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PhD Thesis

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Physical activity and strength training during cancer treatment in children and adolescents with cancer

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PhD thesis

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List of publications

This thesis is based on the following papers

I. Fridh MK, **Schmidt-Andersen P**, Andrés-Jensen L, Thorsteinsson T, Wehner PS, Hasle H, Schmiegelow K, Larsen HB: Children with cancer and their cardiorespiratory fitness and physical function—the long-term effects of a physical activity program during treatment: a multicenter non-randomized controlled trial. Journal of Cancer Survivorship 2023. https://doi.org/10.1007/s11764-023-01499-7[1]

II. **Schmidt-Andersen P,** Stage A, Pouplier A, Bastholm LH, Müller KG, Larsen A, Ness KK, Larsen HB, Christensen J, Fridh MK: Physical capacity in children and adolescents with newly diagnosed cancer: A systematic review and meta-analysis. Pediatric Blood & Cancer 2023:1–13. https://doi.org/10.1002/pbc.30746[2]

III. **Schmidt-Andersen P**, Fridh MK, Müller KG, Pouplier A, Hjalgrim LL, Faigenbaum AD, Schmiegelow K, Hasle H, Lykkedegn S, Zhang H, Christensen J, Larsen HB: Integrative Neuromuscular Training in Adolescents and Children Treated for Cancer (INTERACT): Study Protocol for a Multicenter, Two-Arm Parallel-Group Randomized Controlled Superiority Trial. Frontier in Pediatrics 2022;10:1–11. https://doi.org/10.3389/fped.2022.833850[3]

IV. **Schmidt-Andersen P,** Pouplier A, Faigenbaum,AD, Beth CK, Olsen CC, Lykkedegn S, Hasle H, Müller K, Larsen HB, Fridh MK, Christensen J: Feasibility of an exercise intervention and physical assessments during the first six months of cancer treatment in children and adolescents. Disability and Rehabilitation (Submitted March 5, 2024)[4]

V. **Schmidt-Andersen P,** Boensvang NN, Pouplier A, Müller K, Christensen J, Fridh MK, Larsen HB: Exploring the motivation among children and adolescents for exercise during the first six months of cancer treatment: a qualitative study. Disability and Rehabilitation (Under review—Submitted November 22., 2023)[5]

All studies are referred to by the listed Roman numerals.

Trial registration and ethics approval

The National Committee on Health Research Ethics (RESPECT: H-3-2012-105; INTERACT: H-20040897) and the Danish Data Protection Agency (RESPECT: 2007-58-0015; INTERACT: P-2021–14) have approved the INTERACT trial protocol and data handling.

Further, the Danish Data Protection Agency (J.nr. 2024-52-0066) gave permission to disclose personal information, regarding one severe adverse event presented in Paper IV.

RESPECT: ClinicalTrials.gov NCT01772862 and NCT01772849, first released January 17 and 18, 2013, respectively.

INTERACT: ClinicalTrials.gov (NCT04706676), first released January 5, 2021

List of tables and figures

Abbreviations

ALL	Acute Lymphoblastic Leukemia
BMI	Body Mass Index
BPM	Beats per Minute (in heart rate)
CI	Confidence Interval
CNS	Central Nervous System
HR	Heart Rate
IQR	Inter Quartile Range
RM	Repetition Maximum
SEM	Standard error of the mean
SD	Standard Deviation

Summary

Childhood cancer impacts a substantial number of children and adolescents annually in Denmark, with approximately 170–180 new cases each year. These children are treated in specialized centers receiving a treatment-effective variety of chemotherapy, immunotherapy, radiotherapy, glucocorticoids, and surgery; the five-year survival rate has surged from 72% in 1985 to 87% in 2022, as reported in the latest registries. However, cancer treatment has well-documented side effects on physical capacity. Specifically, cancer treatment induces muscle atrophy and reduced muscle strength, which plays a crucial role in motor development, whole-body homeostasis, and metabolism. Moreover, the sedentary lifestyle during hospitalization and treatment-induced toxicities put these children and adolescents at risk of long-term health complications.

This thesis will present the results of a multicomponent psychosocial-, educational, and physical activity intervention in children undergoing cancer treatment (the RESPECT study, Paper I). From learned experiences, existing evidence, and a systematic review of available evidence (Paper II), the thesis will further present a design and methodology of a monomodal strength training intervention in a protocol article (the INTERACT trial). The INTERACT trial (Paper III) investigates the effectiveness of a strength training intervention using integrative neuromuscular training in children with cancer during the early stages of treatment. The intervention aims to improve physical capacity and sustain exercise motivation during cancer treatment.
The INTERACT trial is ongoing, and therefore, the effects of integrative neuromuscular training will not be presented. Instead, this thesis will present results on the feasibility of the trial (Paper IV) and a qualitative analysis of motivation during the exercise intervention (Paper V).

The RESPECT study (Paper I) demonstrated that a combined psychosocial, educational, and physical activity intervention during cancer treatment could improve cardiorespiratory fitness and physical function in children and adolescents one year after treatment. However, the study's non-randomized design and high attrition rate limited the generalizability of the results. Further, a systematic review (Paper II) indicated the necessity of early-initiated rehabilitative strategies to mitigate the decline in physical capacity in children and adolescents with cancer, as these are markedly impaired within the first months of diagnosis.
Early results from the INTERACT trial emphasized the feasibility of strength training and physical capacity assessment: children will participate in exercise and physical assessment during cancer

treatment, providing viable insights into muscle strength parameters during the first six months of cancer treatment.

Qualitative findings emphasized the role of autonomy in sustaining motivation for exercise during treatment, underscoring the importance of involving children and adolescents in decision-making and tailoring exercise sessions to their preferences and needs (Paper V).

Overall, this thesis contributes valuable insights into the potential impact of exercise interventions on physical capacity and motivation in children and adolescents with cancer. By addressing the challenges and barriers to exercise and physical assessment during treatment, future research can develop more effective strategies to enhance the well-being and quality of life of children and adolescents undergoing cancer treatment.

Danish Summary

Hvert år bliver 170–180 børn og unge diagnosticeret med kræft. Disse børn og unge behandles på specialiserede afsnit, primært med kemoterapi, immunterapi, strålebehandling, glukortikoider og kirurgi. Selvom denne behandling er effektiv; overlevelsesraten på fem år er steget fra 72% i 1985 til 87% i 2022; medfører kræftbehandling veldokumenterede bivirkninger på fysisk kapacitet. Kræftbehandling medfører bl.a. en reduceret muskelmasse og muskelstyrke: faktorer med en afgørende rolle i børns motoriske udvikling, samt for at opretholde kroppens endokrinologiske homeostase og metabolisme. Derudover, oplever børn og unge en nedsat fysisk aktivitet under et kræftforløb. Kombineret med behandlingsrelaterede toksiciteter, er børn med kræft i risiko for langsigtede livstilssygdomme.

Denne afhandling vil præsentere resultaterne fra et interventionsstudie, RESPECT projektet. RESPECT (Studie I) undersøgte langtidseffekterne af en kombineret undervisnings-, psykosocial-, og fysisk aktivitetsintervention under et kræftforløb, hos børn og unge – et år efter afsluttet behandling. Baseret på erfaringer fra RESEPCT-projektet, eksisterende evidens og en systematisk gennemgang af tilgængelig forskning (Studie II), vil denne afhandlingen, ydermere, præsentere en studieprotokol (Studie III); et design og en metode for en styrketræningsintervention til børn og unge under kræftbehandling: INTERACT-studiet. INTERACT vil undersøge effekten af en af en styrketræningsintervention (integrative neuromuscular training) hos børn og unge med kræft gennem de første seks-måneders behandling, i et randomiseret kontrolleret forsøg. Interventionen har til formål at forbedre fysisk kapacitet, samt at opretholde motivationen for træning under kræftbehandling. Da studiet endnu ikke er afsluttet, vil effekterne af INTERACT, ikke blive præsenteret i denne afhandling. I stedet vil resultater om gennemførbarhed (feasibility, Studie IV) samt en kvalitativ analyse af motivation (Studie V), blive præsenteret.

Et systematiske review (studie II) viste et markant fald i fysisk kapacitet hos børn og unge med kræft, på tværs af diagnoser indenfor den første måned af deres behandlingsforløb. Resultater fra RESPECT (studie I) indikerer, at undervisning, socialt samvær og fysisk aktivitet, under kræftbehandling kunne forbedre fysisk kapacitet hos børn efter afsluttet behandling. Overførbarheden af disse resultater er dog begrænset, som følge af studiets ikke-randomiserede design og høje frafald.
Tidlige resultater fra INTERACT viste, at det er gennemførligt (feasible) at udføre styrketræningsinterventioner og fysiske test i løbet af de første seks måneder af kræftbehandling

(studie IV). Resultaterne indikerer, at børn og unge accepterer deltagelse i et træningsforsøg indenfor de første uger af deres kræftbehandling, og at børn og unge både kan og vil deltage i fysisk træning og test under kræftbehandlingen. Disse resultater giver en særlig indsigt i muskelstyrkeparametre i løbet af de første seks måneder af kræftbehandlingen.
Kvalitative fund beskrev, at børn og unges autonomi bør understøttes, for at opretholde og facilitere motivationen for træning under et kræftforløb. Resultaterne understregede nødvendigheden i at inddrage børn i beslutningsprocesser, herunder udformning og tilpasning af træningspas til børn og unges præferencer. Dette bidrager til at facilitere træning og motivation i et kræftforløb med svingende bivirkninger og varierende funktionsniveau.

Dette ph.d.-projekt giver en indsigt i potentialet for træningsinterventioner, herunder deres indvirkning på fysisk kapacitet og motivation, hos børn og unge med kræft. Ved at forstå, og adressere, barrierer for træning under behandlingen, kan fremtidige studier udvikle mere effektive strategier til at udføre træning. Dette kan være medvirkende til at forbedre både trivsel og livskvalitet for børn, der gennemgår et kræftforløb.

Introduction

The landscape of cancer treatment for children and adolescents in Western countries has undergone significant medical progress over the past three decades: the five-year survival rate has surged from 72% in 1985 to 87% in 2022, as reported in the latest registry for Denmark.[6] In the wake of this progress, clinicians[7], researchers[8] , parents[9], and children[10] have called for novel strategies that work beyond survival as both short- and long-term side effects are evident: one-third of all childhood cancer survivors develop chronic health conditions[11] and one-fifth have severely reduced physiological reserves[12] caused by a sedentary lifestyle and treatment-induced toxicities[11,13–24]. Several studies have answered this call and conducted various approaches to physical activity and exercise interventions during cancer therapy. In the Danish context, the first study to explore the potential of physical activity during cancer treatment is the Rehabilitation Including Social and Physical Activity and Education in Children and Teenagers with Cancer (RESPECT) study.[25–31] On the basis of a multi-component intervention addressing cancer treatment's academic, social, and physical challenges, we introduced a novel and pragmatic approach to maintaining normalcy by educating classmates in cancer treatment, facilitating visits from classmates, and offering supervised physical activity throughout the entire cancer treatment trajectory. In so doing, RESPECT aimed to improve the conditions needed for re-entering everyday life upon completing treatment.[25]

Early findings from the RESPECT study indicated a high acceptance and participation rate among children and adolescents with cancer, with over two-thirds successfully attending physical activity sessions throughout their cancer treatment.[30] It also found that children and adolescents with cancer have severe deficits in physical capacity within the first month after diagnosis. More specifically, children and adolescents with cancer showed a 43% reduction in cardiorespiratory fitness, a 21% reduction in leg strength, and 20% lower hand grip strength compared to age-matched children.[29]

The multi-component intervention showed a significantly improved between-group change in cardiorespiratory fitness after six months of intervention compared to usual care (VO_2 peak change: 0.25 mL/kg/min, 9% CI [0.07–0.43]. However, challenges were evident, including the difficulty of assessing physical capacity in children with cancer, particularly cardiorespiratory fitness:[30] less than 25% of all children could complete strenuous cardiopulmonary exercise tests within the initial month of cancer treatment. Additionally, the multifaceted intervention and non-randomized design made it challenging to establish causal effects. We therefore identified a need for initiating a trial—the Integrative Neuromuscular Training in Adolescents and Children Treated for Cancer (INTERACT) trial—with a more narrow-oriented approach to exercise; strength training rather than multi-modal

psycho-social intervention; and suitable for children and adolescents in a randomized controlled setting. The RESPECT study is a predecessor to the INTERACT trial, providing the empirical evidence and clinical experiences necessary to further develop a randomized controlled multicenter trial in a Danish hospital setting. The last participant was included in the RESPECTS study in February 2018, and the last follow-up assessment of the included children was performed in May 2021, one year after ended treatment, which is the primary endpoint of the RESPECT study. The framework for the INTERACT trial was developed in 2019–2020, and the first participant was included in January 2021. Hence, INTERACT was started after the physical intervention of RESPECT was finalized. Yet, only secondary analysis of the effectiveness of the multi-modal intervention during cancer treatment has been conducted and published.[26,29–32] Therefore, the primary endpoint findings in the RESPECT study had not been conducted when the INTERACT was initiated. This thesis will elucidate the iterative process of evaluating a supervised physical activity intervention for children and adolescents undergoing cancer treatment (the RESPECT study, Paper I[1]), and by synthesizing existing evidence (Paper II[2]), developing an exercise intervention during childhood cancer treatment—through the INTERACT trial (Paper III[3])—assessing the feasibility of the chosen design and methods (Paper IV), and conclusively evaluating the potential of the proposed intervention (Paper V).

Background

Childhood cancer, though relatively rare, impacts a substantial number of children and adolescents (hereafter referred to as "children") annually. In Denmark, there are approximately 170–180 new cases per year,[6] corresponding to an incidence of 15–22 per 100,000 children (<18 years).[33] These children are treated in four centers: Copenhagen University Hospital—Rigshospitalet, Aarhus University Hospital, Odense University Hospital, and Aalborg University Hospital.[6]

Children undergoing cancer treatment receive varieties, and often combined treatments, of chemotherapy, immunotherapy, radiotherapy, glucocorticoids, and surgery. While crucial for managing cancer, these treatment modalities are associated with well-documented side effects that impact central and peripheral nervous systems,[34] skeletal muscles,[35] and cardiovascular health.[36] This often leads to noticeable deficits in physical capacity, such as decreased: muscle strength, endurance, balance, and reaction time, contributing to impaired body functions such as impaired gait. Collectively, cancer treatment induces fatigue, and therefore, the combined strain on overall physical capacity is likely due to a combination of treatment side effects and sedentary behavior.[37–40] These

impairments collectively pose significant challenges to both physical and psychosocial well-being, affecting the overall quality of life.[41]

In the following paragraphs, I will explain the importance of skeletal muscle on overall physical capacity during prolonged disease trajectories. Further, I will disseminate the current body of evidence regarding exercise and physical activity interventions during childhood cancer treatment.

Skeletal muscle: muscle mass, -strength, -endurance, power, and metabolism

Muscle mass, muscle strength, muscle endurance, and muscle power, collectively defined as muscle fitness,[42] are fundamental in motor development and preserving whole-body homeostasis.[34,35,43]

Skeletal muscle generates force, thereby creating movement of the skeleton; hence, the size and efficiency of skeletal muscle are the very core of creating sufficient movement in correspondence—and interaction—with the physical and social environment.[44] Hence, adequate muscle fitness is a foundation for securing appropriate motor development and activities of daily living.

Further, skeletal muscle is essential for maintaining whole-body homeostasis and metabolism, primarily through the regulation and storage of amino acids during periods of fasting and food uptake.[43]

Skeletal muscle in the context of cancer and cancer treatment

The acute response of skeletal muscle to critical illness, as seen in advanced cancer, requires a higher demand for amino acids derived from muscle protein synthesis, surpassing the requirements during fasting. This increased demand results from physiological responses necessary for recovery, including accelerated synthesis of immune function proteins and proteins essential for wound healing.[43]

Cancer treatment (including antimetabolites, anthracyclines, radiotherapy, and glucocorticoids) further induces muscle complications such as denervation of muscle fibers, demyelinization, inhibited protein synthesis, and increased muscle breakdown, ultimately resulting in muscle atrophy.[34] Consequently, sarcopenia: loss of muscle strength and muscle mass, have been reported in children with cancer. One study found a decrease in skeletal muscle mass after six months of treatment, measured by Dual-Energy X-ray Absorptiometry (DXA), showing that children in standard risk treatment for Acute Lymphoblastic Leukemia (ALL) had 46% lower muscle mass than mean average normative values (z-score of 1.8).[45] Although children regained some skeletal muscle mass one year after diagnosis, these values plateaued at a z-score of –0.5, corresponding to 20% lower than mean

normative values [45]. Further, loss of muscle quality (force generation per unit of muscle)[35] has been shown in both children in active cancer therapy[46,47] and childhood cancer survivors.[48–50]

Understanding the mediating factors leading to low muscle mass and weakness in childhood cancer patients is challenging due to a limited number of studies based on small sample sizes, diverse evaluation techniques (e.g., limited knowledge of muscle architecture), and varying childhood cancer populations. However, collectively, it appears that sarcopenia is present at diagnosis and is worsened during treatment.[29,47–49,51] While some children may partially regain muscle mass, their muscle quality is likely compromised, leaving them with suboptimal muscle health during survivorship.[45] This compromised muscle fitness and sarcopenia may contribute to the early onset of chronic health conditions, including cardiovascular disease and metabolic syndrome.[35] Therefore, reduced muscle mass and strength may predict low quality of life, morbidity, mortality during the cancer treatment trajectory, and survivorship.[35,52–54] Yet, sarcopenia can be counteracted or treated through exercise.[43]

Exercise and physical activity interventions in children during cancer treatment

When the RESPECT study was initiated in 2013, the body of evidence of exercise intervention studies during active childhood cancer treatment consisted of 15 studies.[51,55–68] Up until the start of INTERACT, the body of evidence consisted of 38 studies,[29–31,38,51,54–86] involving 31 different study populations. Thirteen studies are based on data from small cohort studies that explored within-group changes due to exercise or various forms of physical activity;[56,57,61,63,64,66,67,71–73,76,81,86] 12 studies have quasi-experimental designs with between-group comparisons to either historical controls or non-randomized age-matched healthy controls;[29–31,60,62,65,69,70,77,78,82,84] and 13 studies are randomized controlled trials.[38,51,54,55,58,59,68,74,75,79,80,83,85]

One of the earliest studies, from 2007, is San Juan and colleagues' small cohort comprising seven children aged 4–7 years during maintenance treatment (i.e., the last part of a two-year treatment protocol) for ALL.[56,57] The participants received 16 weeks of supervised resistance and aerobic training. This study's importance is founded firstly due to its novelty: being one of the first studies to conduct strict progressive conventional resistance training (in terms of one set of 8–15 repetitions in 11 different exercises: bench-, shoulder- and leg-press, leg-extension, leg-curl, abdominal-crunch, back-extension, arm-curl, elbow-extension, seated row, and lateral pull-down. Exercises were performed on conventional strength and conditioning machines designed for children. Secondly, it was one of the first studies to show significant within-group improvements in upper body strength (45% bench press improvement), lower body (35% leg press improvement), and cardiorespiratory fitness (35% improvement of VO_2 peak). Due to the uncontrolled design and indirectness (i.e., low

power), the effects of this study are explorative; nevertheless- and most importantly—it showed the potential of exercise: children during cancer treatment can participate (the adherence rate was 85%, and none of the children missed two consecutive exercise sessions) and can undergo a standardized assessment of physical capacity. On this basis, these results were used when designing the RESPECT study, and calculating the proposed sample size.[25]

Quality of exercise and physical activity interventions in children during cancer treatment

To our knowledge, no studies have been able to replicate the magnitude of the results nor applied a similar methodological strictness as of San Juan's exercise intervention. Intervention studies have shown positive effects on muscle mass,[55,57,60,87] flexibility,[55,68,72] cardiorespiratory fitness,[55,57,67,72,82] muscle strength,[55,57,60,67,68,74,79,83,87,88] and health-related quality of life in general,[62,63,67,78,83] albeit, the certainty of evidence in pediatric exercise oncology is graded low, primarily due to a small number of participants and risk of bias due to study designs. This diminishes the overall certainty of effects, compared to standardized care, and ultimately reduces the practicality of implementing the results.[89–91]

Due to the low incidence of children with cancer, many studies include either different or all types of cancer diagnosis—pan cancers—[29–31,38,58,62,64,69,70,73,74,78,79,81,84–86,92,93] within large age spans to achieve sufficient statistical power. This disparity of diagnosis demands a pragmatic approach when designing exercise interventions to comprehend the different varieties of treatment regimens and age groups. The body of evidence in childhood cancer exercise presents different takes on exercice intervention: such as endurance training,[58,65] multi-components of resistance and endurance training,[10,56,57,60,61,63,66–68,72,74,75,80,81,83,84,86,88,92,94,95] undefined general interventions (e.g., general physical activity, physiotherapy or occupational therapy)[25,29–31,38,51,59,62,64,69–71,73,77–79,85,93,96] or including other psychosocial components, such as diet, education or motivation.[29–31,38,59,79,85]

Regarding the timing of exercise interventions, 19 studies include children within the last stages of their treatment blocks[38,55–57,60,61,64–68,71–73,76,77,80,82,85] hereof seven studies concern populations of children receiving hematopoietic stem cell transplantations, primarily due to relapse of cancer.[60,66,72,73,77,80,82] As outlined above, deficits in physical capacity and muscle fitness appear early during treatment[29,47–49,51] and can be counteracted through exercise. Nineteen studies have explored different approaches to exercise during the acute or early stages of cancer (<6 months of treatment).[29–31,51,58,62–64,69,70,74,75,78,79,81,83,84,86,97]

Supervised versus unsupervised interventions—which design is feasible?

