[21]	28	29	11	12	71% children. 29% girls.	66% children. 34% girls.	63% leukemia. 9% MDS. 6% neuroblastoma. 14% hematological disease. 3% soft tissue sarcoma. 5% lymphoma.	43% leukemia. 11% MDS. 6% neuroblastoma. 14% hematological disease. 11% soft tissue sarcoma. 9% lymphoma. 3% nefroblastoma. 3% nasofaringecarcinoma.	Treatment with chemotherapy or radiotherapy.	▪ Age: >5 years. ▪ Indication for an autologous or allogeneic transplantation. ▪ No evidence of cardiac, pulmonary, orthopedic, or neurological diseases. ▪ Disorders with indication for physical therapy. ▪ No insurmountable language barriers.
Stossel et al. 2020[22]	16	17	10,6	11,4	62,5% children. 37,5% girls.	59% children. 41% girls.	50% leukemia. 12,5% CNS-tumor. 37,5% others.	41% leukemia. 12% CNS-tumor. 47% others.	Treatment with chemotherapy and/or radiotherapy.	▪ Age: >4 years. ▪ Patients with an oncological disease.

IG, Intervention group; CG, Control group; ALL, acute lymphoblastic leukemia; MTX, methotrexate; CNS, central nervous system; AML, acute myeloid leukemia; NS, nervous system; NHL, non-Hodgkin lymphoma; CML, chronic myeloid leukemia; MDS, myelodysplastic syndromes.

Table 3. DESCRIPTION OF THE STUDIES.

	AIM	*IG*	*CG*	*MEASUREMENT MOMENTS*	*RESULTS*		*ANALYSIS METHODS*
					PRECLINICAL VARIABLES	**CLINICAL VARIABLES**	
Hartman et al. 2009[17]	To investigate whether an exercise program starting at the beginning of ALL treatment has a beneficial effect on BMD, body composition, motor performance and passive knee dorsiflexion.	**Exercise program**: ▪ Exercises to maintain the function of hands and legs: once a day. ▪ Stretching and jumping exercises: twice a day. ▪ Initial education session. ▪ Follow-up sessions every 6 weeks with the pediatric physiotherapist, over a period of 2 years: evaluation of the child's main motor skills, discussion and adjustment of the program.	▪ Care for this group did not include either an initial session or pre-scheduled follow-up sessions with the physical therapist. ▪ If the child or parents reported motor problems to the doctor, they were assigned a local physical therapist.	T1: 6/8 weeks (End of the intervention) T2: 1 year T3: 2 year (End of the treatment) T4: 3 years	**DMOtotal and DML:** • Dual energy x-ray absorptiometry. **Apparent bone mineral density of the lumbar spine ($BMAD_{LS}$):** • $BMAD_{LS} = BMD_{LS} \times [4/\pi \times width]$	**Passive ankle dorsiflexion:** • Goniometry. • Supine position with knee extended. **Engine performance:** • Bayley Scales of Infant Development of Movement-ABC. For children under 3.5 years old. • Dutch version of the Movement Assessment Battery for Children (movement-ABC). For children over 4 years old.	Mann-Whitney U test/t-student test Repeated measurement analysis