When designing pediatric oncology exercise interventions in clinical studies, scientists are faced with a pivotal choice when dealing with such diverse populations: opting for supervised, unsupervised, or combined interventions. A supervised intervention has the benefits of being controlled; parameters such as the type, anticipated intensity, and adherence to the supervised regimen can be closely monitored and promptly adjusted.[98] Further, children with cancer described supervised interventions as facilitating.[10] However, the exercise volume may be restricted as attendance depends on hospitalization and treatment protocol.

To address the challenge of limited exercise volume, interventions can incorporate—or entirely consist of—unsupervised exercises either conducted at home or within the hospital. Unsupervised interventions have the obvious disadvantages of lacking monitoring and, thereby, control, introducing several uncertainties and biases (e.g., reporting and recollection bias).

Studies with minimal supervision, e.g., studies using monthly follow-up sessions or primarily educational approaches to exercise, generally report low adherence to the intervention and further limited effects of the intervention compared to usual care.[51,97] Therefore, supervision appears as a necessary component when designing feasible and effective interventions for children during cancer treatment.

Twenty-five studies have performed supervised exercise interventions,[29,31,38,55–58,61,62,64,66,67,69,70,72–76,80,81,83–86] seven have performed unsupervised, primarily home-based interventions,[10,51,54,59,63,65,68,71] and four studies[60,77,79,94] have used combined approaches to exercise.

Looking at the body of evidence of supervised exercise interventions, after removing studies with late inclusion (> 6 months after treatment initiation) and children receiving hematopoietic stem cell transplant treatment, 12 studies have conducted supervised interventions,[29–31,58,62,69,70,74,75,81,83,84] nine of which are controlled studies (or part of larger controlled trials).[29–31,58,69,70,74,75,83] These studies are outlined in Table 1.

Table 1: Overview of controlled, supervised exercise studies initiated within 6 months of cancer diagnosis. Studies are presented in order of publication year.

Name cohort/center year	**Demographic**	**Timing and length of intervention**	**Intervention description**	**Author, year design (sample)**	**Outcome (endpoints)**	**Results**	**Adherence**
St. Jude Children's Research Hospital and **Texas Children's Cancer Center,** USA	n = 29 (7–18 years) Solid tumors Acute Myeloid Leukemia	1–5 months after diagnosis. **One week intervention**	**Endurance training:** 1-week aerobic exercise (stationary bike) twice daily, in-hospital Vs. usual care	**Hinds (2007)**[58] Randomized controlled study (n = 29; INT = 14/CON = 15)	**Sleep pattern** (accelerometry) **Fatigue** (self-report) (3 days after discharge—of one-week intervention)	↔ Sleep ↔ Fatigue	85%
University Hospital Münster, Münster, Germany 2006- 2010	n = 52 (8–18 years) Ewing's sarcoma Osteosarcoma	During neo-adjuvant chemotherapy and throughout treatment **(5.3±1.7 days)**	**Combined exercise:** Daily-in-hospital, individually tailored exercise: Strength endurance, coordination, flexibility, games Vs. usual care (other center)	**Winter (2013)**[69] Non-randomized study (n = 31; INT = 16/ CON = 15)	**PA** (Accelerometry): Number of gait cycles per day) (3,6,12,18 months after surgery)	↔PA (any time point)	58.5%
				Müller (2014)[70] Non-Randomized study (n = 21 INT = 10/ CON = 11)	**BMD** **PA** (Accelerometry—Number of gait cycles/day) **(6,12 months after surgery)**	↔BMD ↑Pa in INT (at 6 and 12 months)	77%
PAPEC study Madrid, Spain 2012–2015	n = 49 (4–18 years) Extracranial tumor Rhabdosarcoma Ewings sarcoma Osterosarcoma lymphoma	From diagnosis through neoadjuvant treatment **(9–41 WEEKS)**	**Combined strength and endurance exercise** 3 times weekly strength, In-hospital Vs. usual care	**Fiuza-Luces (2017)**[74] Randomized Controlled Trial (N = 49 INT = 24/ CON = 25)	**Muscle strength** (primary) **VO_2 peak, TUG, TUDS, PA** (post-intervention)	↑leg strength ↑upper body strength ↔VO_2 peak ↔VT ↔TUDS ↔TUG ↔PA	68%
				Fiuza-Luces (2017)[75] Randomized Controlled trial (N = 20; INT = 9/CON = 11)	**Immune Function: Lymphocyte, NK cells** (post-intervention)	↔ lymphocyte ↔ NK cells	
RESPECT Study, Copenhagen Denmark 2013–2023	n = 170 (6–17.9 years) Pan cancer	From diagnosis through treatment **(3 months–2 years)**	**Multicomponent** psychosocial-, educational, and physical activity intervention Vs. usual care (other centers)	**Thorsteinsson (2017*)**[31] Non-controlled cohort (n = 75) compared to 47 sex and age-matched controls	**VO_2 peak** (Diagnosis, 3 and 6 months, one year after cessation of treatment)	VO_2 peak ↑ (all timepoints)	-
				Nielsen (2018*)[30] Non-controlled feasibility study (n = 75)	**Completion rates** of: CPET (primary), STS, TUG, Balance, HG (baseline, 3 and 6 months)	CPET 28% STS 75% TUG 71% Balance 82% HG 83%	-
				Nielsen (2020)[30] Non-randomized study N = 170; (INT = 120/CON = 50)	**VO_2 peak** (primary), **STS, TUG, Balance, Grip strength** (Diagnosis, 3 and 6 months)	VO_2 peak ↑ STS ↔ TUG ↔ Balance ↔ Grip strength ↔	68%
MUCKI Trial Mainz Germany (2015–2018)	n = 35 (age 4–18) Pan cancer	From diagnosis through intensive treatment. **(6–8 weeks)**	**Combined exercise:** Individually tailored exercise: Strength and endurance Vs. usual care	**Stossel (2020)**[83] Randomized Controlled Study n = 35; (INT = 18/CON = 17)	**Knee flexor** **Arm flexor** **6mwt** **Body composition** **Fatigue** **HRQoL** (Diagnosis and post-intervention)	↑ Knee flexor ↔Arm flexor ↑6MWT ↔Body composition ↑Fatigue (only proxy) ↑HRQoL (only proxy)	(2.7 ± 1.2 session/weekly)

*Table 1: * Thorsteinsson (2017) and Nielsen (2018) are both non-controlled studies but are included in this overview, as they are part of the RESPECT trial, and contains relevant results for this thesis.INT = intervention group/Exercise group, CON = Control*

group (unless listed, controls are children receiving standardized care), PA = Physical Activity, BMD = Bone Mass Density, TUG = Timed-up-and-go test, TUDS = Timed-up-and-down-stairs, STS = sit-to-stand, HG = Hand grip strength.

These studies have used combined strength, endurance, or physical activity intervention with a large variation and duration of interventions (from 1 week[58] to two years[29–31]) in five different study populations: three on children with solid tumors treated in the United States[58] Germany,[69,70] or Spain[74,75] and two study populations on children with pan cancers in Denmark[29–31] and Germany.[83]

Two studies, the PAPEC,[74] and the RESPECT studies,[29] reported effects of exercise versus usual care on cardiorespiratory fitness measured after approximately 5[74] and 6 months[29] of intervention. The studies show conflicting results of either no effects on VO_2 peak (1075±136 (SEM) vs. 1035± 114 ml/min) or significant effects (29.6 ± 6.9 (SD) vs 22.1 ± 5.8 ml/min/kg, p = 0.015), respectively. Regarding the duration of the interventions, the PAPEC and RESPECT studies have long-lasting interventions compared to other controlled studies, yet with great variety in both durations: ranging from 9–41 weeks[74] versus 12 weeks—104 weeks,[29] and different approaches to the intervention, and included different cancer populations, which may explain the inconsistency of results.

The PAPEC study reported significant between-group postintervention results of both lower body strength (5 RM leg press: 69.4 ± 34 vs. 63.8 ± 40 kg, p = 0.021) and upper body strength (5RM bench press: 40.1 ± 19 vs. 34.6 ± 20 kg, p = 0.005) compared to controls. This is in line with results from the MUCKI trial [83] on the effectiveness of combined endurance and strength exercise versus usual care (Isometric Knee flexor strength: mean change 15 Newton vs –12.5 Newton, p = 0.03) —albeit, not for between group results on upper body strength [83]. Again, there is considerable variability to both type and length of intervention as well as population between the MUCKI, PAPEC, and RESPECT studies. The MUCKI trial is particularly prone to selection bias due to small and heterogeneous samples. Despite its randomized controlled design, significant differences in baseline muscle strength values favoring the control group are present. Regarding measures of physical function; e.g., sit-to-stand, timed-up-and go, timed-up-and-down-stairs tests, studies reported trends toward a positive effect of interventions, however, no significant difference to controls.[29,74]

Motivation for participation in exercise during cancer treatment

Participating in physical exercise intervention during cancer treatment is complex due to several factors. In addition to the inherent physical strains of cancer, cancer treatment induces fatigue, nausea, and pain.[20] Combined with reduced emotional well-being and reduced quality of life,[10] the cumulative consequences affect motivation. Amotivation is a driver for non-adherence to exercise interventions

and sedentary behavior.[10] Studies have observed that these barriers may result in low adherence to physical assessment at the time of diagnosis and after six months of treatment.[30,31] Qualitative studies have highlighted that, despite experiencing treatment-induced side effects and a decline in physical and emotional well-being, children can engage in physical activity.[9,10,28] Participants stated, that support from exercise professionals and significant others is crucial to their participation.[10,28,99] However, challenges persist as both the hospital facilities and the logistical constraints of treatment, such as adherence to cancer treatment, procedures, regimes, and regulations, hinder scheduled supervised physical activity.[99]

In summary, while muscle fitness is a key component for conserving physical capacity during childhood cancer treatment, cancer treatment directly impairs muscle fitness, reducing both muscle quantity and quality. Therefore, the collective burden of cancer treatment and sedentary behavior have short and long-term consequences for physical well-being and affect costs for emotional well-being.

Although several studies have investigated the effects of exercise interventions during childhood cancer treatment, concerns persist about the quality of evidence and methodology. Moreover, strength training interventions are lacking in the current body of evidence. Recognizing this gap, we are prompted to develop and initiate a large-scale randomized controlled trial using a strength training approach. In this thesis, I will address the evaluation and develop an exercise regime based on the existing evidence, further explore its viability, and finally qualitatively evaluate the potential of the intervention.

Theoretical background

Rehabilitation during childhood cancer treatment—The RESPECT approach

A Danish consensus definition of rehabilitation reads:

> *"Rehabilitation is targeted towards individuals who are experiencing or are at risk of experiencing limitations in their physical, mental, cognitive, and/or social functioning, affecting their everyday lives. The purpose of rehabilitation is to enable a meaningful life with the best possible activity and participation, mastery, and quality of life. Rehabilitation is a collaborative process involving the individual, family members, professionals, and other relevant parties. Rehabilitation interventions are targeted, coherent, and evidence-based, considering the person's perspectives and overall life situation."*[100]

In the background section, I have outlined the complexity and diversity of both the physiological and emotional strain of cancer treatment, which depicts a need for rehabilitation that is equally diverse. Yet there is a need for more specific approaches to exercise to increase the certainty of evidence. While the RESPECT study embraces this demand for diversity through a multicomponent intervention, the INTERACT trial would take on a focused approach to an strength training intervention. The RESPECT study aimed to embrace a broad rehabilitative focus by exploring the effects of a combined approach to rehabilitation on normalcy: merging physical activity and education with the involvement of a significant other (classmates) in a multicomponent intervention.[25] The RESPECT study recognizes the necessity for a more broadly defined intervention, addressing the physical and less recognized yet evident social strains of cancer treatment. This includes the challenges of limited social interaction due to school absence,[101] as children with cancer often experience academic setbacks and social isolation.[102] These factors significantly influence the child's overall life situation and, ultimately, their sense of normalcy and mastery after finishing cancer treatment.[102]

Since its beginning in 2013, several papers have been published emphasizing: the methodology of the RESPECT study,[25] qualitative aspects of visits from classmates,[26,28,103] different aspects of the supervised physical activity intervention and related outcomes.[29–32]

This thesis will present and discuss the primary outcome paper concerning the effects of the RESPECT study's supervised physical activity intervention (Paper I) one year after cancer treatment.[1]

The chosen methods, results, and discovered strengths and limitations will be evaluated and used for developing the INTERACT trial[3] (Paper III).

Integrative Neuromuscular Training: strength training in childhood cancer—the INTERACT approach

Based on experiences from the RESPECT study and exploring a monomodal approach to an exercise intervention, the INTERACT trial investigated the effectiveness of a strength training intervention in children with cancer.

Designing effective strength training interventions for children during cancer treatment, as well as healthy children, presents a challenge due to the substantial variations in children's motor development caused by biological, environmental, and socio-cultural factors.[104,105] The key obstacle is finding a reasonable one-size-fits-all approach capable of accommodating the broad spectrum of children's physical capabilities across ages and motor development while ensuring an appropriate level of challenge and exercise intensity.[44] This is crucial to achieve optimal effects without compromising motivation and adherence to an exercise intervention.[44,104]

An innovative concept in the field of exercise programming for children and adolescents is Integrative Neuromuscular Training, which involves combining different types of physical exercises with the potential for neuromuscular output.[106–108] This exercise paradigm is characterized by sessions of strength and skill-building exercises structured to enhance both health- and skill-related components of physical function. It incorporates a progressive increase in either resistance or difficulty, making it a versatile and adaptable strategy for children and adolescents in various settings;[108] e.g., as an integrated part of a sports-regime,[109–111] as a supplementary activity to mandatory physical education in a school-based setting[107,112–114] or as an individual exercise regime.[112] Rather than focusing on conventional approaches to strength training (such as weight and resistance training using predefined sets, repetitions, intensity, and time-under tension), it more broadly focuses on achieving a high neuromuscular output through combining intensity and difficulty of the exercise, also described as optimal or appropriate challenge.[104] This is achieved by introducing skills that require either velocity (e.g., jumping, skipping, landing), balance, or motor skills (e.g., throwing and catching). Hence, this type of exercise induces neural plasticity, alerting motor unit recruitment, firing frequency, and synchronization of motor unit activation.[106,107,110,115,116]

Even though there is currently lacking specific research on integrative neuromuscular exercise in children and adolescents during cancer treatment, integrative neuromuscular training appears like a promising exercise modality because of its age- and skill-appropriate approach to progressive

exercise and the possibility of pro-and regression of the intensity of exercise to accommodate the daily variation of treatment-related side effects.

Studies on healthy children from 6–15 years have shown promising results of integrative neuromuscular training compared to either customary sports or physical education classes. Randomized controlled studies a variety of subgroups of children: healthy primary school children (ages 5–7 years),[113] prepubertal school children (6–8 years),[114] prepubertal soccer players (ages 7–11 years),[110] early adolescent soccer players (ages 10–12 years)[111] youth volleyball players (ages 12–15 years), have shown significant effects on a variety of muscle fitness parameters[111,113] and overall physical capacity parameters[110,111] including motor competence and fundamental motor skills.[113,114] Further, one quasi-experimental study on integrative neuromuscular training has shown significant within-group physical fitness improvements (hand-eye coordination, sprint time, core muscular endurance, and upper- and lower-body power) in physically active children from 6–14 years in all age groups.[109] For young children (ages 6–10 years), a more play- and game-like approach to integrative neuromuscular training, known as "animals in motion," has been developed.[117] This approach translates neuromuscular training/strength training principles into a framework that is comprehensible for children, giving exercise professionals a basis for conducting and communicating exercise at the child's level. A clinical approach to this concept would be, e.g., addressing squat jumps as frog-hops, and jumping lunges as "lizard jumps," thereby giving children a possibility to express but also co-create and develop these exercises. For young children, the emphasis is on enjoyment and creativity, thereby inducing integrative neuromuscular training that is perceived as fun yet challenging but ultimately rewarding.[117] As stated above, the INTERACT trial would take on a more specific approach to rehabilitation through a mono-modal exercise approach: strength training. However, using integrative neuromuscular training as the framework for strength training, we would include a diverse exercise regime that can be adjusted to both age, motor development, and daily variations of physical performance due to treatment side-effects in children with cancer ages 6–18 years.

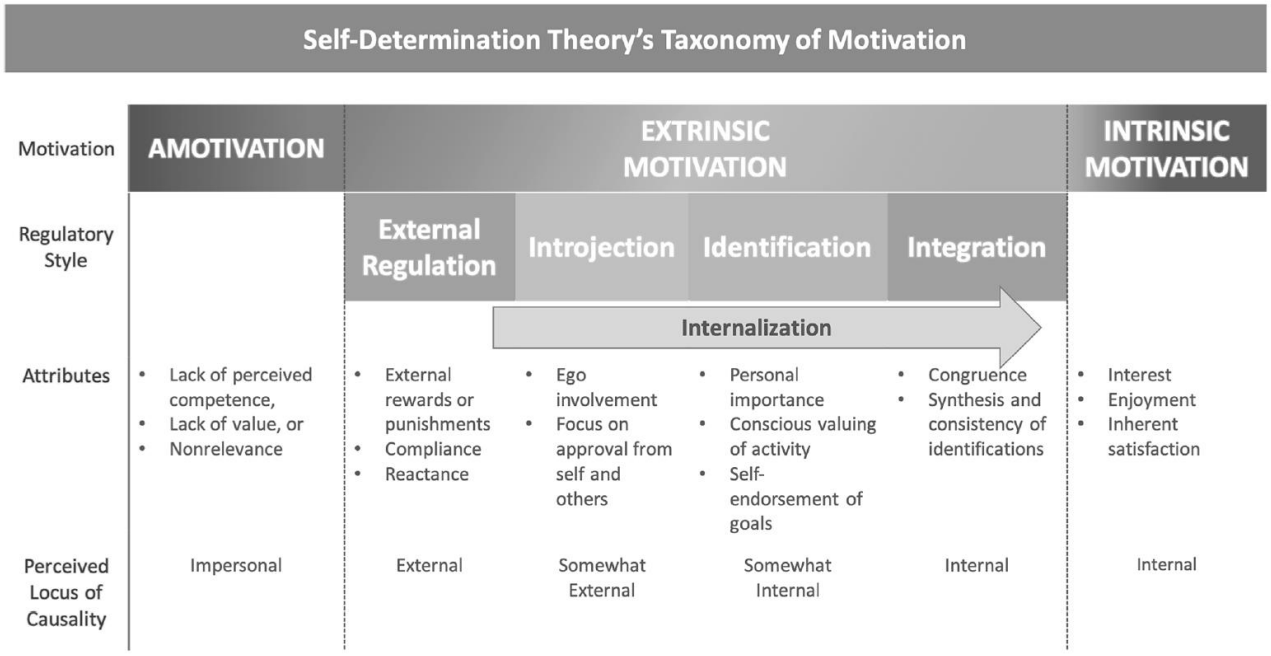
Self-determination Theory

As the INTERACT trial investigates a more specific approach to physical exercise, we found it necessary to integrate a theoretical approach to explore and understand motivation as a mediating factor for participating in exercise during cancer treatment. Self-determination was chosen as an integral part of the analysis of motivational facilitators and barriers due to its high heuristic value; having a wide applicability.[118]

Self-determination theory provides a broad framework for understanding factors that can either facilitate or undermine motivation. The core concept of self-determination theory is that motivation is inherently perceived and driven by personal interest, mastery, and a sense of belonging. The theory identifies these three basic psychological needs as: autonomy, competence, and relatedness. Autonomy involves valuing oneself or one's interests over external control; competence is experiencing a sense of mastery rather than facing unrealistic demands; and relatedness is having a sense of belonging rather than isolation.[118]

Self-determination can be viewed as a spectrum between amotivation and intrinsic motivation, representing two opposite poles of motivation. Pure autonomous intrinsic motivation, the untainted concept of motivation, holds value as a concept but is rarely achievable in practical or analytical settings due to its exclusive reliance on individual needs. When analyzing motivation through self-determination theory, practical situations often involve some degree of extrinsic motivation, scalable within the continuum between amotivation and pure intrinsic motivation. This scale is described in Self-Determination theory's Taxonomy of Motivation, presented in Figure 1 (from Ryan et al. (2020)[118]).