Lam et al. 2018[6]	Reduce fatigue, increase physical activity levels, promote physical activity self-efficacy, muscle strength and QoL in IG participants.	**During hospitalization:** ▪ Usual medical treatment. ▪ Therapeutic exercise education talk. **After discharge:** ▪ Kolb's experiential training program with coaching by nursing students. ▪ 28 home visits (1 hour) from your designated trainer over 6 months. ▪ Performing exercises at 4 levels of difficulty.	**During hospitalization:** ▪ Same education talk. **After discharge:** ▪ Scheduled medical follow-ups. ▪ Home visits (1 hour) that administered placebo interventions to participants.	T1: 6 months T2: 9 months (End of the intervention)		**Hand grip strength:** ▪ Dynamometer. **Quality of life:** ▪ Pediatric Quality of Life Inventory v. 3.0. **Fatigue levels:** ▪ Chinese version of the Fatigue Scale (13 items rated on a Likert scale). **Physical activity:** ▪ Classification of Physical Activity for Children and Young People of the Chinese University of Hong Kong (CUHK-PARCY). **Self-efficacy:** ▪ Physical Activity Self-Efficacy Scale (PASE). **Process evaluation forms** to further verify protocol compliance.	Group x time interaction Anova test with post-hoc comparison
Braam et al. 2018[18]	Motion (QLIM) intervention on physical fitness, psychosocial function, and HRQoL.	**QLIM intervention:** - Individualized exercise program. - 2 sessions of aerobic and strength physical exercise (increasing intensity from 66-77% HRmax to 90-100% HRmax	Usual medical intervention.	T1: 4 months (End of the intervention) T2: 12 months	**Cardiorespiratory fitness:** - Maximum oxygen consumption (VO2peak) expressed in ml.kg.min-1, following the Godfrey protocol on a cycle ergometer. **Body composition:** - Fat mass percentage (%FM).	**Muscular strength:** - Hand dynamometer: 3 repetitions per muscle group. **Physical activity:** - Actical accelerometer (B series, Philips Respironics Actical	Generalized estimating equations Group x time interaction Regression model analysis

) of 45 minutes per week.
- 1 60-minute psychosocial training session once every two weeks.
- 2 social training sessions for parents.

Bone mineral density of the lumbar spine:
- DXA.

MiniMitter , Murryscille , PA, USA).
- Left hip during waking hours.

Fatigue:
- Child self-report version of the PedsQL multidimensional fatigue scale (acute version).

Overall HRQoL:
- Dutch self-report version of the PedsQL generic core scales.
- For children 8-12 years old and 12-18 years old.

Athletic competence and global self-esteem:
- Athletic competence and global self-esteem subscales of the "Self-perception Profile."
- For children 9-11 years old and 12-18 years old.

Behavior problems:
- Youth self-report.
- >11 years.

Depressive symptoms:
- Childhood Depression Inventory.

						- Children 8-18 years old.	
Moyer-Mileur et al. 2009[19]	Increase patients' regular exercise and nutritional intake patterns.	- 12 months with monthly reviews. - Minimum of 3 sessions of 15-20 minutes of moderate-vigorous activity. - Individualized exercise program. - Muscle development, flexibility, aerobic exercise, recreational sports, lifestyle activities. - Nutrition education.	- Activity according to tolerance. - Standard feeding recommendations.	T1: 6 months T2: 12 months		**Z-scores appropriate for age, sex, and height:** - 2000 Center for Disease Control reference growth curves. Physical activity minutes: - Activitygram questionnaire. - PACER laps (round trip race test) - Pedometer (DIGI walker).	Mann-Whitney U test Kruskal-Wallis test Friedman 2-ways
Gaser et al. 2022[20]	To determine the effects of regular supervised resistance exercise interventions on self-reported ADL, motor performance, and PA among pediatric patients with ALL, AML, or NHL.	Specific exercise program: - 2-3 exercise sessions per week. - Specific strength training combined with a standard care exercise program. - For each exercise: 2-3 series, rest of 60s between series and 90s between exercises. - web-based exercise sessions	Standard care without any targeted muscle strengthening (games, sports…)	T1: 57-60 days T2: 136-140 days T3: 218-232 days (end of the intervention aproximatelly)	**PA:** - Accelerometer. - Outpatient periods. - Seven consecutive days.	**ADL:** - Activities Scale for Children (ASK), performance version (ASKp). - ADL functional screen. **Engine performance:** - MOON test (motor performance in pediatric oncology).	Mann-Whitney U test/t-student test Wilconxon test