Figure 1: Self-Determination theory's Taxonomy of Motivation (presented as published in Ryan et al. (2020)[118] ,licensed by CC BY-NC-ND)



Within this approach external motivation can be taxonomized as pure extrinsic motivation, involving externally regulated behavior (e.g., demanded by others, society, or logistics), however, while still holding a minimum of personal value. Introjected motivation and identified motivation are less

externally regulated with the involvement of ego and personal importance, respectively. Integrated motivation is perceived as congruent with one's interests.

In a heavily externally controlled setting—like a hospital, where adherence to therapy and procedures is essential—the need for external regulation, thereby thwarting intrinsic need, will reduce intrinsic motivation and may reduce emotional well-being.[118,119] However, certain traits can be applied in the hospital facility to facilitate intrinsic motivation, such as showing interest in individual needs, providing a well-structured environment, and demonstrating a caring attitude.[118–121] Therefore, ideal qualifications for an exercise professional in a hospital environment involves listening to the child's needs, being responsive to questions, showing attentiveness to the child's interests, and providing children with choices coherent with appropriate challenge (to facilitate mastery).

In this thesis: Self-determination theory was used in designing the intervention for the INTERACT trial—as a pedagogical tool for keeping and facilitating motivation for exercise when hospitalized and during unsupervised home-based exercise, and further maintaining motivation after completing intervention, emphasizing internalization. Further, the theory was applied in the deductive analytical approach for qualitatively evaluating the INTERACT trials' intervention. In the RESPECT study, self-determination was not considered in the design or methods. However, the multicomponent psychosocial-, educational, and supervised physical activity intervention is an example of how to apply autonomy, competencies, and relatedness in a practical setting.

c

Primary aims (and endpoints)

The specific aims for the five papers included in the thesis are:

I. *"…to investigate the effects of a multicomponent social and supervised physical activity intervention on cardiorespiratory fitness, muscle strength, and physical function one year after end of treatment t compared with both childhood survivors of cancer controls and children no history of cancer."*[1]

II. *"…to summarize the body of evidence on cardiorespiratory fitness, muscle strength, and physical performance status of children (ages 1–18) with newly diagnosed cancer."*[2]

III. Present a study protocol, including methods and design for*: "investigating the effects of a 6-month integrative neuromuscular training intervention compared with unsupervised home-based exercise on isometric knee extension strength in children and adolescents (6–18 years) during anti-cancer treatment. Our secondary objectives are to investigate the effects of the*

intervention on markers of metabolic syndrome, days of hospitalization, health-related quality of life, upper-body muscle strength, exercise capacity, physical function, physical activity behavior, and body composition."[3]

IV. *"…to investigate feasibility of conducting a randomized controlled early-initiated strength training intervention including assessment of physical function in children and adolescents during the first six months of cancer treatment."*[4]

V. *"…to improve our understanding of what influences the motivation of children and adolescents diagnosed with cancer (ages 6–17) to engage in a strength training exe intervention during the first six months of cancer treatment. In this study, motivation will be operationalized by the following three areas: amotivation, controlled regulation, and autonomous self-regulation.*[5]

Since the INTERACT trial is ongoing, the primary endpoint, the effects of integrative neuromuscular training on leg muscle strength, will not be included or discussed in this thesis.

Methods

A summary of the methodological framework across the five included papers is described in Table 2.

Table 2: Summary of the methodological framework across included papers

	Paper I[1] Non-RCT	Paper II[2] Systematic Review	Paper III[3] Study Protocol	Paper V[4] Feasibility	Paper V[5] Qualitative
Recruitment	Participants identified by oncologist at Rigshospitalet, Aarhus, or Odense University Hospital	(Not applicable)	(Not applicable)	Participants identified by oncologist at Rigshospitalet, Aarhus, or Odense University Hospital	Participants included in the intervention arm of the INTERACT trial (>3 months)
Population	RESPECT **Intervention gr.:** - 6–18 years - Any cancer diagnosis - Treated with chemotherapy or radiation therapy - Enrolled in school - Treated at Rigshospitalet **Patient Control gr.:** - (as above) - Treated at Odense and Aarhus University Hospital **Community Control gr.:** 1) Sex and age-matched children - Children with no history of cancer	- <18 years - Any cancer diagnosis **Studies reporting:** - Objective measures of: cardiorespiratory fitness, muscle strength, or physical performance - Assessment was reported with one month of cancer treatment initiation **Studies were not included if they:** - <10 participants - Children with relapse of cancer - HSCT	INTERACT - 6–18 years - Any cancer diagnosis - Treated with chemotherapy and or radiation therapy (initiated within 14 days before study inclusion) - Treated at Rigshospitalet, Odense or Aarhus University Hospital - And parents to the included children	- 6–18 years - Any cancer diagnosis - Treated with chemotherapy and or radiation therapy (initiated within 14 days before study inclusion) - Treated at Rigshospitalet, Odense or Aarhus University Hospital - And parents to the included children	- 6–18 years - Any cancer diagnosis - Treated with chemotherapy and or radiation therapy (initiated within 14 days before study inclusion) - Treated at Rigshospitalet, Odense or Aarhus University Hospital - And parents to the included children
Intervention	**Phys. Activity intervention:** Supervised physical activity while hospitalized during the entire treatment period **Educational intervention:** 90-minute school class education **Psycho-social intervention:** Visits from classmates	(Not applicable)	**Intervention:** 24 weeks of integrative neuromuscular training (supervised and home-based exercise) **Active control group:** Unsupervised, self-administered-home-based exercise and physical activity	**Intervention:** 24 weeks of integrative neuromuscular training (supervised and home-based exercise) **Active control group:** Unsupervised, self-administered-home-based exercise and physical activity	12–24 weeks of integrative neuromuscular training (supervised and home-based exercise)
Data collected	- Anthropometric data (height, weight, BMI), medical characteristics (e.g., diagnosis, date of diagnosis, treatment protocol) **Primary** - VO_2 peak[122] **Secondary** - STS,[123] TUG,[124] Handgrip strength	- Study characteristics - Cardiorespiratory fitness - Muscle strength - Physical performance - Adverse events	Anthropometric data (height, weight, BMI)[125], medical characteristics (e.g., diagnosis, date of diagnosis, treatment protocol) **Primary** Isometric knee extension **Secondary Primary** Markers of MetS[126] **Secondary** Isometric bench pres, handgrip strength,[127] 6MWT[128] VO_2 peak,[129] STS,[123,130] TUG,[124] DXA scan, QoL[131] **Explorative** PedMTNS,[132] accelerometry, counter-movement jump, markers of dysmetabolism, Self-reported PA, HRQoL,[133] fatigue,[133] Physiotherapy referrals	- Availability (no. of children Screened for eligibility) - acceptance - attrition - adherence (to intervention and assessment) - practicality - transparency (no. of registration in training logs) and safety (adverse or minor adverse events) - days from initiation of treatment till inclusion	Purposeful criterion-based sampling strategy[134] Participants' and their parent's experiences in relation to the intervention through semistructured interviews
Data analysis	- ANCOVA - Sub/adjusted analysis for: 1) sex-dependent effects of relative age differences 2) cancer-type-dependent effects of time since diagnosis - two- and three-factor interactions	- Study quality and risk of bias: Newcastle-Ottawa Scale - Certainty (GRADE)[135] - Meta-analysis (Random effects) - Two-sample t-test or Wilcoxon rank-sum-test[136,137]	General linear mixed models	Descriptive statistics Mann-Whitney U test[138]	Deductive thematic analysis of semistructured interviews[139] with participants and their parents based on self-determination theory[118]

Table 2: HSCT: Hematopoietic stem-cell transplantation, GRADE: Grading of Recommendations Assessment and Evaluation, STS: Sit-To-Stand, TUG: Timed-Up-and-Go, 6MWT: Six-Minute-Walk-Test, MetS: Metabolic Syndrome, DXA: Dual-energy X-ray Absorptiometry scan

Population in the thesis—thesis-population

This thesis addresses children and adolescents (age 6–17.9 years) throughout their cancer disease trajectory. Included children are "newly-diagnosed with any malignant or benign neoplasia, receiving either chemotherapy or radiation therapy at Copenhagen University Hospital—Rigshospitalet, Aarhus University Hospital or Odense University Hospital."[1–5]

Samples and design

Specifically, this thesis is based on three different samples

a) *RESPECT study sample—Paper I*[1]

The RESPECT study is a Danish multicenter non-randomized controlled study.[25] From January 2013 to February 2018, the study included 170 children within the thesis population who had undergone a multicomponent psychosocial-, educational, and supervised physical activity intervention throughout their entire cancer treatment (n = 120) or participated as controls (n = 50). Children with mental disability, severe co-morbidities (e.g., severe hemiparesis, paralysis, or cardiovascular diseases), and children with recurrence of their primary cancer were excluded from the study. The children and their parents needed to understand verbal instructions to participate in the intervention and answer questionnaires; therefore, participants who were not able to communicate in Danish were excluded.

Children treated at the University Hospital of Copenhagen—Rigshospitalet were placed in the intervention group, while those treated at Odense and Aarhus University Hospital constituted the patient control group, receiving usual care.

Moreover, the study included 94 age- matched children without a cancer history and chemotherapy/radiation treatment, as a community control group. This community control group was identified through participants in the intervention group school classes (n = 64) and via an ongoing study within the Copenhagen University Hospital (n = 30).[140]

b) *Population of interest in systematic review—Paper II*[2]

The systematic review investigated a population of children newly diagnosed with cancer (ages 1–18 years)—within the first month of cancer treatment.

We restricted the population not to include children receiving hematopoietic stem cell transplantation and children with relapse of their initial cancer disease.

The systematic reviews included studies reporting objective measures of cardiorespiratory fitness, muscle strength, physical performance, and adverse events related to physical assessment.

c) INTERACT trial sample—Papers III, IV, and V

The INTERACT trial is an ongoing Danish multicenter, two-arm, parallel-group randomized controlled superiority trial consisting of children included within the early stages of their cancer treatment (within 14 days of cancer treatment initiation) within the thesis population. Furthermore, we included the parents of the participants. Children have been recruited from the three involved centers, Copenhagen University Hospital—Rigshospitalet, Odense University Hospital, and Aarhus University Hospital, since January 2021. The inclusion of children is projected to stop in October 2024. As of March 2024, the trial has included 105 participants. We prespecified that children with mental or physical deficits (i.e., if physicians restricted participation in all physical exercise and physical assessments) were excluded. Further, children and parents unable to communicate in Danish were excluded.

The INTERACT trial will include children with recurrence of their primary cancer, including children receiving hematopoietic stem cell transplantation. Children undergoing hematopoietic stem cell transplantation will be regarded as a subgroup, as their treatment trajectory, treatment protocols, and logistics severely differ from other cancer diagnoses. This subgroup is described in Paper III[3] but was not included in either Paper IV or Paper V.

The study methods within these three populations are described in the following.

Recruitment and subsamples

In the RESPECT study and INTERACT trial, children were identified by a treatment-responsible physician employed at the children's cancer ward in each of the three recruitment centers. By notice of the physician, a study coordinator at each site provided children and their parents with written information concerning the study/trial, including trajectory and protection of privacy rights in accordance with Danish (The National Committee on Health Research Ethics and the Danish Data Protection Agency) and International Law (The Helsinki Declaration II and General Data Protection Regulations). Information concerning the study would be given verbally, and all participants were given a minimum of 24 hours to consider participation. Hereafter, written consent was obtained from children and parents accepting participation. None of the participants received any remuneration in relation to participating in either study.

In Paper I, a community control group—94 age-matched children without a history of cancer—was included. Sixty-four children were identified through participants from the RESPECT study's school

classes.[1] Schoolmates applied to be included in the study, and were selected in collaboration with the child's teacher, the RESPECT study's research team, parents, and the child with cancer's preference.[25] Further, 30 children—either friends or siblings of cancer survivors, were identified and included via the National Clinical Cohort Study of Late Effects Among Survivors of Acute Lymphoblastic Leukemia (ALL-STAR) study at the Copenhagen University Hospital.[140]

Subsamples and design of Papers IV and V

For the feasibility study (Paper IV, we included a subsample from the consecutively eligible participants who either accepted or rejected participation in the INTERACT trial between January 2021 and December 2023.

For the qualitative study, we used a subsample of participants and parents from the INTERACT trial's intervention group. We used a purposeful criterion-based sampling strategy,[134,141] selecting children who had been included in the intervention group for at least three months or were no longer than two months past ended intervention. The sampling strategy aimed to encompass children with diverse diagnoses, ages, sexes, and adherence rates to the exercise intervention.

Design of the INTERACT protocol

Paper III will describe the content of the INTERACT protocol[3] and follows the SPIRIT recommendations for reporting clinical trials protocols.[142]

Interventions

Multicomponent-intervention and control group: the RESPECT study (Paper I)[1]

In short, children in the intervention group of RESPECT received a multicomponent psycho-social and physical activity intervention during cancer treatment consisting of:

1) The child's school class received a 1½-hour presentation from nurses employed by the study, with an educational purpose concerning the purpose of the RESPECT study, treatment trajectory, including cancer etiology, cancer treatments, typical side effects, supportive care, everyday life at the hospital, and the importance of maintaining "normal" physical activity levels.
2) Projectably, at least once every 14th day, admitted to the hospital, the child with cancer would receive visits from two assigned classmates.
3) The child would receive individual or group-based supervised physical activity during hospitalized days, as described in Table 3 (From Paper I, Fridh et al. (2023)[1])

Table 3: The in-hospital RESPECT activity program (presented as published in Fridh et al. (2023)[1] licensed via CC-BY-NC)

Training/weekday	Monday	Tuesday	Wednesday	Thursday	Friday	Weekend
Able to walk/ not in isolation	Individual session 5–30 minutes Cardiorespiratory fitness Muscle Strength Balance	Group Session 30–120 minutes Cardiorespiratory fitness Muscle Strength Balance	Individual session 5–30 minutes Cardiorespiratory fitness Muscle Strength Balance	Group Session 30–120 minutes Cardiorespiratory fitness Muscle Strength Balance	Individual session 5–30 minutes Cardiorespiratory fitness Muscle Strength Balance	No training
Able to walk/ In isolation	Individual session 5–30 minutes Cardiorespiratory fitness Muscle Strength Balance	Individual session 5–30 minutes Cardiorespiratory fitness Muscle Strength Balance	Individual session 5–30 minutes Cardiorespiratory fitness Muscle Strength Balance	Individual session 5–30 minutes Cardiorespiratory fitness Muscle Strength Balance	Individual session 5–30 minutes Cardiorespiratory fitness Muscle Strength Balance	No training
Bedbound	Individual session 5–30 minutes Muscle Strength	Individual session 5–30 minutes Muscle Strength	Individual session 5–30 minutes Muscle Strength	Individual session 5–30 minutes Muscle Strength	Individual session 5–30 minutes Muscle Strength	No training

Table 3: RESPECT = Rehabilitation including Social and Physical Activity and Education in Children and Teenagers with Cancer

Irrespective of allocation, all participants received usual care, including physiotherapy, according to the individual institutional resources.

Strength training: integrative neuromuscular training and active control group—INTERACT trial (Papers III, IV, and V)

In the INTERACT trial, the intervention group was offered integrative neuromuscular training (INT) for 24 weeks initiated within the first two weeks of cancer treatment as a supplement to usual care. The exercise intervention targeted various physical elements, was adapted to individual needs, and included both supervised and home-based unsupervised sessions. Training intensity and length were adjusted based on chemotherapy cycles to accommodate potential side effects. We found inspiration in Kirkham and colleagues' study on periodizing exercise according to planned chemotherapy blocks, lowering the intensity of treatment immediately after a treatment block to accommodate anticipated treatment-related fatigue.[143] Due to the heterogeneity of treatment protocols, which is often individualized, we found the trajectory of childhood cancer treatment too diverse to employ a strict, predefined structure for this kind of periodization. Instead, we developed a taxonomy to pro-and regress exercise either on a motor skill level or strength exercise technique level (Figure 2) and underlined for the intervention staff conducting the intervention that this taxonomy should be applied and that a lower intensity of exercise should be expected in the immediate days after a treatment block. We further modified the taxonomy for children (ages 6–10) as "animals-in-motion" as described by Bruno and Faigenbaum (Figure 2, C).[117]

Figure2: Taxonomy for INT during cancer treatment

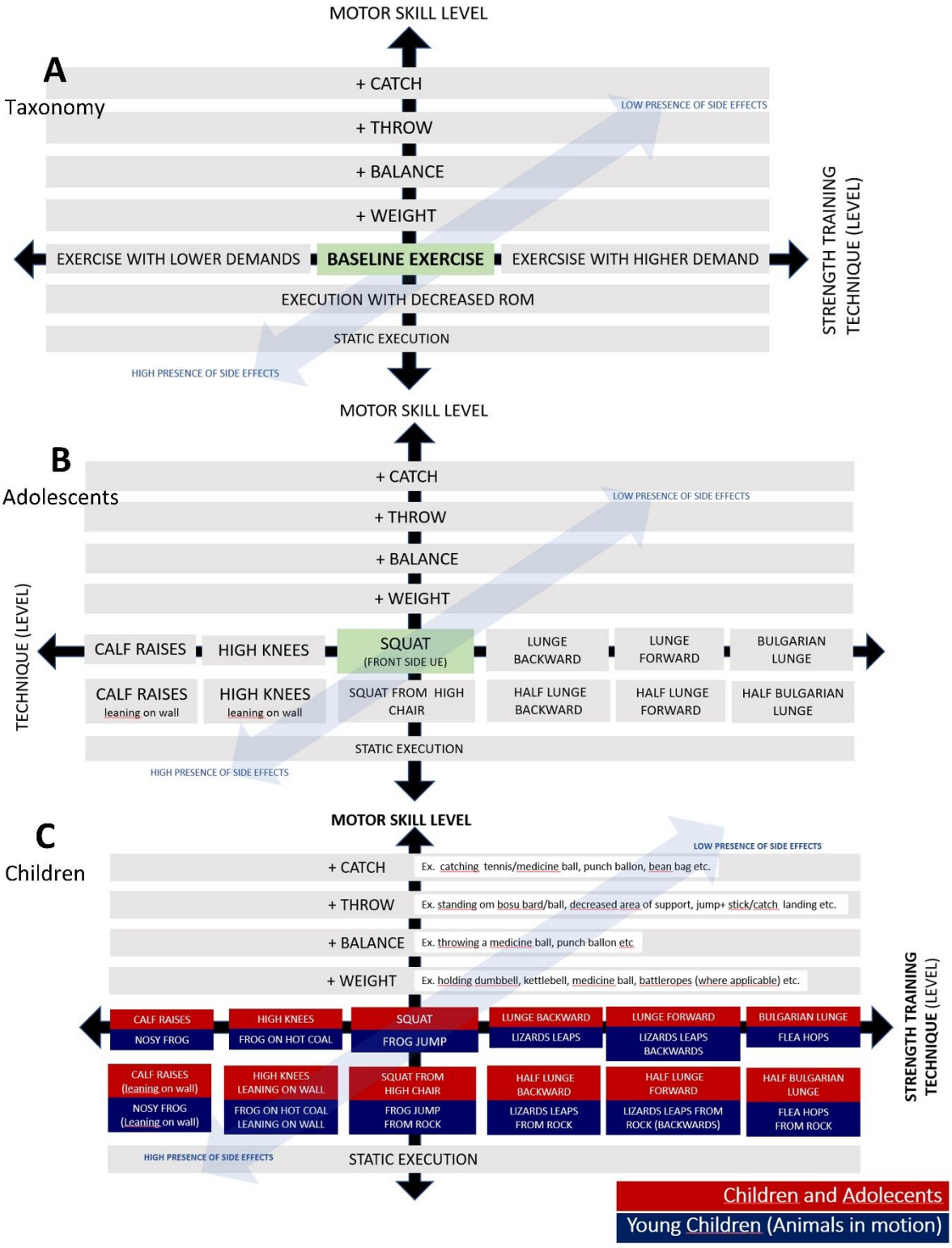


Figure 2: A: a generic template of the taxonomy. B: An example of the taxonomy fitted to children and adolescents, and C: fitted for young children

A description of the intervention, and active control intervention, including requirements, are listed in Table 4 (modified from Paper IV, Schmidt-Andersen et al. (2024)[4]).

Table 4: Overview of contents and requirements in the intervention and active control group (modified from Paper IV (submitted), Schmidt-Andersen et al. (2024)[4]).