		using the ZOOM platform .				
Senn-Malashonak et al. 2019[21]	Determine the physical and psychosocial effects of a structured and individually adapted supervised exercise therapy regime during pediatric HSCT compared to a non-exercise control group.	Specific exercise program. - 5 sessions weekly during their inpatient period. - Combines exercise intervention with endurance, strength, and flexibility components. - Each session lasted between 30 and 60 min. - For each subject the number of sets and repetitions was individualized.	Specific program. - 5 sessions weekly during their inpatient period. - Mental and relaxation training.	**T0: Hospital admission.** **T1: Day of discharge.**		**Strength:** - Knee extension strenght. Force transducer system (ASYS co, SPOREG). - Hand grip strenght. JAMAR hand-held dynamometer. **Endurance:** - 6-minute-walking-test. - Spiroergometric. **QoL:** - Generic and corresponding KINDL questionnaire and its disease specific oncology-module.
Stossel et al. 2020[22]	Evaluation of the effect of exercise training in muscle function in childhood cancer patients.	Usual medical care and a specific exercise program: - 6-8 week. - Supervised by an exercise scientist. - Moderate intensity endurance and strenght training. - The exercises were surrounded by playful games.	- Usual medical care.		**Body composition:** - **Bioelectrical Impedance analysis (BIA EgoFit).** - **Measure phase angle (phA).**	**Muscle strenght:** - Knee strenght and elbow flexor strenght. - Handheld dynamometer. **Walking performance:** - 6MWT. **Fatigue:** - German language questionnaire PedsQL 3.0

							Multidimensional Fatigue Scale. **Health-related quality of life:** - German language KINDL questionnaire. **PA level:** - German MoMo questionnaire. - Semi-structured interview for evaluated the PA.

N, sample; IG, Intervention group; CG, Control group; ALL, acute lymphoblastic leukemia; BMD, bone mineral density, QLIM, quality of life in motion; DXA, bone densiometry; PA, physical activity; DMO, bone mineral density; QoL, quality of life; HRQoL, health related quality of life; HRmax, maximum heart rate; ADL, activities of daily living; HSCT, Hematopoietic stem cell transplantation; 6MWT, 6-meters walking test

Table 4. RESULTS OF THE STUDIES.

	VARIABLES	*INTERVENTION GROUP*	*CONTROL GROUP*	*SIGNIFICANCE LEVEL and COHEN'S d VALUE*
Hartman et al. 2009[17]	**Bone mineral density of total body:** Dual energy x-ray absorptiometry	T0-T3 MEAN DIFFERENCE PRE-POST: -0.75 SDS T3-T4 MEAN DIFFERENCE PRE-POST: 0.42 SDS	T0-T3 MEAN DIFFERENCE PRE-POST: -0.96 SDS T3-T4 MEAN DIFFERENCE PRE-POST: 0.35 SDS	T0-T3 INTERVENTION GROUP: p<0.05 T0-T3 CONTROL GROUP: p<0.05 T3-T4 INTERVENTION GROUP: p<0.05 T3-T4 CONTROL GROUP: p<0.05 ‡
	Bone mineral density of lumbar spine: Dual energy x-ray absorptiometry	T0-T3 MEAN DIFFERENCE PRE-POST: -0.66 SDS T3-T4 MEAN DIFFERENCE PRE-POST: 0.12 SDS	T0-T3 MEAN DIFFERENCE PRE-POST: -0.36 SDS T3-T4 MEAN DIFFERENCE PRE-POST: 0.04 SDS	‡
	Motor performance: Bayley Scales of Infant Development of Movement-ABC *(score)*	T0-T3 MEAN DIFFERENCE PRE-POST: -0.37	T0-T3 MEAN DIFFERENCE PRE-POST: -0.68	‡
	Passive ankle dorsiflexion: goniometry *(º)*	T0-T3 MEAN DIFFERENCE PRE-POST: 5.2º	T0-T3 MEAN DIFFERENCE PRE-POST: 4.6º	‡
Lam et al. 2018[6]	**Cancer-related fatigue:** Chinese version of the Fatigue Scale *(score)*	T0 - M(SD): 49.2 (7.5) T1 - M(SD): 48.2 (7.2) T2 - M(SD): 47.6 (7.5)	T0 - M(SD): 49.7 (6.9) T1: - M(SD): 53.7 (7.0) T2: - M(SD): 54.7 (6.7)	WITHIN GROUP T2: p<0.05, d = 1.00 WITHIN GROUP T1: p<0.05, d = 0.77
	Physical activity levels: Chinese University of Hong Kong Classification of Physical Activity for Children and Young People (CUHK-PARCY) *(score)*	T0 - M(SD): 2 (1.2) T2 - M(SD): 4 (2)	T0 - M(SD): 2 (1.3) T2 - M(SD): 1.9 (1.3)	WITHIN GROUP T2: p<0.05, d = 1.24
	Physical activity self-efficacy: Physical activity self-efficacy scale (PASE) *(score)*	T0 - M(SD): 7.8 (2.3) T1 - M(SD): 8.4 (1.8) T2 - M(SD): 8.6 (2)	T0 - M(SD): 7.7 (2.7) T1 - M(SD): 6.4 (2.0) T2 - M(SD): 6.3 (2.2)	WITHIN GROUP T2: p<0.05, d = 1.09 WITHIN GROUP T1: p<0.05, d = 1.05
	Right hand grip strength: dynamometry *(kg)*	T0 - M(SD): 14.8 (4.6) T1 - M(SD): 15.3 (4.5)	T0 - M(SD): 14.6 (4.2) T1 - M(SD): 13.4 (2.6)	WITHIN GROUP T2: p<0.05, d = 1.30 WITHIN GROUP T1: p<0.05, d = 0.52