	Intervention group (Integrative neuromuscular training)	Active control group
Description	24 weeks of supervised in-hospital strength training + unsupervised home-based exercise, initiated with two weeks of treatment initiation	24 weeks of unsupervised home-based exercise, initiated with two weeks of treatment initiation
Detailed description of unsupervised sessions	Week-to-week prescribed strength training based on in-hospital interventions. If the child participates in leisure time physical activities (e.g., soccer, gymnastics), these can replace prescribed exercise. If the child is not motivated, the participant is urged to do any physical activity (e.g., walking, jumping on a trampoline)	Control participants are recommended to follow an exercise plan (combined aerobic, strength, and stretching exercises) or be physically active
Registration of exercise	Supervised strength training: All sessions in logged by the exercise staff Unsupervised exercise: Participants/parents log activities in a printed exercise log	Unsupervised exercise: Participants/parents log activities in a printed exercise log
Requirements/Demands		
Volume	Weeks 1–7: ≥2 strength training sessions/week Weeks 8–24: 3 strength training sessions/week (Total: 65 strength training sessions, of which 24 are expected to be supervised sessions)	2 Exercise sessions/week (Total: 48 exercise sessions)
Intensity	Weeks 1–7: ≥2 different exercises hereof ≥1 lower body exercise (primary exercises) * Weeks 8–24: ≥3 different exercises hereof ≥2 lower body exercise (primary exercises) *	-

*Table 4: Description of contents and requirements of prescribed exercise in intervention and active control group. * Activities and exercises with a focus on lower body strength were categorized as primary exercises. Other activities, targeting other muscle groups or with a resitutional purpose or diverting attention from treatment-related side effects, were categorized as secondary activities.*

The active control group followed a home-based training program, including strength and stretching exercises for the upper and lower body, monitored through exercise diaries.

A health counseling/motivational intervention was conducted monthly for both groups. The Intervention focused on self-determination theory principles to foster internal motivation for exercise engagement.

Both groups received usual (standardized hospital-) care, including physiotherapy as needed, with different referral procedures among the centers.

Outcomes—physical capacity

For the RESPECTS study, children with cancer were included and baseline tested within the first 31 days of diagnosis.

In the INTERACT trial, participants were included, baseline tested, and randomized within 14 days of treatment initiation.

Overview and primary endpoints.

In the long-term follow-up study from the RESPECT study (Paper I), physical capacity in the study sample was measured one year after the ended treatment, which was the primary endpoint for the RESPECT study.[1] This follow-up study (Paper I) focused on the physical activity components and the outcome measures relevant to this domain. The RESPECT study uses several other outcome measures, besides the one listed in Figure 3 and described below, for the three intervention components, which are described elsewhere.[25]

VO_2 peak is the primary outcome of the physical activity component in the RESPECT study.[1,25]

In the INTERACT trial (Papers III, IV, and V), the primary endpoint for the primary outcome was six months after treatment initiation[3]. The primary outcome of the INTERACT trial was muscle strength, measured by isometric knee extension.

An overview of the study trajectory in both RESPECT and INTERACT, measured outcomes, and endpoints is described in Figure 3 (modified from Paper III (Schmidt-Andersen et al. (2022)[3]).

Figure 3: Study trajectories in the RESPECT study and INTERACT trial (modified from Paper III (Schmidt-Andersen et al. (2022)[3])

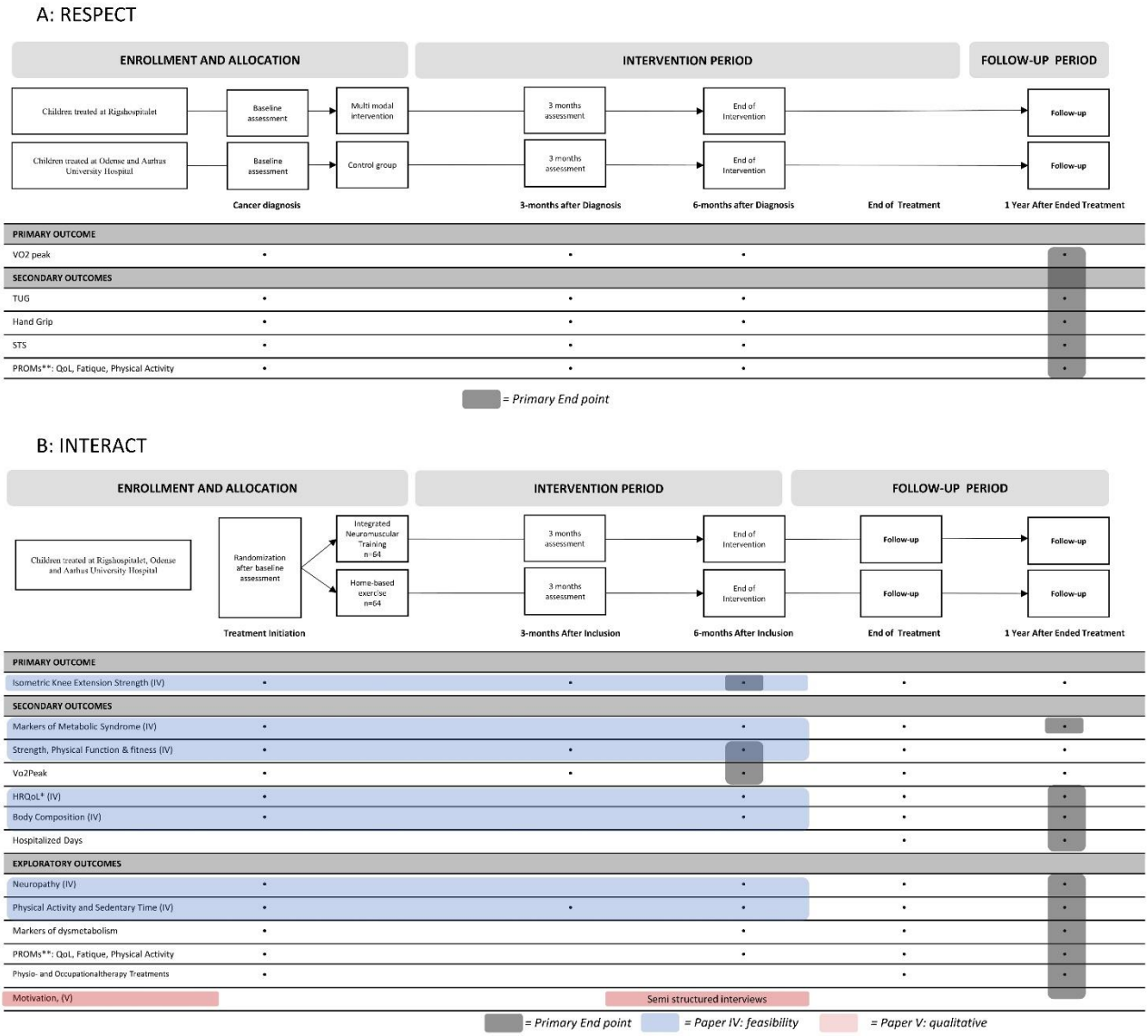


Figure 3: Overview of study trajectories in the RESPECT study (A) and INTERACT trial (B). For the INTERACT trial outcomes, especially of interest in the included papers have been colored either blue (Feasibility study) or red (Qualitative study).
**HRQoL = Health Related Quality of Life (through the PedsQL Generic Core Scale).*
*** Patient Reported Outcome Measures (through Peds QL cancer scale, PedsQL Multidimensional Fatigue Scale and general physical activity questionnaires)*

During all tests of physical capacity, strong verbal encouragement was applied.

VO_2 peak—Cardiopulmonary exercise testing (Papers I and III)

VO_2 peak was measured by cardiopulmonary exercise test (CPET) following a modified Godfrey protocol[129]—a step incremental exercise protocol—performed on a bike ergometer. The test protocol

required the child to keep a steady tempo (approximately 80 RM) while resistance was stepwise increased by 10 watts every minute until the child reached a level of exhaustion.

The test started at a steady state aerobic intensity—at a resistance level where the participant's heart rate would level at approximately 150 BPM. The "steady state" test was performed before the CPET and functioned as a warm-up routine.

Gas exchange was measured using a breath-by-breath spirometry system (Innovision, Odense Denmark or Jaeger Master Screen® CPX System (MS-CPX) and JLAB Software Package™), and the average continuously measured highest measure within one minute expressed VO_2 peak (ml/kg/min) was used in the analyses.

Acceptable measures of VO_2 peak required three criteria to be fulfilled:

1) The participants should show visible (subjective) signs of exhaustion
2) Heart rate should exceed 180 BPM
3) The Respiratory exchange ratio should exceed 1.05

Basic functional mobility—Timed up-and-go test (Papers I, III, and IV)

Basic functional mobility was measured using the timed up-and-go test.[144] From a sitting position in a chair that allowed 90 degrees of knee flexion, the participants walked three meters forth and back, returning to the seated position, walking as fast as possible. The lowest score (seconds) of three attempts was noted.

Lower extremity muscle strength and endurance—Thirty-Seconds (Papers I, III, and IV) and One-Minute Sit-to-Stand Test (Papers III and IV)

Lower extremity muscle strength was estimated using the thirty-second sit-to-stand test.[145] Similarly to the timed-up and-go test, the participants sat in a chair, allowing 90 degrees of knee flexion, and were asked to complete as many cycles as possible of standing up (to fully extended hips and knees) and returning to the seated position. Arms were instructed to be folded across the chest. One attempt was made, and the number of total cycles (repetitions) was noted.

In the Interact trial, the test was continued for another 30 seconds, to achieve a potentially more precise estimate of muscle endurance.[146] Number of repetitions for 30 and 60 seconds, were noted.

Handgrip strength—handgrip dynamometer (Papers I, III, and IV)

In both the RESPECT study[1] and INTERACT trial[3], Isometric hand grip strength was measured using hand dynamometers (Saehan, Glanford Electronics, Scunthorpe, UK, and Jamar, Patterson Medical, Illinois, USA, respectively). The participants were encouraged to grip as hard as possible, either from a standing position or sitting if the participants were not able to stand.

For the INTERACT trial, we standardized that participants were sitting during grip strength testing, keeping elbows supported on a chair.[147] Measures were performed twice on each hand, and each hand's highest score (kg) was noted.

Lower-body muscle strength—Isometric knee extension strength (Papers III and IV)

Isometric knee extension strength was measured using a custom-build strength-ergometer (Gym 2000®, Vikersund, Norway), with a build-in dynamometer (U2A100 kg, Hottinger, Germany)

Participants were sitting in an upright position; knees and hips were kept in 90-degrees flexion, while a strap was secured around the ankle. The participants were asked to "press" (i.e., extend the knee), keeping a maximal time-under-tension for five seconds. A minimum of three and a maximum of five attempts were carried out until a peak value was noted. The highest score (kg) was noted.

Upper-body muscle strength—Isometric bench press (Papers III and IV)

Isometric bench press was measured using the same equipment as for isometric knee extension. The participants layed in a supine position, knees bent, gripping a bar securred to the dynamometer, keeping elbows in a 90-degree flexion and shoulders in a 45-degree abduction while maintaining brachium at a horizontal level. The participants were asked to "push" (i.e., extend the arms), keeping a maximal time-under tension- for five seconds. A minimum of three and a maximum of five attempts are carried out until a peak value was noted. The highest score (kg) was noted.

Walking distance—Six-minute walk test (Papers III and IV)

Walking distance was measured using the six-minute-walk-test.[148] Participants were instructed to walk between two cones 20 meters apart as fast as possible. We noted the perceived rate of perceived exertion (using the Borg-20 scale[149]) at the start and completion of each test. Further, we measured HR at the start of the test, average HR during the test, and HR at the end of the test. Distance covered (meters) was noted.

Balance—Modified Clinical Test of Sensory Interaction in Balance (Papers III and IV)

To assess impairments balance dependency on vision, vestibular, and somatosensory, the Modified Clinical Test of Sensory Interaction in Balance test was used.[150]

The participants were asked to keep a feet-together position, with hands on hips, and maintain balance for 30 seconds, through four different conditions:

1) with open eyes.
2) with closed eyes
3) with open eyes standing on a foam mat.
4) with eyes closed standing on a foam mat.

Within each condition, the participant could achieve a score of 30 (per second maintaining balance) and, thereby, a maximum score of 120.[150].

Outcomes: Metabolic syndrome, body composition, physical activity, neuropathy, and questionnaires

In the INTERACT trial, metabolic syndrome, body composition, neuropathy, and questionnaires were assessed at baseline, six months after treatment initiation, after the end of treatment, and one year after the end of treatment.[3]

Metabolic syndrome (Papers III and IV)

Markers of metabolic syndrome were measured as waist and hip circumference (cm), BMI, blood pressure (mmHg), and six different blood markers: triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol, fasting blood sugar, and insulin in accordance with recommendations from the International Diabetes Foundation.[126]

Body Composition (Papers III and IV)

Body composition was assessed through Whole-body Dual-Energy X-ray Absorptiometry (DXA) Scan (Lunar, Lunar Corporation Madison, WI, USA), providing measures of fat mass, fat-free mass, and bone mineral density.

Physical activity and sedentary time—accelerometry (Papers III and IV)

Physical activity and sedentary time were measured throughout a seven-day period using an accelerometer (ActiGraph™, ActiGraph LLC, Pensacola FL, USA). Accelerometers were handed out after physical assessment sessions, and the participant was asked to wear the monitor, placed at the hip, for the next seven consecutive days.

Neuropathy (Papers III and IV)

Chemotherapy-induced peripheral neuropathy was measured through the Pediatric Modified Total Neuropathy Score (Ped-mTNS). The Ped-mTNS assesses impairments of sensory, motor, and autonomic symptoms; perception of light touch, pin, and vibration. Additionally, it examines muscle strength in distal musculature and evaluates deep tendon reflexes, providing a composite score of neuropathic impairments.

Self-and parent proxy-reported outcomes (Papers III and IV)

Table 5: Table 5: Feasibility outcomes (as presented in Paper IV (Schmidt-Andersen et al. (2024)[4])

FEASIBILITY OUTCOMES			
Domain	**Measure**	**Calculation**	**Cut-off**
FEASIBILITY OF EARLY INITIATED EXERCISE			
Availability	Children within the target population fulfilling inclusion criteria	Participants fulfilling inclusion criteria/ Children diagnosed with cancer	>90%
Acceptance	Children approached who enrolled	Participants available for baseline assessment/ children eligible for trial	>80%
Attrition	Children who left study before completion	Participants dropped out during intervention period/ participants available for feasibility study	<10%
Adherence—demands (INT)	Children in intervention group adhering to all supervised interventions	Participants adhering to prescribed volume (24 supervised sessions)/ participants in intervention group at the end of intervention	>50%
Practicality (explorative)	Median supervised sessions fulfilling requirements for intensity	Supervised sessions** fulfilling requirements for intensity (prescribed number of primary and secondary exercises)/ participants in intervention group at the end of intervention	>40%
Adherence—demands (CON)	Children in control group adhering to all home-based interventions	Participants adhering to prescribed volume (48 home-based sessions)/ participants in control group at the end of intervention	>50%
Group-based Adherence - **INT** (primary) - **CON**	 Median adherence to intervention Median adherence to control intervention	 Median of total supervised sessions/participant (INT) Median of total home-based sessions/participant (CON)	>70% - -
Safety early initiated exercise	Children reporting severe adverse events during exercise	Reported events/eligible children	<5%
FEASIBILITY OF PHYSICAL ASSESSMENT			
Adherence physical assessment	Children adhering to physical testing	Participants participating in physical assessment/ participants available for feasibility study	>80%
Safety physical assessment	Children reporting mild, moderate or severe adverse events during physical assessment	Reported events/eligible children	<5%
Safety physical assessment (sub-analysis)	Adverse event rate/test session	Reported events/total number of test session	-

Table 5: Overview of feasibility domains, measure, calculation, and pre-defined cut-off values for achieving feasibility. INT = exercise intervention group, CON = active control group

Questionnaires concerning health-related quality of life (PedsQL 3.0 Cancer Scale[133]) and fatigue (PedsQL Multidimensional Fatigue Scale[133]) were collected from children (ages 8–17.9 years) and parents (proxy questionnaires for children ages 6–17.9 years)

In supplement to the above test, medical characteristics were collected.

Outcomes—feasibility

An overview of feasibility outcomes (Paper IV) is described in Table 5 (as presented in Paper IV, (submitted) Schmidt-Andersen et al. (2024)[4]. Table 5 also includes a predetermined cut-off value, describing a threshold rate for achieving feasibility within each feasibility domain.

Adverse events

In Paper IV, adverse events are reported in accordance with the National Cancer Institute's definitions of mild, moderate, and severe adverse events.[151]

Mild adverse events were defined as: "transient or mild discomfort from the participant, causing no limitation in activity and no therapy required."[151] Moderate Adverse events were defined as: "mild to moderate limitation in activity, with no or minimal therapy required."[151] Severe Adverse events were defined as: "marked limitation in activity, needing therapy, medical intervention, hospitalization."[151]

Sample size considerations and predicted trajectory considerations

In the RESPECT study, a power calculation was made, emphasizing the primary endpoint, VO_2 peak, one year after treatment. We anticipated a 10% higher VO_2 peak in the intervention group compared to the control group and based the calculation on previously published data on baseline VO_2 peak measures (24.3 ± 5.9 (mL/kg/min)).[57] We set a significance level of 0.025 and a power of 0.90, estimating that 120 children were required in each group.[25]

For the INTERACT trial, we calculated that 53 children were needed in each group based on the effects achieved in a previous exercise intervention study in children during cancer treatment, measuring baseline values of isometric knee strength (41.4 ± 30.4).[74] We sat a significance level of 0.05 and a power of 0.80. With an attrition rate of 20%, we estimated that a total of 127 participants was needed. Based on the attrition rate, we projected—at the initiation of the INTERACT trial—that a timeline of 2.2 years would be necessary to include this projected number of participants.

In Paper V, based on published guidelines for sample sizes in pilot studies, 30–50 participants should be included in both the intervention and control groups.[152,153]

Randomization

In the INTERARCT trial, participants were randomly (2:2) assigned to either the intervention or active control group stratified by sex, pubertal stage, and diagnosis. Blinding was maintained for baseline assessors and the statistician. After baseline assessment, the allocation of the participants was known to the participants, intervention staff, and assessors due to the nature of the intervention[3].

Data analysis

Paper I

In the RESPECT study, outcome measures from cardiopulmonary exercise tests (VO_2 peak, VO_2, Max Watt), sit-to stand-test, Timed-up-and-Go test, and handgrip strength will be presented as mean or mean differences and standard deviations, including 95% confidence intervals. Days since

diagnosis and number of physical activity sessions will be presented as median and interquartile range (respectively: 10^{th} and 90^{th}, and 25^{th} and 75^{th} percentile).[1]

In Paper I, we used an ANCOVA model analyzing between-group differences at follow-up assessment.[1] The model was used to adjust for several inherent differences, which may confound the interpretation of the results. We chose to compare the groups in three different scenarios: firstly, a raw model; secondly, a demographic-adjusted analysis based on sex-dependent modification relating to relative differences in age; and thirdly, an adjustment for the influence of cancer diagnosis effect over time, as diagnosis and treatment length vary considerably. Level of significance was set at 0.025.[1]

Paper II

In general, the results from the meta-analysis are reported as standard mean difference or mean difference including standard deviations. Within-study differences were reported as mean difference and standard deviations including 95% confidence intervals.

The methodology of Paper II follows the Prisma statement.[154]

A systematic search of the literature was carried out (latest search: December 19, 2022) in the electronic databases: MedLine, CIHNAL, EMBASE, Scopus, Cochrane Library, and Web of Science. Six sets of keywords were utilized, focusing on population (e.g., "neoplasm" OR "cancer" AND "adolescent" OR "child" NOT "animals"), outcomes (e.g., "6-minute walk test" OR "VO2 peak"), and study type ("case reports" OR "meta analysis" AND "journal article"). The search strategies were customized for each search engine, incorporating keywords in titles, abstracts, and subject headings as per the specifications of each platform. A generic example of the search matrix is available in Supplementary Figure 1 (in Paper II). Title/abstract screening, full-text screening, data extractions, quality assessment, and certainty assessment of the included studies were done independently by two authors, and any conflicts were discussed and solved between the authors—if not—a third reviewer was used.

When applicable, we performed meta-analyses (using an inverse variance random effect model).

As we expected to include different varieties of data, we took several precautions for standardizing and imputing data for comparison: A) If outcome measures were reported as median and IQR values, these were transformed to a mean value and SD.[155,156] B) If included studies did not perform comparisons to either healthy control or normative values, we imputed normative values for published cohorts. C) For data unavailable for meta-analysis, and no within-study comparisons were conducted,

a two-sample t-test or Wilcoxon rank sum test was conducted. If not, applicable data was presented narratively.

Risk of bias was assessed using the Newcastle-Ottawa scale for cross-sectional studies.[137]

Certainty of evidence was evaluated using the Grading of Recommendations Assessment and Evaluation (GRADE)[135] and presented in a modified evidence profile.