		T2 - M(SD): 16.7 (4.5)	T2 - M(SD): 12 (2.4)	
	Left hand grip strength: dynamometry *(kg)*	T0 - M(SD): 12.7 (4.1) T1 - M(SD): 13.8 (4.1) T2 - M(SD): 15.1 (4.1)	T0 - M(SD): 12.8 (3.8) T1 - M(SD): 12.0 (2.7) T2 - M(SD): 10.8 (2.4)	WITHIN GROUP T2: p<0.05, d = 1.28 WITHIN GROUP T1: p<0.05, d = 0.51
	Quality of life: Pediatric Quality of Life Inventory v. 3.0 *(score)*	T0 - M(SD): 63 (7.1) T1 - M(SD): 64.0 (6.0) T2 - M(SD): 64.7 (6)	T0 - M(SD): 62.3 (9.2) T1 - M(SD): 60.4 (9.0) T2 - M(SD): 58 (8.5)	WITHIN GROUP T2: p<0.05, d = 0.91
Braam et al. 2018[18]	**VO2 peak:** *(ml.kg.min)*	T0 - M(SD): 30.1 (8.5) T2 - M(SD): 33.8 (8.7)	T0 - M(SD): 31.4 (9.5) T2 - M(SD): 35.8 (8.4)	
	Upper body muscle strength: *(N)*	T0 - M(SD): 367.4 (114.0) T2 - M(SD): 382.1 (95.8)	T0 - M(SD): 370.2 (133.7) T2: - M(SD): 416.0 (144.5)	T0-T2 INTERVENTION GROUP: p<0.05, d = 0.14
	Lower body muscle strength: *(N)*	T0 - M(SD): 587.7 (174.2) T2 - M(SD): 660.5 (206.9)	T0 - M(SD): 564.0 (206.6) T2 - M(SD): 622.0 (219.2)	T0-T2 INTERVENTION GROUP: p<0.05, d = 0.38 WITHIN GROUP: p<0.05, d = 0.18
	Physical activity: Accelerometry *(cpm)*	T0 - M(SD): 153.4 (120.1) T2 - M(SD): 213.1 (135.3)	T0 - M(SD): 169.2 (97.4) T2 - M(SD): 191.8 (110.1)	T0-T2 CONTROL GROUP: p<0.05, d = 0.21
	Bone mineral density of lumbar spine *(g/cm2)*	T0 - M(SD): 0.78 (0.21) T2 - M(SD): 0.83 (0.23)	T0 - M(SD): 0.75 (0.18) T2 - M(SD): 0.78 (0.21)	T0-T2 INTERVENTION GROUP: p<0.05, d = 0.23 T0-T2 CONTROL GROUP: p<0.05, d = 0.15
	General QoL: Dutch self-report version of the PedsQL Generic Core Scales *(score)*	T0 - M(SD): 68.4 (18.2) T2 - M(SD): 77.2 (16.4)	T0 - M(S): 73.8 (14.1) T2 - M(SD): 84.5 (13.1)	T0-T2 INTERVENTION GROUP: p<0.05, d = 0.50 T0-T2 CONTROL GROUP: p<0.05, d = 0.78
	Fatigue: Child Self-Report Version of the PedsQL Multidimensional Fatigue Scale (Acute Version) *(score)*	T0 - M(SD): 67.7 (19.8) T2 - M(SD): 76.6 (19.9)	T0 - M(SD): 74.3 (15.7) T2 - M(SD): 82.0 (17.3)	
	Depressive Symptoms: Childhood Depression Inventory *(score)*	T0 - M(SD): 42.3 (31.3) T2 - M(SD): 27.8 (29.4)	T0 - M(SD): 40.1 (26.2) T2 - M(SD): 28.2 (26.7)	T0-T2 CONTROL GROUP: p<0.05, d = 0.44
	Athletic competence: athletic competence and global self-esteem subscales of the "Self-perception Profile" *(score)*	T0 - M(SD): 40.1 (28.8) T2 - M(SD): 51.9 (34.4)	T0 - M(SD): 39.9 (31.9) T2 - M(SD): 38.2 (29.9)	
	Global self-esteem: *athletic competence and global self-esteem*	T0 - M(SD): 55.6 (29.6) T2 - M(SD): 74.9 (25.9)	T0 - M(SD): 57.3 (24.2) T2 - M(SD): 63.4 (32.5)	