The level of significance was set at 0.05

Paper III

In Paper III, the included outcomes are projected to be analyzed using a linear mixed model. The model will calculate means, standard deviations, and 95% confidence limits for the intervention and active control groups at each time point. Further, the trajectories; how each outcome develops over time, will be analyzed. The level of significance was set at 0.05.

Due to the INTERACT trials projected timeline, none of these analyses will be presented in this thesis.

Paper IV

In Paper IV, outcome measures regarding feasibility will be presented as descriptive statistics: rates, percentages, or median values and interquartile ranges when applicable. We used the Mann-Whitney U test [30] to compare differences in baseline completion rates of physical capacity relative to the number of days since accepting participation in the trial from days since treatment initiation.

Paper V

In Paper V, participants were interviewed in-person, by telephone or through online virtual interviews, using in-depth- semi structured interviewing[157] by two different interviewers.

Self-determination theory was an integrated part of the study design, data collection, and analysis. Hence, we used a deductive thematic analysis.[139] The interview guides were designed based on the four core categories of self-determination theory: autonomy, relatedness, competence, and extrinsic motivation. The analysis contained the following steps: the transcribed data were coded into meaning units, then condensed according to the four core categories; and further condensed into the three behavior regulation domains of self-determination theory's taxonomy of motivation: amotivation, controlled regulation, and autonomous self-regulation.[118] A visual presentation of the deductive analysis, including identified themes, is presented in the results section in Figure 6.

<u>Measures to secure the trustworthiness of the results (Paper V):</u>

In Paper V, we employed measures to improve the trustworthiness of the results based on concepts of credibility, dependability, and transferability.[158]

To secure credibility and transferability: to capture different aspects of motivation, we chose a purposeful criterion-based sampling strategy,[134,141] obtaining a wide variety of sex, ages, diagnoses, and participation in the exercise as possible within the INTERACT trial sample.

To secure the credibility of the semi-structured interviews, we used two interviewers who had not previously met the children. We further developed three different interview guides, with questions targeted either children (<11), adolescents (≥11), or parents (Paper V, supplementary file 1[5]).

To secure dependability, we used an a priori-developed interview guide, which was not altered during the data collection period. However, as we simultaneously interviewed and analyzed data to assess the potential saturation of data (i.e., that no new themes would emerge), we may have affected dependability: the interviewers may have narrowed their focus by being aware of the preliminary results. However, the deductive approach facilitates that the scope of the study is maintained.

Analytical software and data management

Statistical analysis was performed using R Statistical Software (v4.3.0; R Core Team 2023),[159] and meta-analyses were performed using Review Manager (RevMan, v5.4; the Cochrane Collaboration 2020).[160] Study data were collected and managed using REDCap (REDCap, v LTS 13.7.14; REDCap electronic data capture)[161] hosted at Region Hovedstaden.

Results

Participants (Papers I, IV, and V)

Within a timespan from January 2013 to February 2018 and January 2021 to December 2023, a total of 192 children with cancer and their parents and 94 community controls were included in the RESPECT study and INTERACT trial. An overview of participants included in RESPECT and INTERACT (Papers I, IV, and V), including patient characteristics, can be found in Table 6.

Table 6: Participant characteristics in Papers I (modified from Fridh et al. (2023)[1] licensed via CC-BY-NC), IV (Schmidt-Andersen et al. (Submitted, 2024)[4]) and V (Schmidt- Andersen et al. (Under review, 2024)[5])

	Paper I[1] NON-RCT			Paper IV[4] Feasibility		Paper V[5] Qualitative	
	RESPECT			INTERACT			
	INT (n = 75)	CON (n = 33)	Com.Con (n = 94)	INT (n = 44)	CONT (n = 40)	Participants (n = 12)	Parents (n = 12)
Sex (males)	45/30 (61%/39%)	19/14 (58%/42%)	55/39 (59%/41%)	25/19 (57/43%)	26/14 (65/35%)	9/3 males (75/25%)	4/10* (29/71%)
Age	13.4 ± 3.1	13.5 ± 2.5	12.9 ±3.0	11.6 ± 3.9 years	11.6 ± 3.4 years	11 [6–17]	
Height	1.58 ± 0.16	1.63 ±0.16	1.6 ± 0.16	147.0 ± 39.3 cm	152.6±32.4 cm	-	-
Weight	51.87 ± 16.18	53.9 ± 15.29	51.3 ± 16.2	44.6±19.1 kg	46.7±19.8 kg	-	-
BMI	20.4 ± 4.5	19.9 ± 3.3	19.4 ±3.5	17.3±3.3	18.2±4.0	-	-
Diagnosis							
- Hematological cancers	55 (73%)	23 (70%)	-	-	-	6	-
○ Acute lymphoblastic leukemia	-	-	-	14 (32%)	10 (25%)	-	-
○ Other hematological cancers	-	-	-	15 (34%)	15 (38%)	-	-
- Extracranial solid tumors	16 (21%)	9 (27%)	-	12 (27%)	10 (25%)	5	-
- CNS tumors	4 (5%)	1 (3%)	-	3 (7%)	5 (13%)	1	-

*Table 6: * two sets of parents were interviewed together*

Paper I

In the RESPECT study, of 120, a total of 75 (attrition rate 0.63) survivors in the intervention group and 33 of 50 survivors from the control group (attrition rate 0.66), respectively, completed follow-up assessment of physical capacity 1-year post-treatment. An overview of the results of Paper I is presented in Table 7 (as presented in Paper I (Fridh 2023)[1]).

Table 7: Cardiorespiratory Fitness, Muscle Strength, and Function 1-Year Post-Treatment: Comparison of the Intervention Group with the Patient Control Group (as presented in Paper I (Fridh et al. (2023)[1] licensed via CC-BY-NC)

	Unadjusted analysis estimate [95% CI]	P	Demographic-adjusted* estimate [95% CI]	P	Demographic- and diagnosis-adjusted** estimate [95% CI]	P	Comparison at age 8 years in a demographic- and diagnosis-adjusted model with age-dependent difference between groups*** estimate [95% CI]	P	Comparison at age 18 years in a demographic- and diagnosis-adjusted model with age-dependent difference between groups*** estimate [95% CI]	P
VO_2 peak (mL/kg/min)	4.7 [0.4 to 9.1]	**0.034**	4.7 [0.5 to 8.8]	**0.028**	4.3 [0.4 to 8.2]	**0.033**	9.8 [0.4 to 19.2]	**0.042**	0.6 [−6.3 to 7.5]	0.86
VO_2 (L/min) (% of level among patient controls)	14 [−11 to 47]	0.30	15 [−3 to 35]	0.09	12 [−5 to 33]	0.16	27 [−15 to 90]	0.24	3 [−23 to 39]	0.82
Watt Max (W)	9 [−20 to 37]	0.55	7 [−11 to 26]	0.43	3 [−16 to 21]	0.77	7 [−37 to 52]	0.74	1 [−32 to 33]	0.97
Sit-to-Stand (Repetitions)	6.7 [4 to 10]	**<0.001**	7 [4 to 10]	**<0.001**	7 [4 to 10]	**<0.001**	−1 [−8 to 6]	0.78	12 [7 to 17]	**<0.001**
Timed Up and Go (% of level among patient controls)	−20 [−26 to −13]	**<0.001**	−21 [−27 to −14]	**<0.001**	−21 [−28 to −14]	**<0.001**	−7 [−25 to 16]	0.50	−29 [−39 to −18]	**<0.001**
Right Handgrip Strength (% of level among patient controls)	24 [−4 to 61]	0.095	29 [12 to 49]	**0.001**	31 [12 to 53]	**0.001**	35 [−12 to 106]	0.15	29 [−3 to 70]	0.074
Left Handgrip Strength (% of level among patient controls)	25 [−1 to 59]	0.065	31 [15 to 48]	**<0.001**	32 [16 to 52]	**<0.001**	24 [−14 to 77]	0.23	38 [8 to 77]	**0.012**

Table 7: CI=confidence interval

**Adjusted for sex-dependent associations with relative age.*

***adjusted for sex-dependent associations with relative age, and diagnosis-dependent time since diagnosis.*

****estimated in a model including sex-dependent associations with relative age, diagnosis-dependent time since diagnosis, and group-dependent associations with relative age.*

VO2 (L/min), Timed Up and Go, Right Handgrip Strength and Left Handgrip Strength were log-transformed; results are therefore presented as % difference from the level in the patient control group.

The results indicate that children receiving a multicomponent psycho-social and physical activity intervention can improve long-term cardiorespiratory fitness, muscle endurance, functional capacity, and hand grip strength (only adjusted analysis) compared to usual care alone.

The intervention group presented comparable values from the Sit-to-stand test, timed-up-and-go test, and hand grip strength to age-matched community controls (mean difference between groups: Sit-to-stand = 0 rep., 95% CI = −2 to 2; TUG = -3 seconds, 95% CI = −7 to 1; and hand grip = -4 kg, 95% CI = −17 to 10) indicating a regained muscle endurance, functional capacity, and grip strength, after ended treatment.

However, children in the intervention group showed significantly lower VO2 peak levels compared to age-matched community controls (mean difference between groups: VO2 peak = −4.7 mL/kg/min, 95% CI = −7.1 to −4.7), indicating an impaired cardiorespiratory fitness compared to normative values on year after ended treatment.

In summary, Paper I indicates that the intervention group in the RESPECT study could improve physical capacity compared to usual care and restore muscle endurance and functional capacity to levels comparable to community controls. Previous studies from the RESPECT study sample have shown that baseline measures of physical capacity are significantly lower than community controls[29,31], providing a central context: that this improvement in physical capacity stems from impaired cardiorespiratory fitness, muscle strength, and physical performance within the early stages of cancer treatment. These results indicate a need for early-initiated rehabilitative strategies to mitigate these impairments. Therefore, we identified a need for synthesizing the existing evidence of physical capacity within the first month of childhood cancer treatment in a systematic review.

Paper II

From 10,109 studies screened, we identified 13 studies reporting data on 18 different outcome measures of interest. An overview of outcome measures, relative deficits, including mean differences from the eight meta-analyses (on exercise tolerance, VO_2 peak, hand grip, isometric knee and ankle strength, Six-minute walk test, Timed-up-and-Go, and Timed-up-and-down-stairs test) and certainty of evidence can be found in Table 8: modified evidence profile (as presented in Paper II, Schmidt-Andersen et al. (2022)[2]).

Table 8: Modified evidence profile (as presented in paper II, Schmidt-Andersen et al. (2022)[2] licensed via CC-BY-NC)).

Outcome	Measure	Certainty assessment						№ of patients		Relative deficit (mean difference) in children with cancer compared to healthy controls [95% CI]	Certainty
		№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Children with cancer	Healthy Reference		
Cardiorespiratory Fitness											
Exercise Tolerance	Adapted Yo-yo and CPET	3 (4 patient groups)	Not serious	Not serious	Serious[a]	Serious[b]	Large effect	78	783	–2.55 SMD [–2.82, –2.27]	⊕◯◯◯ Very low
VO_2 peak	CPET	2 (3 patient groups)	Not serious	Not serious	Serious[a]	Very serious[b]	Large effect	67	765	–19.63 ml/kg/min [–21.43, –17.83]	⊕◯◯◯ Very low
Muscle Strength											
Hand grip, R	Handdynamometer	5	Not serious	Very serious[c]	Serious[a]	Not serious	None	321	1667	–6.42 kg [–12.16, –0.69]	⊕◯◯◯ Very low
Lower body strength	Iso. Knee ext	2	Serious[d]	Serious[e]	Serious[f]	Not serious	None	132	378	–62.29 newton [–124.32 to –0.26]	⊕◯◯◯ Very low
Lower leg strength	Iso. Ankle dorsi flex	2	Serious[d]	Serious[e]	Serious[f]	Not serious	None	132	378	–17.86 newtons [–63.77 to 28.04]	⊕◯◯◯ Very low
Explosive lower limb muscle strength	Med. Ball throw	1	Serious[d]	N/A[e]	Serious[g]	Very serious[b]	Large effect	24	28	–1.85 meters [–2.85 –0.70]	⊕◯◯◯ Very low
Leg strength	STS (5 rep)	1	Serious[d]	N/A[e]	Serious[g]	Serious[b]	None	32	28	1.49 sec. (slower) [0.68 to 2.29]	⊕◯◯◯ Very low
Physical Performance											
Walking distance	6MWT	4	Very serious[h]	Serious[i]	Serious[a]	Not serious	Large effect	168	1971	–226.71 [–255.26, –198.16]	⊕◯◯◯ Very low
Functional capacity	TUG	3 (4 patient groups)	Serious[d]	Very serious[c]	Serious[a]	Not serious	None	133	198	0.92 seconds (slower) [0.47, 1.36]	⊕◯◯◯ Very low
Functional capacity 2	TUDS	2	Serious[j]	Serious[a]	Serious[a]	Serious[b]	None	43	774	2.19 [1.49, 2.90]	⊕◯◯◯ Very low
Functional mobility	FMA	1	Serious[d]	Serious[e]	Serious[g]	Very serious[b]	None	49	503	–30.34 [–36.15 –24.53]	⊕◯◯◯ Very low
Muscle endurance	STS (30 sec)	1	Not serious	N/A[e]	Not serious	Serious[k]	None	90	62	–7.5 repetitions [–9.48 to –5.52]	⊕◯◯◯ Very low
Static balance	Static stand	1	Serious[d]	N/A[e]	Serious[g]	Serious[b]	None	32	33	3.6 ground contacts [–2.16 to 8.44]	⊕◯◯◯ Very low
Balance (sway)	Ultrasound-based motion analysis	1	Very serious[l]	N/A[e]	Serious[g]	Very serious[b]	None	12	11	N/A*	⊕◯◯◯ Very low
Motor skill development	BOT2-SF	1	Not serious	N/A[e]	Serious[g]	Not serious	None	109	N/A**	(23.2 ± 2.5 vs. 50.0 ± 3.4, P<0.001)	⊕◯◯◯ Very low
Motor skill development	Bayley and Movement ABC	1	Serious[d]	N/A[e]	Serious[g]	Not serious	None	51	51	N/A*	⊕◯◯◯ Very low
Motor skill development	Movement ABC	1	Not serious	N/A[e]	Serious[g]	Serious[b]	None	14	17	N/A*	⊕◯◯◯ Very low
Adverse events	-	5	Serious[d]	Not serious	Not serious	Not serious	Very large effect	327/0	1717/0	RR = 1 [1,1]	⊕⊕⊕◯ Moderate

*Table 8: *Not applicable (data presented in SDs). **Not applicable (age-specific percentile ranks were used for comparison). A. Different cancer diagnosis between studies. B. Low power. C. I^2 = 75¬–100% (considerable). D. Some concerns regarding selection, comparability, and assessment of outcome. E. NA–single study. F. Only ALL G. Single study-not all cancer diagnoses. H. Some concerns regarding selection (representativeness and description of non-responders), comparability, and assessment of outcome. I. I^2 = 50–90% (substantial). J. Some concerns regarding selection (description of non-responders), comparability, and assessment of outcome. K. Outcome is a surrogate measure of physical performance and not directly transferable. L. Some concerns regarding selection (representativeness, description of non-responders, and ascertainment of exposure), comparability, and assessment of outcome. Abbreviations: CPET = cardiopulmonary exercise test, Iso.= isometric, Med. = Medicine, STS = Sit-to-stand test, 6MWT = Six-minute-walk test, TUG = Timed-up-and-go test, TUDS = Timed-up-and-down-stairs test, FMA, c BOT2-SF = The Bruininks-Oseretsky Test of Motor Development*

For all outcomes relating to physical capacity, the certainty of the evidence was rated very low. For adverse events, we found moderate certainty of evidence.

Cardiorespiratory fitness: Within the first month of cancer treatment, children with cancer showed significantly lower exercise tolerance (three studies;[29,74,92] standard mean diff.: –2.55 [95% CI, –2.82 to –2.27] and VO_2 peak (two studies;[29,75] mean diff.: –19.63 ml/min/kg [95% CI, –21.43 to –17.83] compared to normative values.

Muscle strength: Within the first month of cancer treatment, children with cancer showed significantly lower muscle strength, in terms of hand grip strength (five studies;[47,79,162–164] mean diff.: –6.42 kg [95% CI, –12.16 to –0.69]) isometric knee strength (two studies;[47,165] mean diff.: –62.29 Newton [95%CI: –124.32 to –0.26], and measures of explosive lower limb strength, using medicine ball throw (one study,[162] mean diff.: = –1.85 meters [95% CI: –2.85 to –0.70] and five-repetition-sit-to-stand-test (one study,[162] mean diff.: = 1.49 seconds, [95% CI, 0.68 to 2.29]) compared to normative values. Isometric leg strength was comparable in children within the first months of cancer treatment compared to normative values (two studies;[47,165] mean diff.: –17.86 Newtons [95%CI: –63.77 to 28.04].

Physical performance:

Within the first month after cancer diagnosis, children with cancer showed significantly reduced physical performance in terms of reduced walking distance (four studies;[166–169] mean diff.: –226.71 meters [95% CI –255.26 to –198.16]), functional capacity (Timed-up-and-Go: three studies,[29,74,164] mean diff.: 0.92 seconds [95% CI, 0.47 to 1.36], and Timed-up-and -down-stairs: two studies,[74,92] mean difference: 2.19 seconds [95% CI, 1.49 to 2.90]), muscle endurance (30 sec. sit-to-stand, one study:[29] mean diff.= –7.5 repetitions [95% CI, –9.48 to –5.52]), and functional mobility (one study[170] mean diff.: –30.34 Functional Mobility Assessment Scale scores [95% CI, –36.15 to –24.53]) compared to normative values.

Three studies[47,51,171] used three different and non-comparable outcome measures of motor skill level; nevertheless, all three—coherently—showed reduced motor performance in children within the first months of cancer treatment compared to normative values.

Finally, the systematic review identified two studies reporting different measures of balance. One study[172] reported that children within the first month of cancer have impaired balance, whereas the other[162] reported similar levels compared to normative values.

In summary, concerns of indirectness, imprecision, and inconsistency affect the certainty of evidence; however, the direction of impairments across nearly all included outcomes increases the confidence of the synthesized evidence; underlining an important context: that children with cancer have reduced cardiorespiratory fitness, muscle strength, and physical performance within the first month of cancer treatment. To counteract these early-identified impairments of physical capacity, the INTEARCT trial was initiated to investigate the effectiveness of a mono-modal exercise intervention (Paper III[3]). To secure transparent reporting for future reviews when planning future trials and evaluating the preliminary findings of The INTERACT trial in a subsample, we identified a need to conduct a feasibility study concerning the viability of the early-initiated mono-modal exercise intervention and physical assessment during the first six months of childhood cancer treatment.

Paper IV

Between January 2020 and December 2023, 125 children with cancer were admitted, and 110 (88% Availability) met inclusion criteria. Of these, 84 (76% Acceptance) accepted participation. Reasons for refusal included difficulty comprehending information and insufficient time for decision-making. A flowchart of the screening and inclusion process, intervention period, and assessments can be found in Figure 4 (modified from Paper IV, Schmidt-Andersen et al. (2024)[4]).

Figure 4: Flowchart and overview of feasibility outcomes (modified from Paper IV, Schmidt-Andersen et al. (submitted 2024)[4]).

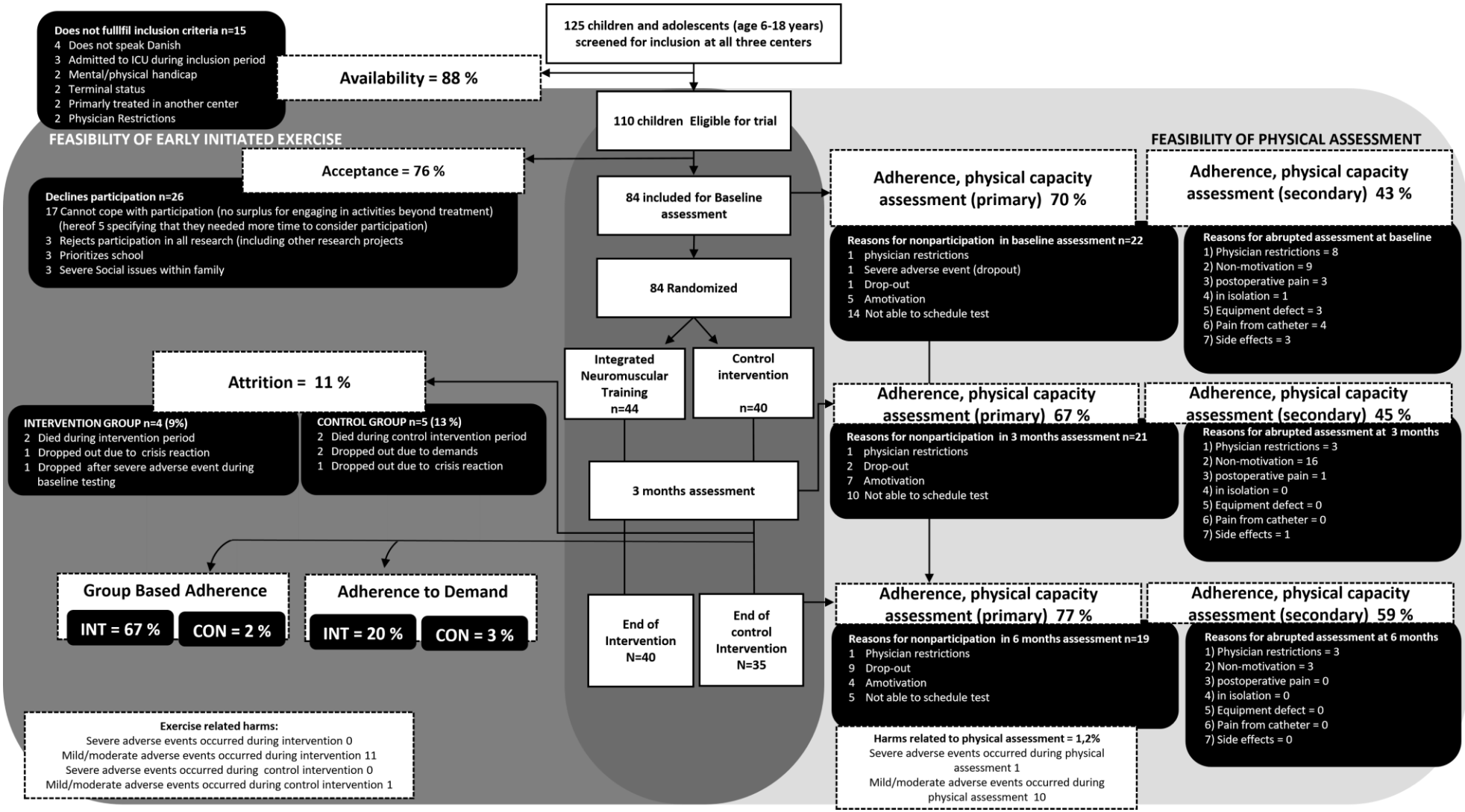


Figure 4: ICU=Intensive Care Unit

At the end of the intervention period, the attrition rate was 9% in the exercise group (n = 4) and 13% in the control group (n = 5), totaling 11% attrition.

Adherence—Intervention Group

Forty children engaged in 1,422 exercise sessions (hereof 685 supervised and 737 unsupervised home-based sessions). Twenty percent of the children in the intervention group adhered to the a priori anticipated minimum criteria for acceptable adherence to 24 supervised sessions. Median group-based adherence to the intervention was 67% (IQR: 42–96), and the participants' primary reason for non-compliance was undergoing treatment-related procedures (31%), severe side effects (21%), or lack of motivation (19%).

Adherence rates to supervised exercise varied between diagnosis, with high adherence rate in Children with leukemia (median adherence = 73%; IQR: 63–96%) and solid tumors (71%; IQR: 50–100%), and slightly lower in children with hematologic cancers (57%; IQR: 39–67%). One participant diagnosed with a tumor located inside the central nervous system adhered to a median of 29% of supervised intervention.

Adherence—Control Group

Thirty-five children completed the control intervention, with only 3% adhering to the a priory anticipated minimum criteria for acceptable adherence. Median control group adherence was 2% (IQR: 0–40), and the primary reason for non-compliance was reported as lack of motivation (95%).

Feasibility of Physical Assessment

A complete overview of adherence to all reported physical assessments is described in Table 9 (as presented in Paper IV, Schmidt-Andersen (2024)[4]).

Table 9: Results: feasibility of physical assessment (as presented in Paper IV, Schmidt-Andersen (Submitted, 2024)[4])

RESULTS, FEASIBILITY OF PHYSICAL ASSESSMENT					
DOMAIN	**TIMEPOINT**	**TEST PARAMETER**	**RESULTS GROUP**	**INT**	**CON**
Adherence physical testing	**BASELINE** 62 of 84 (74%) were able to participate in baseline assessment	Iso.knee extension	n = 59 (70%)	-	-
		Iso. bench	n = 44 (52%)		
		TUG	n = 59 (70%)		
		Balance	n = 55 (66%)		
		STS 30	n = 51 (61%)		
		STS60	n = 51 (61%)		
		Handgrip	n = 62 (74%)		
		6MWT	n = 49 (58%)		
		TOTAL (all test)	n = 36 **(43%)**		
		Physical Activity	n = 46 (55%)		
		DEXA	n = 47 (56%)		
		Met.syndr.	n = 58 (69%)		
		Neuropathy	n = 45 (54%)		
		Question. Child*	n = 41 (62%)		
		Questionnaire proxy	n = 54 (64%)		
	3 MONTHS 63 of 82 (78%)	Iso.knee extension	n = 55 (67%)	n = 29 (69%)	n = 26 (65%)
		Iso. bench	n = 48 (59%)	n = 26 (62%)	n = 22 (55%)
		TUG	n = 55 (67%)	n = 29 (69%)	n = 26(65%)
		Balance	n = 56 (68%)	n = 31 (74%)	n = 25 (63%)
		STS 30	n = 53 (65%)	n = 28 (67%)	n = 25 (63%)
		STS60	n = 52 (63%)	n = 28 (67%)	n = 24 (60%)
		Handgrip	n = 63 (77%)	n = 34 (81%)	n = 29 (73%)
		6MWT	n = 46 (56%)	n = 25 (60%)	n = 21 (46%)
		TOTAL (all test)	n = **37 (45%)**	n = **19 (45%)**	n = **18 (45%)**
		Physical Activity	n = 34 (41%)	n = 11 (26%)	n = 15 (38%)
	6 MONTHS 66 of 75 (85%)	Iso.knee extension	n = 58 (77%)	n = 32 (80%)	n = 26 (74%)
		Iso. bench	n = 55 (73%)	n = 31 (78%)	n = 24 (69%)
		TUG	n = 62 (83%)	n = 38 (95%)	n = 24 (69%)
		Balance	n = 63 (84%)	n = 37 (93%)	n = 26 (74%)
		STS 30	n = 61 (81%)	n = 36 (90%)	n = 25 (71%)
		STS60	n = 61 (81%)	n = 36 (90%)	n = 25 (71%)
		Handgrip	n = 66 (85%)	n = 38 (95%)	n = 27(77%)
		6MWT	n = 56 (75%)	n = 33 (83%)	n = 23 (66%)
		TOTAL (all test)	n = **44 (59%)**	n = **24 (60%)**	n = **20 (57%)**
		Physical Activity	n = 34 (45%)	n = 17 (43%)	n = 17 (48%)
		DEXA	n = 56 (75%)	n = 30 (75%)	n = 26 (74%)
		Met.syndr.	n = 65 (87%)	n = 32 (80%)	n = 33 (94%)
		Neuropathy	n = 51 (68%)	n = 25 (63%)	n = 26 (74%)
		Question. Child*	n = 48 (69%)	n = 24 (69%)	n = 24 (69%)
		Questionnaire proxy	n = 53 (71%)	n = 29 (73%)	n = 24 (69%)
Safety of physical assessment					
- Severe adverse events (primary)	**1 (1%)**				
- Rate of severe adverse event	**0.005 severe adverse event/ test session.**				
- Minor adverse events	**10 (8.4%)** 2 transient pain from patella during iso.leg ext. 6 transient pain from shoulder during bench pres 2 transient nausea (no fainting) during balance testing				

Table 9: Overview of feasibility results regarding feasibility of physical assessment
INT = Exercise intervention group, CON = Active control group
Due to dropouts, 82 participants were eligible for 3-month assessments (42 INT, 40 Con), and 75 participants at 6 months (40 INT, 35 CON)
**for questionnaires: children were eligible for children aged 8–18 years (for baseline assessment, 67 children were eligible, and 70 were eligible for 6-month assessment (35 in intervention, 35 in control group)*

At baseline assessment, 74% of the eligible participants were able to participate in physical assessment. Seventy percent of the eligible participants were able to complete the primary outcome,

the isometric knee extension test and 43% were able to complete the entire test battery of physical capacity.

In a sub-analysis (Figure 5, as presented in Paper IV, supplementary file 2 (Schmidt-Andersen et al. (2024)[4]) we found that children who completed the entire physical capacity test battery were included within a median of 3 days (IQR: 1.0–6.0) after treatment initiation. Children who did not complete the entire test battery were included within a median of 5.5 days from treatment initiation (IQR: 2.25–8.75). A Mann-Whitney U test showed a significant difference in days from treatment initiation till inclusion between the two groups (Z = 609, p = 0.0443).

Figure 5: Boxplot of completed versus incomplete test at baseline, as presented in Paper IV (Schmidt-Andersen et al. (submitted, 2024)[4])

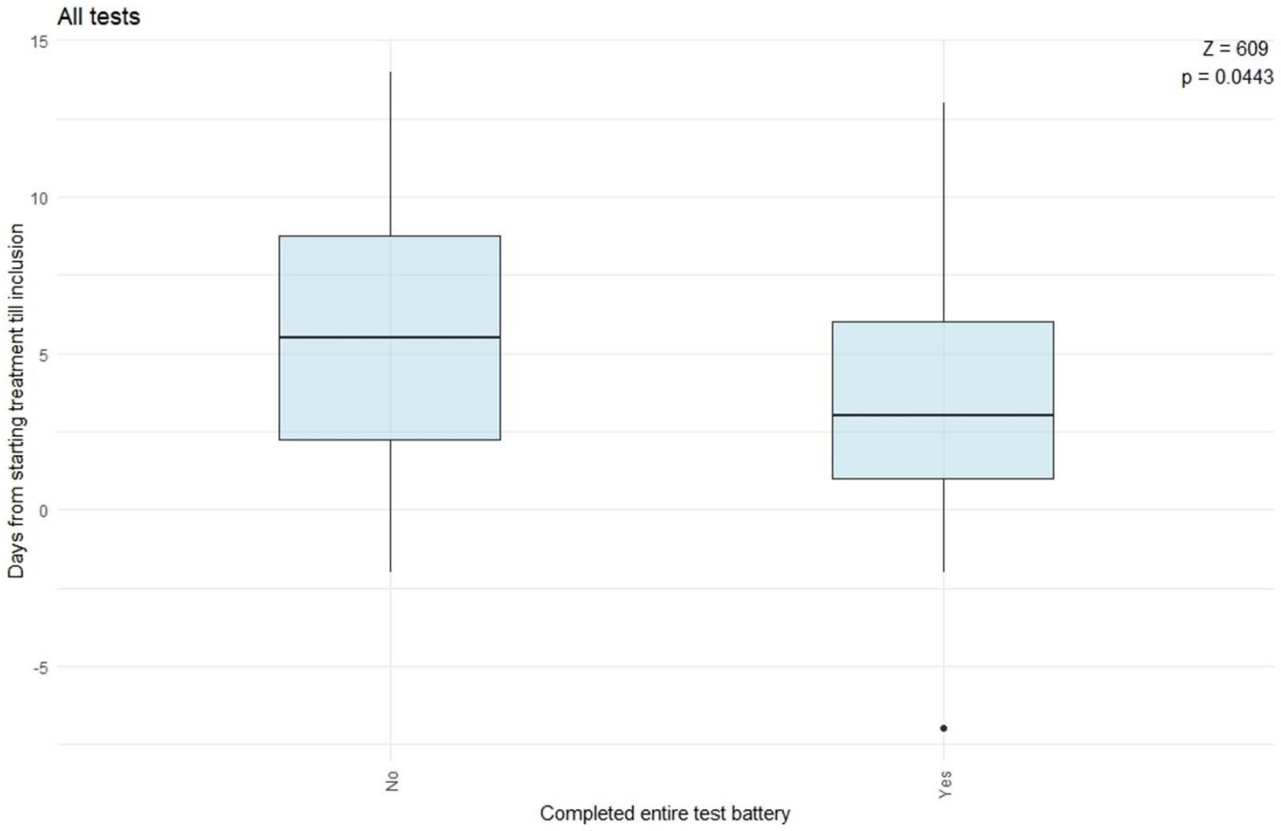


Figure 5: The influence of time since inclusions (from treatment initiation) on completion rates of the entire physical capacity assessment battery at baseline.

At the three-month assessment, 78% of eligible participants were able to participate in physical assessment. Sixty-seven percent were able to complete the isometric knee extension test, and 45% were able to complete the entire test battery of physical capacity.

At the six-month assessment, 85% of eligible participants could participate in physical assessment. Seventy-seven percent were able to complete the isometric knee extension test, and 59% were able to complete the entire test battery of physical capacity.

One severe adverse event (bone fracture) occurred during 192 test sessions (rate = 0.005/session).

Ten minor adverse events (two transient pain from the patella, six transient cases of pain from the shoulder, and two transient cases of nausea (no fainting)) were reported during physical assessment.

No severe adverse events occurred in 1,410 supervised or home-based exercise sessions. Seven minor (three acute nausea, two temporary distress /crying, two pain from stomach), two moderate adverse events during supervised sessions (two occasions of transient but prominent delayed muscle soreness), and two moderate adverse events occurred during home-based sessions or leisure time activities (two sprained limbs during home-based exercise with complete recovery) in the intervention group. One moderate adverse event occurred in the control group (sprained ankle during leisure time activity with complete recovery).

From Paper IV, we identified that barriers persist for conducting exercise during cancer treatment: children during treatments must adhere to treatment-related procedures, have severe side effects or state that they lack motivation[4]. As specified in the background section, motivation is a driver [10,119] for adhering to exercise interventions, and, therefore, we deemed it necessary to explore the perceived barriers to motivation for exercise during cancer treatment, evaluating the potential effectiveness of the programmed intervention of the INTERACT trial.

Paper V

Twenty-four interviews, 12 from children in the intervention group and 12 from their parents, comprised the data for the qualitative study (Paper V). An overview of participants can be found in Table 6: Participant characteristics in Papers I, IV, and V.

An overview of the reported themes (including the inductive analysis) can be found in Figure 6 (modified from Paper V, Schmidt-Andersen et al. (2024)[5]).

Figure 6: Visual illustration of the deductive analysis, including identified themes and subthemes (modified from Paper V, Schmidt-Andersen et al. (under review, 2024)[5])

SDT Domains	Quote, excerpts	Condensed Meaning Unit
Autonomy	"Oh, yes. Well, I could definitely [do exercises on my own initiative]. It's not so much that I play basketball because sometimes I find it a bit annoying with the CVK I have."	I can do PA on my own
	" So, we've said, 'come on over and play football.' He usually wants to, and the four times he said no, he came cycling over right after we started anyway. And sometimes he say that he needs to stop a bit earlier that usual. But still, he can come over and give it a try."	Initiative
	"I actually think it's been good to train while I've been hospitalized. I mean, it's been nice to be able to think about something else for a while."	PA helps me focus on other things than being sick
	"He (the exercise professional) was very good at introducing himself, saying, 'This is what I do, this is what we're working towards.' Then he gave me some time. He wasn't like, 'You have to join in! We need to hurry! We don't have time for this.' He was very good at just taking it easy and calmly."	Time and trust make me feel in control/secure
	"If he didn't have the energy or the desire one day, it's possible that we tried to push a little, but if he said, 'I don't want to,' we have also respected that, and we haven't forced him to do it."	Saying NO!
	"When he's really low in numbers, it doesn't make any sense at all (to train), because he's been lacking both blood and all sorts of other things, so he doesn't have the energy for it. And then it's just fine that a couple of days pass before he can take up exercise again."	I CAN'T
	"I feel that this trail has helped us keeping him active. And even though we may not have been able to do much with him because he has been really tired, we have at least reminded each other that (boy) needs to out. That has often meant taking a walk or going up and down the stairs. We have used it to keep him on track and ourselves a bit disciplined in making sure it gets done."	Mediating role of Parents
Relatedness	The reason I've stepped back (leaving the room when exercise was occurring) is that I have a sense that he follows (exercise professional's) instructions more when I'm not around. There's something about me observing. (The exercise professional) might be able to get him to do certain things more easily when I'm not there.	PA as Social activities
	"Sometimes as an adult, you can have an idea that, 'I have to attend (training) three times a week,' these are the kind of frameworks one sets for oneself. It's difficult for him to comprehend. He's still at the stage where it's all play for him. When he goes out to play basketball, he's not training; he's out there playing. And he's skilled with a ball."	I don't do exercise - I do fun and games
	"I also think that (exercise professional) is good at assessing (when enough is enough) [...] And it's nice that he knows her so well that she doesn't need to use many words to say, 'I can't handle it anymore' or 'I can't do it now.' Because that can also be difficult."	PT-patient relationship
Competence	"I can actually participate in a lot more. Today we're even going up to the 13th floor [stairs]. I've come a long way. I've improved a lot and their it much more I can do"	Benefits of exercise
	"Because of cancer, I can no longer participate in, football and karate (...). My muscles shrink completely, so I am very weak, which makes it difficult to exercise"	Negative effects of treatment
	"It's easier to get back into the training rhythm, and there's not as long of a way to go to be physically strong as if you hadn't done anything, you know."	Appropriate challenge
	"Well, we tried when the weather was a little better. We borrowed one of those heavy balls (medicine balls) and brought it home, where we tried to fill some bottles with water and went out in the garden and did some bowling and that sort of thing. […] So it was, ok, but, I think he thinks it's a bit boring when it's just been mum or dad saying: "now we're going to do this!" He does more what (the exercise professional) says."	Guidance
	"Yes, I don't think training should be easy. I mean, we do a lot of the exercises I used to do when I played basketball, and I've gotten better at them, and maybe I have a bit more control over the technique."	Appropriate challenge
Extrinsic Motivation	"Well, yes, I've done what he (the exercise professional) has said. He said I should do my best to stay active, do it 2-3 times a week, so I've definitely done that, including squats and such. I don't think I would have come up with it myself or wanted to do it. So, I've done it because I thought it's good and because (the exercise professional) recommended it."	I do some of the "prescribed" exercises
	"[...] and then he's said, 'Why are you forcing me to do it?' And we've tried to explain, 'Well, we actually do it because you need to get stronger.' 'I know it's tough when you have no strength.' 'But you'll have even less strength if you don't do it.' And then he could actually see the point in it.	Paternalism - facilitator
	Mother: "You do know it's healthy for you, right?" Child: "No, it's really unhealthy for me. I really enjoy relaxing."	Paternalism – barrier

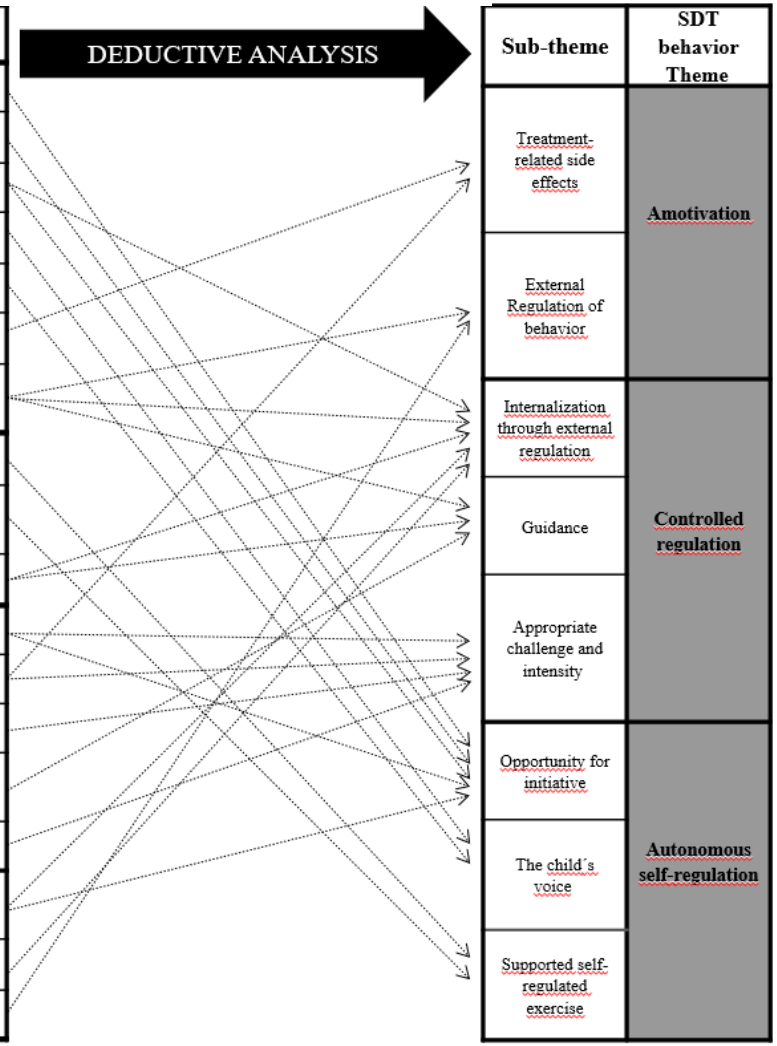


Figure 6: When subthemes had been defined within the four SDT domains: autonomy, relatedness, competence, and extrinsic motivation, these subthemes were fitted into the three SDT behavioral model domains: amotivation, controlled regulation, and autonomous self-regulation.