	subscales of the "Self-perception Profile" (score)				
Moyer-Mileur et al. 2009[19]	**Physical activity** *(minutes/distance)*	T0 - M(SD): 58.6 (19.6)		T0 - M(SD):52.2 (27.7)	INTERVENTION > CONTROL WITHIN GROUP T2: p<0.05
	Progressive Aerobic Cardiovascular Endurance Run (PACER) *(laps)*	T0 - M(SD): 8.0 (1.8)		T0 - M(SD): 7.1 (2.3)	INTERVENTION > CONTROL WITHIN GROUP T2: p<0.05
	Pedometer *(steps/distance)*	T0 - M(SD): 5539 (1050)		T0 - M(SD): 7460 (1233)	INTERVENTION > CONTROL WITHIN GROUP (% of change) T1: p<0.05 INTERVENTION > CONTROL WITHIN GROUP (% of change) T2: p<0.05
	Upper body strength: push-ups *(n)*	T0 - M(SD): 4.8 (3.9)		T0 - M(SD): 9.0 (3.0)	
	Flexibility: sit-and-reach *(cm)*	T0 - M(SD): 29.6 (5.5)		T0 - M(SD): 23.6 (7.1)	
Gaser et al. 2022[20]	**Physical function of ADLs:** Activities Scale for Kids (ASK) score, Activities Scale for Kids-Performance version score (ASKp) and Functional ADL Screen	**ASK** *(score)*	T0 - M(SD): 60.1 (19.5) T3 - M(SD): 84.7 (12.5)	T0 - M(SD): 66.8 (17.7) T3 - M(SD): 84.8 (14.4)	T0-T3 INTERVENTION GROUP: p<0.05, d = 1.50 T0-T3 CONTROL GROUP: p<0.05, d = 1.11
		ASKp *(score)*	T0 - M(SD): 62.6 (18.8) T3 - M(SD): 84.7 (12.5)	T0 - M(SD): 69.4 (19.8) T3 - M(SD): 86.7 (12.2)	T0-T3 INTERVENTION GROUP: p<0.05, d = 1.38 T0-T3 CONTROL GROUP: p<0.05, d = 1.05
		Functional ADL screen *(score)*	T0 - M(SD):26.1 (4.2) T3 - M(SD): 28.0 (0.2)	T0 - M(SD): 27.0 (3.7) T3 - M(SD): 26.9 (3.8)	T0-T3 INTERVENTION GROUP: p<0.05, d = 0.70

Motor performance: MOON-test	**Hand-eye coordination:** Inserting pins *(s)*	*Differences to reference values (%)* T0 - M(SD): 15.3 (32.3) T2 - M(SD): 5.1 (32.9)	*Differences to reference values (%)* T0 - M(SD):13.7 (30.6) T2 - M(SD): 12.2 (34.0)	
	Static balance: Static stand *(n of contacts)*	*Differences to reference values (%)* T0 - M(SD): 15.4 (65.3) T2 - M(SD):0.4 (6.9)	*Differences to reference values (%)* T0 - M(SD):1.3 (6.7) T2 - M(SD): 0 (6.7)	
	Speed: Reaction test *(s)*	*Differences to reference values (%)* T0 - M(SD): 12.9 (14.9) T2 - M(SD): 4.1 (16.2)	*Differences to reference values (%)* T0 - M(SD): 15.4 (31.8) T2 - M(SD): 10.5 (22.1)	
	Upper extremity coordination: throwing at a target *(hits)*	*Differences to reference values (%)* T0 - M(SD): 16.3 (76.2) T2 - M(SD): 35.6 (17.6)	*Differences to reference values (%)* T0 - M(SD): 16.8 (30.1) T2 - M(SD): 9.6 (35.1)	
	Flexibility: Stand and reach *(cm)*	*Differences to reference values (%)* T0 - M(SD): 9.2 (11.4) T2 - M(SD): 9.8 (11.3)	*Differences to reference values (%)* T0 - M(SD): 9.2 (12.0) T2 - M(SD): 10.2 (10.3)	
	Explosive muscle strength: Medicine ball shot *(m)*	*Differences to reference values (%)* T0 - M(SD): 23.4 (16) T2 - M(SD): 20.3 (8.0)	*Differences to reference values (%)* T0 - M(SD): 27.2 (18.2) T2 - M(SD): 34.5 (12.8)	WITHIN GROUP: $p<0.05$, $d = 1.33$
	Legs muscular resistance*: sit-to-stand (s)*	*Differences to reference values (%)* T0 - M(SD): 46.1 (100.0) T2 - M(SD): 18.0 (66.6)	*Differences to reference values (%)* T0 - M(SD): 24.9 (37.0) T2 - M(SD): 11.4 (26.1)	
	Right hand grip strength: *dynamometry (kg)*	*Differences to reference values (%)* T0 - M(SD): 20.3 (24.6) T2 - M(SD):22.7 (31.5)	*Differences to reference values (%)* T0 - M(SD): 29.5 (16.2) T2 - M(SD): 32.4 (24.8)	