Theme 1—Amotivation

Amotivation in children undergoing cancer treatment is prompted by illness and treatment-related side effects, particularly fatigue. The repetitive strenuous aspects of treatment deprive participants of energy and motivation, leading to a decline in exercise. External regulation, enforced by parents or exercise professionals, may temporarily compel children to exercise, but it often results in a perceived lack of value and contributes to amotivation. Fluctuating periods of illness and activity further frustrate both parents and participants.

Theme 2—Controlled Regulation

Controlled regulation serves as a necessary tool to initiate physical activity and exercise. External regulation through guidance from familiar exercise professionals, supports children in establishing routines, particularly during hospitalization, and are crucial for facilitating internalized motivation. Parents acknowledge the need for guidance from exercise professionals, whose external influence fosters motivation and facilitates physical activity. Adjusting exercise intensity to accommodate side effects and motivation variations is crucial for maintaining engagement. A positive relationship with exercise professionals encourages children to push their boundaries and promotes sustained motivation.

Theme 3—Autonomous Self-Regulation

An autonomy-supported approach is essential in a controlled hospital environment to foster initiative and motivation. Children benefit from having a say in their exercise sessions, co-creating activities, and even leading sessions. The child's voice—the ability to say "No" when feeling unwell—is similarly crucial for sustaining exercise throughout the intervention. Learning to regulate exercise based on current needs enhances self-reliance and motivates children to remain active. Supported self-regulated exercise, whether with peers or family members, is a facilitator, emphasizing social connections and providing a reference for physical competencies.

Discussion

This thesis describes two practical approaches to childhood exercise interventions: a multicomponent intervention (RESPECT study) and a monomodal intervention (the INTERACT trial). The key findings and chosen methods will be discussed in the following sections.

Discussion of results

Early initiation of exercise interventions (Papers I, II, and IV)

Physical capacity is reduced within the first months of cancer treatment[2] it will further decline during the cancer treatment trajectory,[29,37,38,45,69,173] and it persists after treatment in the current rehabilitative setting.[1,84] From a reverse-chronological trajectory perspective, Paper I showed that the multicomponent intervention from the RESPECT study could improve long-term cardiorespiratory fitness compared to usual care, one year after ended treatment and cessation of the intervention.[1] However, cardiorespiratory fitness levels were still 11% lower than matched community controls (mean VO_2 peak: 37.0 ± 6.0 versus 41.5 ± 6.6 mL/kg/min).[1] Combined with the results of Paper II, we can indicate that these improvements are of relevant clinical value, as children present precursory lower levels of cardiorespiratory fitness within the first months of cancer treatment (40% decline in VO_2 peak) alongside similar impaired levels of muscular strength and physical performance compared to normative values.[2]

Previous results from the RESPECT study,[29] in accordance with results from similar cohorts,[37,38,45,69,173] indicate that cardiorespiratory fitness and muscular strength (hand grip strength) further decline in children receiving usual care during the following three and six months after treatment initiation. Nevertheless, these physical impairments can be mitigated through exercise.[29,58,69,70,74,75,83,88,92] As the treatment-related muscle complications, loss of axons, and denervation of muscle fibers have an early onset;[19,34,35] we hypothesized that an early initiated timing of an exercise intervention (within 14 days of treatment initiation) should be prioritized to counteract the impairments as they occur, yet before they are further progressed (Paper III).[3] Hence, we investigated the feasibility of this approach.

Early Inclusion in exercise interventions

The results from Paper IV,[4] showed an acceptance rate under the predetermined criteria for success (yet, near feasible) for participating in early-initiated exercise. The reported reasons for declining participation are in accordance with results from previous studies[174,175] and demonstrate the complexity of early initiation. Parents and children experience acute feelings of distress during the initial stages of receiving the cancer diagnosis and initiating treatment,[174,175] and they (24%) are reluctant to participate in exercise intervention studies within the first weeks of cancer. However, rates for participating in early-initiated intervention vary considerably across studies (from 51–90%[1,51,78,83,96,97]). Fifty-one percent of mothers and 40% of fathers report diagnostic criteria for acute stress disorder.[174] and present severe symptoms of anxiety and avoidance. This raises an ethical

concern about including children and their parents in studies during this period. Paper V indicates that parents did not have the emotional capacity to make qualified decisions for partaking in the INTERACT trial and, therefore, declined participation.[5] Conversely, these results further question whether parents accept participation on an informed basis. Studies have reported that having trust and confidentiality with the recruitment staff and involving children and adolescents is crucial to support decision-making for partaking in intervention studies during the early stages of cancer treatment.[176] Further, altruism—being able to help future children with cancer—has further been described as an essential motivational perspective, facilitating participation.[175,176] Two weeks from treatment initiation is a relatively short window of opportunity for the recruitment staff to gain the participant's trust and provide detailed information to facilitate shared decision-making and altruism. This underlines the importance of qualified recruitment personnel with experience in communicating with parents and children during immediate acute feelings of distress.

In perspective, acceptance rates for intervention studies with a later onset of exercise report a similar variance (68–91%),[65,71,76,94] and children still report having worries and concerns about treatment disease trajectory[68]—up until one year into planned treatment. Therefore, ethical concerns persist, including children and parents in intervention studies.

Feasibility and motivation (Papers IV and V): Measured Adherence versus" described adherence"/reason for non-adherence

Adherence to the intervention is crucial in exercise intervention trials, as the effect of the intervention is only expected to occur if the intervention group is exposed to a sizeable part of the intervention. Hence, monitoring and detailed reporting of adherence—and non-adherence—are crucial to inform future studies and practice.[177] Paper IV showed that one-fifth of the participants in the intervention could participate in 24 supervised sessions during the 24-week intervention period (group-based adherence: 67%).[4] We registered that 40% of non-adherence was due to either side effects (21%) or lack of motivation (19%), consistent with results from qualitative studies.[9,10] In Paper V, participants confirmed these reasons and elaborated that fluctuating periods of severe fatigue and nausea deprived them of energy and diminished motivation, resulting in prolonged periods without exercise.[5] Lack of energy and bad mood can be mitigated through exercise;[104,178] however, despite children reporting access to exercise equipment during treatment, they are still reluctant to participate in exercise due to the logistics of cancer.[9,10] Therefore, supportive behavioral strategies for facilitating motivation are necessary complementary components to exercise interventions.

Self-determined children with cancer: supporting autonomy instead of demanding autonomy

In previous studies, parents have described that their children's autonomy is compromised: they are socially isolated, have diminished motivation, and are therefore reluctant and unable to be physically active.[9] Paper V challenges the concept of complete autonomy and voluntariness, as children report preferring sedentary activities during periods with severe side effects unless activities are externally facilitated or have been internalized.[5] Children in our study report that they will participate in exercise if an autonomy-supported approach is utilized, using co-creation and shared decision-making.[5] Hence, self-determined motivation is a key driver,[119] and developing effective strategies to motivate children to engage in exercise may be equally important as the exercise regime itself.[10]

This is in line with current pediatric exercise guidelines stating the importance of "building a basis of trust" as crucial for engaging children in exercise.[179,180] Our results specify that trust and confidentiality with the exercise professional are key facilitators for conducting the exercise, particularly when challenging autonomy by regulating, guiding, and internalizing behavior.[5]

Also, Paper V addressed that social parameters—such as involving friends and siblings—can enhance motivation,[5] which underlines the potential of the social component of the RESPECT study. However, involving peers (i.e., classmates or siblings) should be utilized with consideration. Earlier findings from the RESPECT study report that, especially during intense days of procedures and periods with severe side effects, peer participation in physical activity, should not be completely omitted, yet be considered, relative to the emotional state of the child.[27,103]

Is it possible/feasible to increase adherence, and at what cost?

Due to logistical constraints, we anticipated that children could be offered one supervised session per week. In Paper IV, we showed that children could attend a median of 0.67 (IQR: 0.42–0.96) supervised exercise sessions per week and a median of 16 sessions during the intervention period (IQR: 10–23).[4] This rate is similar to adherence rates in the RESPECT study (median of 0.64 adherence, equaling 0.6 sessions/week)[1,29] and comparable to a strength training intervention by Gaser et al. (1.06 sessions/week). Still, a trial by Stössel et al. (from the MUCKI trial) indicated that higher attendance can be achieved if higher flexibility of supervised exercise is implemented, showing that children during cancer treatment could attend 2.7 ± 1.2 (SD) weekly exercise sessions.[83] The high adherence might be due to a resourceful intervention with supervised sessions offered at the hospital and in the patients' homes on weekdays and weekends.

One criticism of Stössel et al.'s findings is the financial feasibility and transferability of the resource-intensive intervention into a less resourceful setting. Nonetheless, their research provides valuable

insights for developing effective strategies to improve adherence to exercise interventions during acute childhood cancer treatment.

Adherence to exercise and assessment across diagnosis

The median adherence for exercise in the intervention group varied considerably between diagnoses as children diagnosed with hematologic cancers (i.e., other than leukemia) adhered to a median of 57% (n = 15, IQR: 39–67%) and one child with a tumor inside the CNS adhered to 29%. For some hematologic cancers, such as non-Hodgkin lymphoma, cancer treatment varies from two to five months, depending on stage,[181] which can explain the lower adherence. Five children in the intervention group were treated for non-Hodgkin lymphoma, which was removed from the adjusted analysis of adherence in Paper IV.[4] Children with tumors inside the CNS may differ in clinical manifestation, with neurological or cognitive symptoms that may affect participation in exercise and physical assessment. The severity and symptoms depend on the tumor's location inside the CNS.[182] Nonetheless, one study reported no difference in adherence rates in children with cerebral tumors versus children with bone or soft tissue tumors participating in a four-week non-specific physiotherapy intervention,[76] indicating that children with CNS tumors are willing to participate. However, this subgroup may be prone to attrition bias, as earlier studies from the RESPECT study report that children with CNS tumors have significantly lower adherence to physical assessment, primarily due to impairments (not being able to stand/walk).[30] This emphasizes that the importance of choosing assessment methods that reflect the study population.

Assessment of physical capacity: choosing outcome measures and assessment point

In the systematic review (Paper II), in line with other studies and reviews,[79,89,90] we showed that the current body of evidence employs various outcome measurements and surrogate markers,[2] making comparing and synthesizing evidence complex.[79,89,90] Using outcome measures with established and acceptable measurement properties increases comparability and, ultimately, the certainty of evidence.[183] In the RESPECT study, the cardiopulmonary exercise test was chosen as the primary outcome with a primary endpoint 1 year after treatment. The cardiopulmonary exercise test is considered the golden standard for measuring cardiorespiratory fitness,[129] however, likely due to the demands of performance to the point of exhaustion, less than half of all tests could be performed on baseline (30%),[30] at three months (25%), six months assessment (26%),[29] and one year after ended treatment (45%) (Paper I).[1] Isometric leg extension was chosen due to pragmatic considerations, being relevant to the participants, the targeted intervention, and comparable to other trials.[57,67,72,74,87,88,92,94] Results from Paper IV indicated a higher adherence compared to the RESPECT

study, at baseline (70%), three (67%), and six months (77%).[4] The practical considerations of choosing isometric muscle strength can be discussed, and we could have chosen an outcome with a closer resemblance to an activity, such as "medicine ball shot" (throwing distance with 1 kg medicine ball), comparable to other interventions during childhood cancer.[88,184] Nevertheless, as the treatment-induced sarcopenia is apparent,[19,34] retrieving muscle strength seems a relevant outcome for the participants.

Unexpectedly, a severe adverse event occurred during isometric leg extension, as one participant suffered a bone fracture. To our knowledge, this is a singular event, as we cannot find any similar reports in the literature[47,97,165] or from ongoing trials.[140]

Methods discussion

Early inclusion

The inclusion periods were shortened from 31 days from cancer diagnosis in the RESPECT study to 14 days from treatment initiation in the INTERACT trial. We expected that a short inclusion time and baseline assessment within 14 days of treatment initiation would reflect fewer treatment-induced impairments and less within-group heterogeneity of physical capacity. Despite the low inclusion time, we still found a significant difference in time since inclusion in children completing the assessment battery (median of 3 days, IQR: 1–6) versus children who did (median of 5.5 days, IQR: 2.25–8.75), indicating that children that had undergone a longer duration of treatment were less likely to complete the entire test battery.[4] This is in line with previous studies,[30] showing that shorter time since administration of chemotherapy correlated with higher completion rates, likely due to the early onset of treatment-related side effects.[39,185] Hence, the early inclusion may increase the completion rate of the test battery.

"Date of diagnosis" and "date of treatment initiation" are often identical—and used interchangeably in the body of evidence. However, as some discrepancies in the date of diagnosis persist, e.g., because some children with solid tumors initiate treatment before the exact type of tumor is diagnosed—we specified "date of treatment initiation" as a baseline benchmark in the INTERACT trial.[3]

Design

Based on the early results of the RESPECT study, showing between-group improvements in cardiorespiratory fitness after six months of intervention compared to usual care,[29] and motivation for participating in physical activity,[28] we found an incentive to investigate the effectiveness of a strength training intervention on physical aspects in a randomized controlled trial. We could have chosen to

continue the RESPECT study's multicomponent intervention in a similar randomized controlled design, potentially increasing the certainty of the results. However, due to ethical considerations concerning the delivery of the intervention, we anticipated that children in the control group would feel socially isolated, being "denied" the possibility of having visits from schoolmates during hospitalization. Therefore, this was not considered an option. We could have considered applying a superiority trial approach to the RESPECT study, as seen in Gaser et al., which had two supervised intervention arms, physical activity, and strength training.[88] Such a design would require at least two exercise professionals to conduct each intervention arm in each center to avoid contamination bias, and resources should be adapted accordingly.

As of January 2019, the educational modus and visits from schoolmates from the RESPECT study were continued as an implemental research project in all four treatment centers in Denmark. Hence, both the intervention and active control groups in the INTERACT trial are "exposed" to visits from schoolmates.

Due to ethical considerations, the INTERACT trial included an active control group. As parents and participants were informed of the benefits of exercise through the study information before being allocated in the trial, we found it obligatory to provide them with tools for initiating exercise: written information and a generic exercise program. Hence, the INTERACT trial was designed as a superiority trial, investigating the effect of supervised strength training (including unsupervised training) versus an active unsupervised intervention.[3] We did not include information on our hypothesis in the study information: that supervised interventions were expected to be superior to unsupervised exercise. Nevertheless, this might be obvious to parents and participants. Being aware of their allocation and the hypothesized inferiority of the active control group, participants may have altered their behavior or response, subjecting the control group to response bias. Hence, participants were not blinded to the allocation.

In the INTERACT trial, the statistician in charge of allocating the participants and conducting the final analysis was blinded. Participants were randomized after baseline assessment; hence, the assessors and participants were blinded to the allocation at baseline.

Population

The RESPECT study and INTERACT trial included a pan-cancer population to achieve a higher precision (i.e., power) within the projected study period. Being aware of the heterogeneity between diagnoses, we used an ANCOVA model (Paper I)[1] adjusted for covariance, sex, and cancer-type-

dependent- effects of time since diagnosis.[1] To further elucidate the within-group changes throughout the entire intervention of the RESPECT study, we could have used a linear mixed model, incorporating repeated measures at baseline, three and six months—as planned in the statistical analysis of the INTERACT trial (Paper III).[3] However, as "one year after ended treatment" is heterogeneous (varies from 1.4 years in children with certain types of lymphomas and up to 3.2 years in children with acute lymphoblastic leukemia), we deemed an ANCOVA model appropriate. In the INTERACT trial, the primary endpoint for isometric leg extension is six months after treatment initiation. Hence, we expect time to be less heterogeneous. However, the primary endpoint for metabolic syndrome (secondary primary outcome) is one year after ended treatment. To avoid heterogeneity, "baseline measures" of metabolic syndrome are preset, as being at ended treatment.

Choosing a monomodal intervention: strength training

Since the INTERACT trial was initiated, the results of a randomized controlled trial with parallels to the INTERACT trial have been published. A trial by Gaser et al. investigated the effects of a monomodal approach to supervised in-hospital strength training during the acute stages of cancer treatment.[88] The study included 41 children with hematologic disease (intervention length ranging from 3–10 months). On a composite score[184] of physical capacity and motor performance,[184] the study found indications that strength training was superior to a standard care exercise program (of sportive games, endurance- and coordination exercises): a sub-measure of leg strength showed significant between-group changes (medicine ball shot (% difference in reference values): –20.3 ± 8(SD), 90% CI: –29 to –12; vs. –34.5 ± 12.8, 90%CI: –41 to –28, p = 0.012) favoring strength training. However, no significant changes were found in the summarized score[184] of physical capacity and motor performance (including muscle endurance and hand grip strength).

The results of Gaser et al. are subjected to imprecision due to low power, indicate that a more comprehensible investigation of a supervised strength training intervention is needed.

Supervised versus unsupervised exercise

As described in Paper V, repeated supervised sessions are crucial[5] for guiding proper intensity and appropriate challenge of INT, facilitating motivation for exercise during hospitalization, and aiding and facilitating unsupervised home-based exercise. Supervised interventions allow close intervention monitoring; however, we included an unsupervised home-based intervention in the INTERACT trial due to the anticipated logistical constraints, limiting supervised interventions to less than one session per week. Unsupervised exercise was based on voluntariness: we encouraged the participants and their parents to be active, incorporating integrative neuromuscular training (INT) in their home

environment and leisure time activities. To monitor these activities, we further introduced the participants to written exercise logs. In accordance with other studies, we retrieved limited registrations from participants and parents in the intervention group;[186] hence, the reported adherence to unsupervised exercise in the intervention group varied considerably and was subjected to information bias. In the active control group, these registrations were almost non-existent. However, in Paper V, participants and their parents describe a "carry-over-effect" from the supervised intervention to un-supervised sessions, as participants would get inspiration for exercise from the supervised sessions, which they would bring home and conduct with siblings or schoolmates.[5] Further, parents described feeling more secure exercising with their children and being aware of their barriers and abilities.[5] Studies report that physical activity levels decline when transitioning from a supervised to an unsupervised intervention,[82,93] indicating that continuously supervised intervention is necessary.[82,93] During their acute cancer treatment, children and their parents are only at the hospital for a limited time. An unsupervised intervention is an opportunity to explore and promote a higher exercise frequency, and based on our findings, more controlled approaches, such as video consultations, as seen in other studies[88], should be considered to increase transparency.

Navigating dual roles as practitioner and researcher

Throughout the RESPECT study and INTERACT trial, I have taken the roles of both practitioner and researcher, which enables a deeper engagement in the field.[187] This involvement, however, questions the validity of the results[188] and the trustworthiness of the qualitative findings in Paper V.[187] I facilitated the intervention (as an instructor) for both the intervention and control groups of the INTERACT trial conducted physical assessments in one of the three centers, coordinated the trial between centers, and conducted interviews and the deductive analysis in Paper V.[5]

From a quantitative perspective, being unblinded to the allocation of the groups, we prioritized standardized objective assessment to limit that assessors could transfer attitudes to the intervention or control group [188]. Further, instructors did not influence standardized care; both groups were offered physiotherapy in accordance with local guidelines. Nevertheless, we cannot rule out unconscious influence on control intervention or outcome assessment.

From a qualitative perspective, being an integral part of both the trial and the deductive analysis may have compromised my objectivity to the research question and the credibility of the findings. To ensure credibility and transferability—thus trustworthiness, we took several precautions: 1) we secured that the interviewer and the participants had not met previously, 2) we used investigator triangulation throughout the analysis to discuss the analysis and findings, and secure intercoder

reliability,[189] and 3) we provided transparent, detailed (thick) descriptions and reporting of the data collection and analysis.[190]

However, applying knowledge, experience, and an understanding of the analyzed field is a necessity for conducting qualitative research.[191] In our context, having experiences communicating with children and hands-on experiences with conducting exercises with children were necessary to contextualize questions and analyze the results. Hence, remaining objective when exploring a qualitative phenomenon is a fallacy; however, remaining impartial to the outcomes and being reflexive throughout the process should be aspired.[187,191]

Generalizability

The RESPECT study and INTERACT trial presented acceptance rates just below the a-priory considered acceptable criteria for feasibility. The reported reasons for declining participation were: not being able to comprehend information and being in a current state of distress following diagnosis. Most parents report symptoms of acute stress during the first weeks of cancer treatment, regardless of their child's cancer diagnosis,[174] indicating that reasons for declining participation are consistent across the diagnosis. Also, similar exercise intervention studies report comparable or lower acceptance rates in pan-cancer populations (51–90%) without compromising the representativeness across diagnosis.[51,78,83,96,97] We, therefore, regard the intervention group in the RESPECT study and the entire study sample of the INTERACT trial as an unselected, representative group of children from 6–17.9 years.