		Left hand grip strength: *dynamometry (kg)*	*Differences to reference values (%)* T0 - M(SD):19.3 (26.9) T2 - M(SD): 21.3 (29.8)	*Differences to reference values (%)* T0 - M(SD): 26.4 (18.1) T2 - M(SD): 30.4 (15.8)	
Senn-Malashonak et al. 2019[21]	**Maximal knee extension strength:** dynamometer *(Nm)*		T0 - Median(Range):74.9 (42.0-90.6) T1 - Median(Range):69.0 (50.0-94.4)	T0 - Median(Range):70.7 (38.9-85.4) T1 - Median(Range):61.1 (45.6-80.2)	T0-T1 CONTROL GROUP: p<0.05
	Hand grip strength: hand grip dynamometer *(kg)*	**Dominant**	T0 - Median(Range):13.9 (1.5-45.0) T1 - Median(Range):12.5 (3.5-35.0)	T0 - Median(Range):14.8 (3.5-40.0) T1 - Median(Range):12.6 (2.5-32.0)	T0-T1 CONTROL GROUP: p<0.05
		Non-dominant	T0 - Median(Range):11.9 (1.0-41.5) T1 - Median(Range):10.9 (3.5-36.5)	T0 - Median(Range):14.3 (3.9-38.5) T1 - Median(Range):11.3 (2.0-32.5)	T0-T1 CONTROL GROUP: p<0.05
	Walking and cardiorespiratory performance: 6-minutes walking test (6MWT)	**Distance (adjusted to sex and age)** *(m)*	T0 - M(SD): 76.6 (11.7) T1 - M(SD): 73.7 (16.1)	T0 - M(SD): 74.3 (11.9) T1 - M(SD): 59.6 (15.9)	T0-T1 CONTROL GROUP: p<0.05; d = 1.04 WITHIN GROUP: p<0.05, d = 0.88
		VO_2 peak *($ml \cdot kg^{-1} \cdot min^{-1}$)*	T0 - M(SD): 28.3 (6.0) T1 - M(SD): 24.3 (7.8)	T0 - M(SD): 25.7 (5.2) T1 - M(SD): 20.6 (6.8)	T0-T1 INTERVENTION GROUP: p<0.05; d = 0.57 T0-T1 CONTROL GROUP: p<0.05; d = 0.84
		Ventilatory threshold *($ml \cdot kg^{-1} \cdot min^{-1}$)*	T0 - Median(Range): 16.3 (13.6-25.2) T1 - Median(Range): 16.6 (10.9-19.4)	T0 - Median(Range): 18.1 (13.8-24.8) T1 - Median(Range): 14.1 (9.5-22.6)	
	Quality of life: KINDL questionnaire (self-report version)		T0 - Median(Range): 75.5 (42.1–90.6) T1 - Median(Range): 72.7 (38.9–85.4)	T0 - Median(Range): 67.9 (50.0–94.4) T1 - Median(Range): 61.1 (45.6–80.2)	T0-T1 INTERVENTION GROUP: p<0.05 T0-T1 CONTROL GROUP: p<0.05 Mental health dimension WITHIN GROUP: p<0.05 Well-being and family dimension T0-T1 CONTROL GROUP: p<0.05

Stossel et al. 2020[22]	**Muscle strength:** dynamometry	**Knee flexor** *(N)*	T0 - M(SD): 74.6 (41.4) T1 - M(SD): 89.6 (45.9)	T0 - M(SD): 128.1 (49.7) T1 - M(SD): 115.6 (44.4)	WITHIN GROUP: $p<0.05$, $n^2_p = 0.22$
		Arm flexor *(N)*	T0 - M(SD): 92.3 (41.1) T1 - M(SD): 93.86 (42.3)	T0 - M(SD): 103.8 (49.7) T1 - M(SD): 95.5 (37.4)	
	Walking and cardiorespiratory performance: 6-minutes walking test (6MWT) *(m)*		T0 - M(SD): 470.6 (179.7) T1 - M(SD): 515.2 (136.1)	T0 - M(SD): 531.8 (81.5) T1 - M(SD): 517.3 (54.5)	WITHIN GROUP: $p<0.05$, $n^2_p = 0.14$
	Fatigue: PedsQL 3.0 Multidimensional Fatigue Scale *(score)*		T0 - M(SD): 70.5 (17.4) T1 - M(SD): 79.1 (12.0)	T0 - M(SD): 71.1 (18.1) T1 - M(SD): 70.9 (21.6)	T0-T1 INTERVENTION GROUP: $p<0.05$, $d = 1.11$
	Quality of life: Health-Related Quality of Life German Version	**Total** *(score)*	T0 - M(SD): 63.7 (9.1) T1 - M(SD): 68.7 (9.4)	T0 - M(SD): 81.1 (12.3) T1 - M(SD): 77.7 (14.7)	Self-esteem dimension WITHIN GROUP: $p<0.05$, $n^2_p = 0.53$ Strenght and endurance dimension WITHIN GROUP: $p<0.05$, $n^2_p = 0.51$
	Physical activity level: Semi-structured interview *(score)*		T0 - M(SD): 5.0 (3.1) T1 - M(SD): 6.8 (1.8)	T0 - M(SD): 6.0 (3.0) T1 - M(SD): 4.8 (3.2)	WITHIN GROUP: $p<0.05$, $n^2_p = 0.26$

ADLs, Activities of daily living; SDS, Standard deviation scores; M, Mean; SD, Standard deviation.

Figure 1