In the RESPECT study, the control group is underpowered, and the multicomponent intervention's comparability with usual care is limited. Also, we detected between-group differences in muscle endurance and functional capacity measures, favoring the RESPECT intervention group at baseline assessment, indicating selection bias. However, these differences may result from early cancer treatment-induced impairments, as there was a substantial difference in the timing of baseline testing (12 days (median) from diagnosis in the intervention group and 27 days in the control group).[29]

The primary outcome of the RESPECT study—cardiorespiratory fitness—is prone to attrition bias. Of 120, a total of 52 (adherence rate 0.43) survivors in the intervention group and 25 of 50 survivors from the control group (adherence rate 0.50) could participate in the cardiopulmonary exercise test, which is a small improvement from baseline and six months attrition rates[29,30.] Similarly, the INTERACT trial presented attrition rates, which raises some concern of attrition bias, albeit of a substantially smaller proportion (attrition rates of 0.70, 0.67, and 0.77 at baseline, three-month, and six-month assessments, respectively).[4]

In summary, the RESPECT study's intervention group and the INTERACT trial sample are considered unselected groups. Therefore, the results concerning the feasibility of interventions, physical assessments, and exercise-related harms are considered generalizable to clinical practice. The effectiveness of the primary analysis in both studies may be subjected to attrition bias and, therefore, type one and two errors.

Limitations and bias

In the RESPECT study, the non-randomized design, geographical differences in the population, and between-center differences introduced selection biases. Therefore, socio-demographic differences between the groups, which are not accounted for, may be present. Further, high-risk cancers—considered to carry a larger potential for complications or adverse effects[6]—are treated at the University Hospital of Copenhagen. Therefore, the treatment burden is regarded as higher, as accounted for in national registries.[6] In Paper I,[1] more cases of relapse of cancers were present in the intervention group at the University Hospital of Copenhagen (n = 18, 15%) versus the control group at Aarhus and Odense University hospitals (n = 3, 6%). It is speculative and highly unlikely that the multimodal intervention would cause this difference in cancer relapse, but this between-group difference is nevertheless present due to the design.

In the INTERACT trial, randomization was stratified by age, sex, and diagnosis (Paper III).[3] We chose not to stratify according to treatment center, as further stratification might skew the allocation of participants between the intervention and active control groups. Consequently, the control group and intervention group may not be equally distributed across the centers, and therefore, the same heterogeneity, as seen in the RESPECT study, may be present. However, this will be due to coincidence, not systemically, as seen in the RESPECT study.

Strength training as Integrative neuromuscular training (INT) lacks prior use in children with cancer, which is a limitation of this thesis. However, INT was adjusted to children and adolescents diagnosed with cancer[117] and adapted to the variability of cancer treatment based on methods of periodizing exercise according to planned administrations of chemotherapy to accommodate treatment-related fatigue.[143] Further, the described intervention based on principles of INT does not provide a generalized exercise program, as seen in other exercise interventions applying INT, which may limit reproducibility.[114,192] Due to the heterogeneity of treatment protocols, we found the trajectory of childhood cancer treatment too variable to employ a strict, predefined structure. Instead, we developed a taxonomy to accommodate treatment-related variations, which, as a concept, can be transferred to future trials. As our described approach to INT is adjusted to and responsive to the

challenges of cancer treatment, we regard it as a viable method to explore the effects of strength training in a larger population.

A limitation of the feasibility study (Paper IV) is that it was done as a part of the INTERACT trial rather than as an independent pilot study conducted before the initiation of the trial. Hence, we could not qualify, remove, or alter decisions of the design or selected methods based on findings from the feasibility trial before starting the intervention. Several aspects would be considered altered based on these findings, including the chosen number of outcome measures and flexibility of the supervised and unsupervised intervention. These are described in the perspectives section. Still, we see it as a strength that we provide thorough insight into the feasibility of the INTERACT trial and publish these results before the primary trial results, which we regard as an essential marker for transparent reporting and informing future studies.

Paper V uses self-determination theory, which is a significant strength due to its applicability to various contexts, cultures, and age groups.[118,119,121] However, this high heuristic value comes at a cost, as the theory has been criticized for lacking simplicity (low parsimony) and, therefore, transferability.[118,121] This is pronounced in Paper V, as multiple factors facilitate or negatively affect motivation.[5] Other motivational theories, such as: stages of change[193] or behavioral change wheel,[194] which have been utilized in childhood cancer populations,[194] have a higher parsimony; with a restrictive focus on behavioral change. However, this is outside the scope of the INTERACT trial.
Another relevant theory to apply could be the theory of planned behavior.[195] Using self-reported questionnaires, this theory has been used in childhood cancer populations to quantify behavioral intent (within three domains: attitude, subjective norm, and perceived behavioral control) to account for participation in physical activity[196] and attendance to follow-up care.[197] This quantitative approach could be a relevant supplement to triangulate the evaluation of the INTERACT trial. However, several precautions should be taken before drawing parallel conclusions, as the theory of planned behavior and self-determination theory have not previously been integrated.

By including an unsupervised intervention, we may have introduced less transparency regarding the frequency of exercise, as feedback from the exercise log was either insufficiently reported or susceptible to social desirability bias or recall bias.[5] Hence, the data from unsupervised exercise sessions, and particular data concerning the active control intervention, are prone to information bias.

Conclusion

This thesis adds important knowledge on the magnitude of physical capacity impairments within the first months of childhood cancer treatment, the effectiveness of a multicomponent intervention to mitigate these physical impairments, and the potential of an alternate monomodal strength training intervention regarding feasibility and facilitating motivation.

A systematic review showed that physical capacity significantly declines within the first months of cancer treatment. Nevertheless, uncertainties persist, and the magnitude of impairments across diagnoses is uncertain. However, the direction of impairments across nearly all included outcomes calls for effective early-initiated exercise interventions.

An in-hospital supervised multicomponent psychosocial, educational, and physical activity intervention during cancer treatment benefits cardiorespiratory fitness and muscle strength in children one year after cancer treatment; however, impairments persist, and measures of cardiorespiratory fitness are not returned to normal values. Further, to secure transferability and investigate the effectiveness of exercise, these methods should be repeated in a randomized controlled setting using a focused monomodal approach.

Initial findings from a pragmatic early-initiated monomodal integrative neuromuscular strength training intervention, in a randomized controlled trial, emphasized the feasibility of strength training and physical capacity assessment: children during cancer treatment will participate in exercise and physical assessment, providing viable insights into muscle strength parameters during the first six months of cancer treatment. Further, supporting autonomy is a key facilitator for sustaining motivation and participation in exercise during the cancer treatment trajectory.

Collectively, pragmatic, adjustable approaches to supervised strength exercise—and unsupervised exercise—are recommended to maintain a high exercise frequency, as treatment-related side effects pose barriers for participating in exercise. Involving the child, parents, and peers and having familiar exercise professionals is fundamental for sustaining motivation during cancer treatment, even with considerable side effects.

Perspectives

We have shown that children have markedly impaired physical capacity within the first months of cancer treatment. Physical capacity will further deteriorate during the cancer treatment trajectory[37,38,45,69,173] and persist after ended treatment (Paper I).[1] This underlines an urgent need for rehabilitation initiated within the early stages of childhood cancer.

Even if effective rehabilitative exercise strategies during the acute stages of cancer treatment are implemented long-term follow-up screening for deficits in physical capacity remains necessary. In accordance with Paper I,[1] a study showed improved cardiac function (left ventricular function) after cessation of cancer treatment in children receiving in-hospital exercise, compared to usual care.[84] However, worryingly—follow-up measures of cardiac function showed comparable cardiac function to the control group one year after the ended treatment and a further decline in both groups at the subsequent two to five years of follow-up measures, indicating that the effects of exercise interventions during treatment are not maintained. [84] Further, as our results from Papers IV and V indicate: that exercise during cancer treatment is not universally effective, and some children are less motivated, i.e., less receptive, to partaking in exercise interventions during treatment, a rehabilitative need persists after cancer treatment.

One trial has investigated the effectiveness of a monomodal strength training intervention and concluded that the content of interventions (i.e., strength training) may play a subordinate role and that regular exercise sessions to sustain physical activity levels during treatment—of low to moderate intensity—based on the patient's performance and health status, should be prioritized.[88] Based on the findings from papers IV and V, this perspective should be elaborated; during periods with severe side effects and lack of motivation, suitable exercise activities with the intent of maintaining or facilitating motivation should be conducted. Appropriate challenge (i.e., optimal intensity) should be strived for in all exercise sessions and accommodate the patient's performance and health status. Given the importance of muscular strength in childhood cancer treatment, we recommend that all sessions accommodate the targeted approach, even at low intensities.

Our findings from Paper IV[4] underlined the importance of timing, duration, and sequential order of outcomes in a physical assessment battery during acute cancer treatment in children and adolescents. Considering these results, we recommend that physical assessments should be conducted either at the initiation of cancer treatment or as close as possible to the administration of chemotherapy. When physical assessment is required within the first month of diagnosis, the chosen test battery should only contain a few prioritized outcome measures, ideally lasting less than one hour.

Based on our results from Paper V, achieving complete autonomy for children during hospitalization and cancer treatment is a misconception; it cannot be achieved in a hospital setting where regulated

behavior and compliance are a necessity.[5] While externally regulated behavior involving pressure and negative reinforcement can serve as a necessary, yet temporary, tool for prompting short-term exercise compliance in sedentary children, it is crucial to recognize the limitations of such approaches. Internalizing motivation by supporting the child's autonomy, addressing concerns, and tailoring exercise plans to their current physical state is essential for fostering sustained engagement and long-term adherence.[119] In addition to published guidelines for exercise in pediatric oncology, emphasizing "voluntariness" as a guiding principle,[179] our results elaborate that regulating behavior through supporting autonomy, e.g., through shared decision-making, involving the participants in scheduling and designing each training session, can facilitate motivation during periods with high presence of side effects.

In the RESPECT study and the INTERACT trial, the interventions are restrained to the amount of exercise compatible with the human resources available in a daytime shift. Hence, both interventions were conducted by one exercise professional/physiotherapist, working within "normal" daytime hours and never on weekends. Specifically, in the INTERACT trial, one physiotherapist was employed full-time at Rigshospitalet. At Aarhus and Odense University Hospital, two physiotherapists were part-time employed (28 and 12 hours, respectively) to conduct the intervention. We believe that this cost of human resources is transferable to other settings. However, as the effectiveness of the RESPECT study can be questioned, and the effectiveness of the INTERACT trial has not been explored, it is not possible to determine the potential profitability of these rehabilitative strategies relative to their cost. In perspective, a multimodal strength and endurance training intervention initiated from cancer diagnosis, with a median intervention duration of 22 weeks (IQR: 14–28), showed a significantly lower total economic cost of hospitalization (corresponding to a 17% reduction).[84] If these results are transferable, future trials should investigate more controlled approaches, employing either supervised home-based interventions, as described by Stössel et al.,[83] or video-supported virtual exercise to increase the potential effectiveness of trials.

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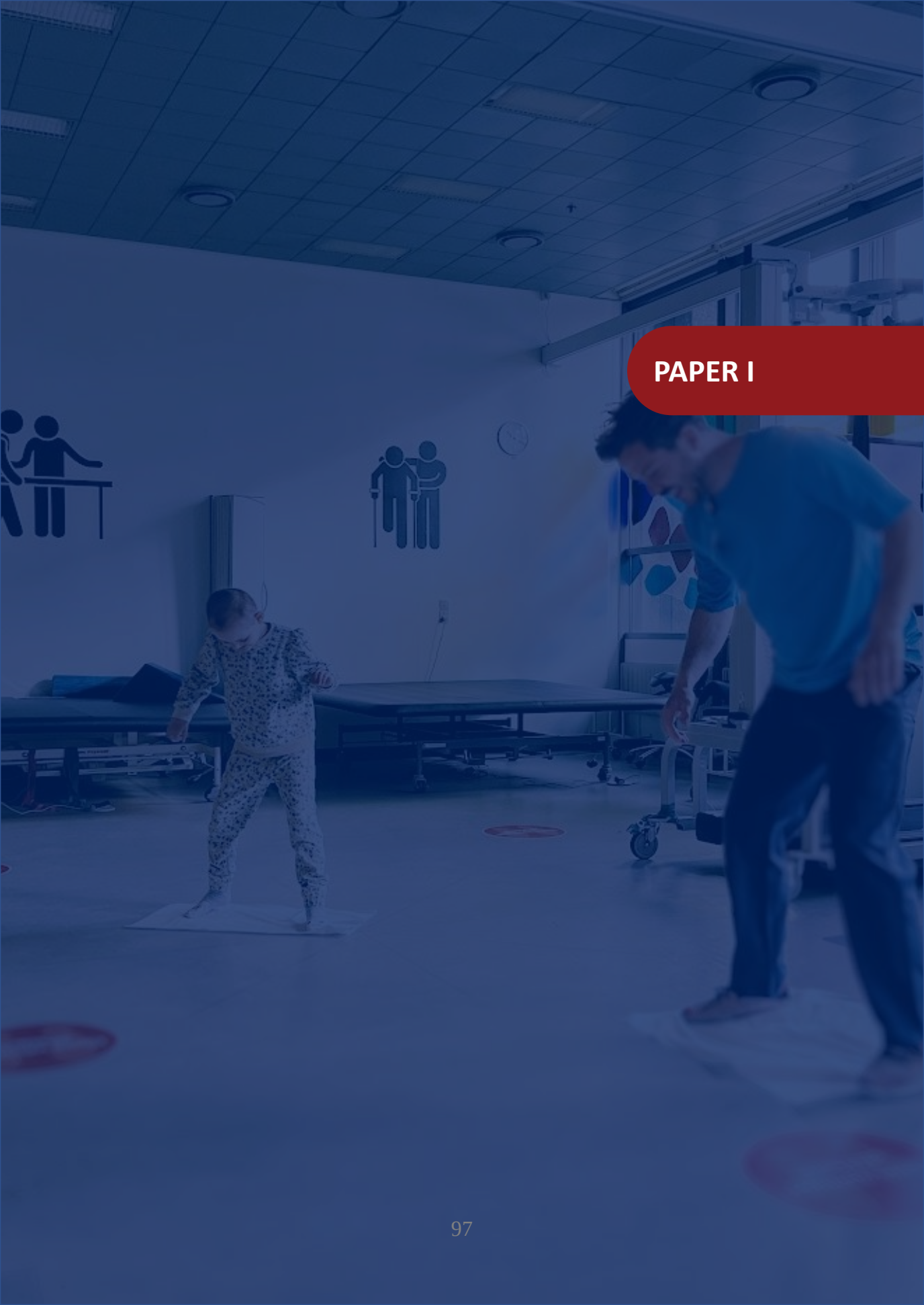
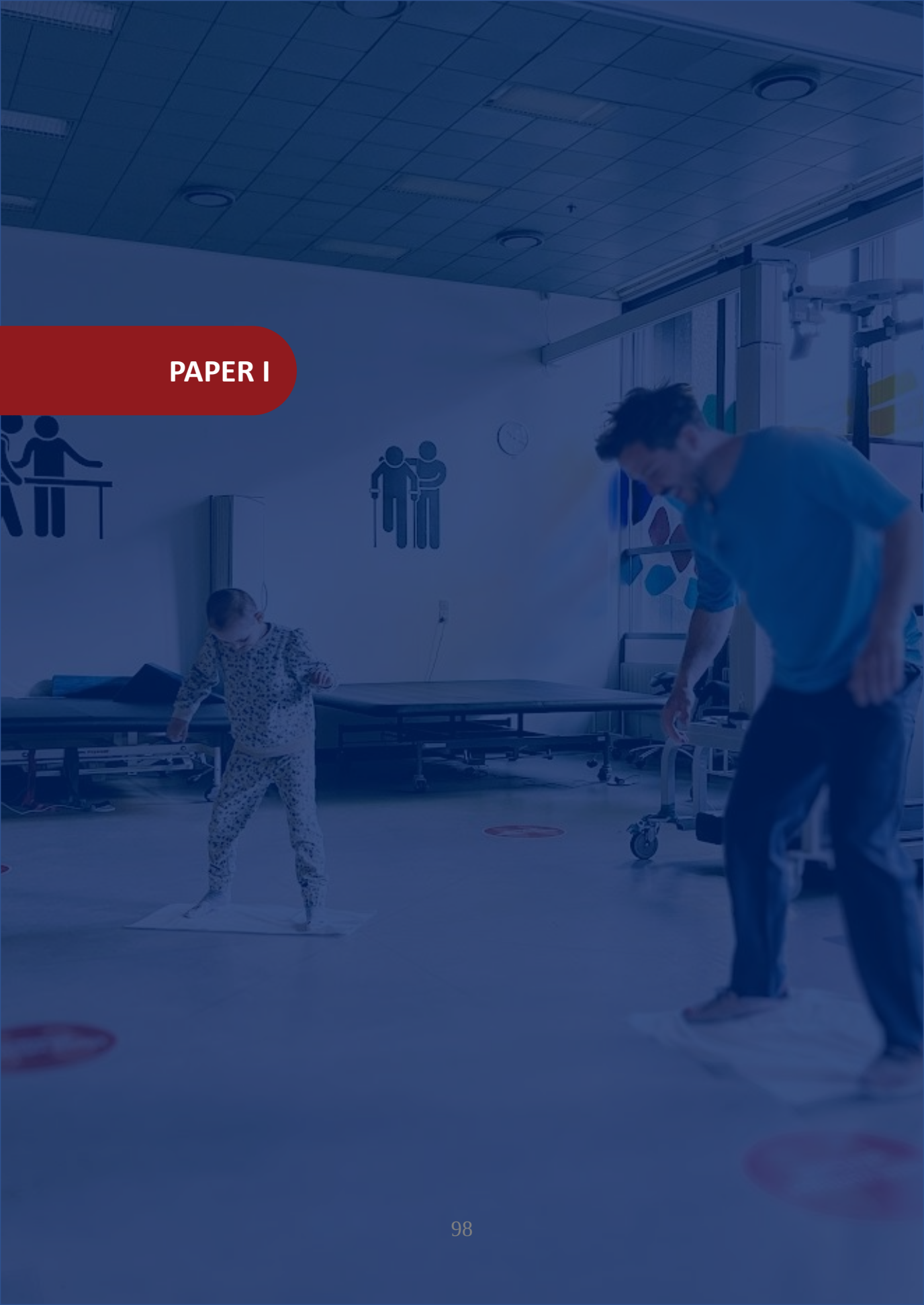
Appendencies



PAPER I



PAPER I

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Children with cancer and their cardiorespiratory fitness and physical function—the long-term effects of a physical activity program during treatment: a multicenter non-randomized controlled trial

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Abstract

Purpose We aimed to determine the effects of a classmate-supported, supervised, in-hospital physical activity program during treatment primarily on cardiorespiratory fitness and secondarily on physical function.

Methods A multicenter non-randomized controlled intervention study including children diagnosed with cancer, 6–18 years at diagnosis treated with chemo-/radiotherapy. The intervention comprised (i) an educational session on cancer in the child's school class; (ii) selection of two "ambassadors"—classmates who were co-admitted, supporting the child's everyday hospital life; and (iii) supervised in-hospital physical activity from diagnosis and throughout intensive treatment. One-year post-treatment, physical testing included cardiorespiratory fitness (primary outcome), Sit-to-Stand test, Timed-Up-and-Go, and Handgrip Strength.

Results The intervention group included 75 of 120 children (61% boys, 13.4 ± 3.1 years); the control groups included 33 of 58 children with cancer (58% boys, 13.5 ± 2.5 years), and 94 age- and sex-matched children without a cancer history. One-year post-treatment, cardiorespiratory fitness tended to be higher in the intervention group (37.0 ± 6.0 mL/kg/min) than in the patient control group with cancer (32.3 ± 9.7 mL/kg/min) (mean difference 4.7 [0.4 to 9.1], $p = 0.034$). The intervention group performed better in the secondary outcomes. Compared with community controls, both patient groups had lower cardiorespiratory fitness. The patient control group had lower Sit-to-Stand, Timed Up and Go, and Handgrip Strength, while the intervention group had strength comparable to that of the community controls.

Conclusions Peer-supported, supervised, in-hospital physical activity during treatment may improve cardiorespiratory fitness and muscle strength 1-year post-treatment in children with cancer; however, survivors continue to have lower cardiorespiratory fitness than community controls.

Implications for Cancer Survivors Children with cancer may benefit from in-hospital physical activity in improving long-term cardiorespiratory fitness and muscle strength.

Keywords Childhood cancer · Cardiorespiratory fitness · Muscle strength · Physical activity intervention · Peer support intervention

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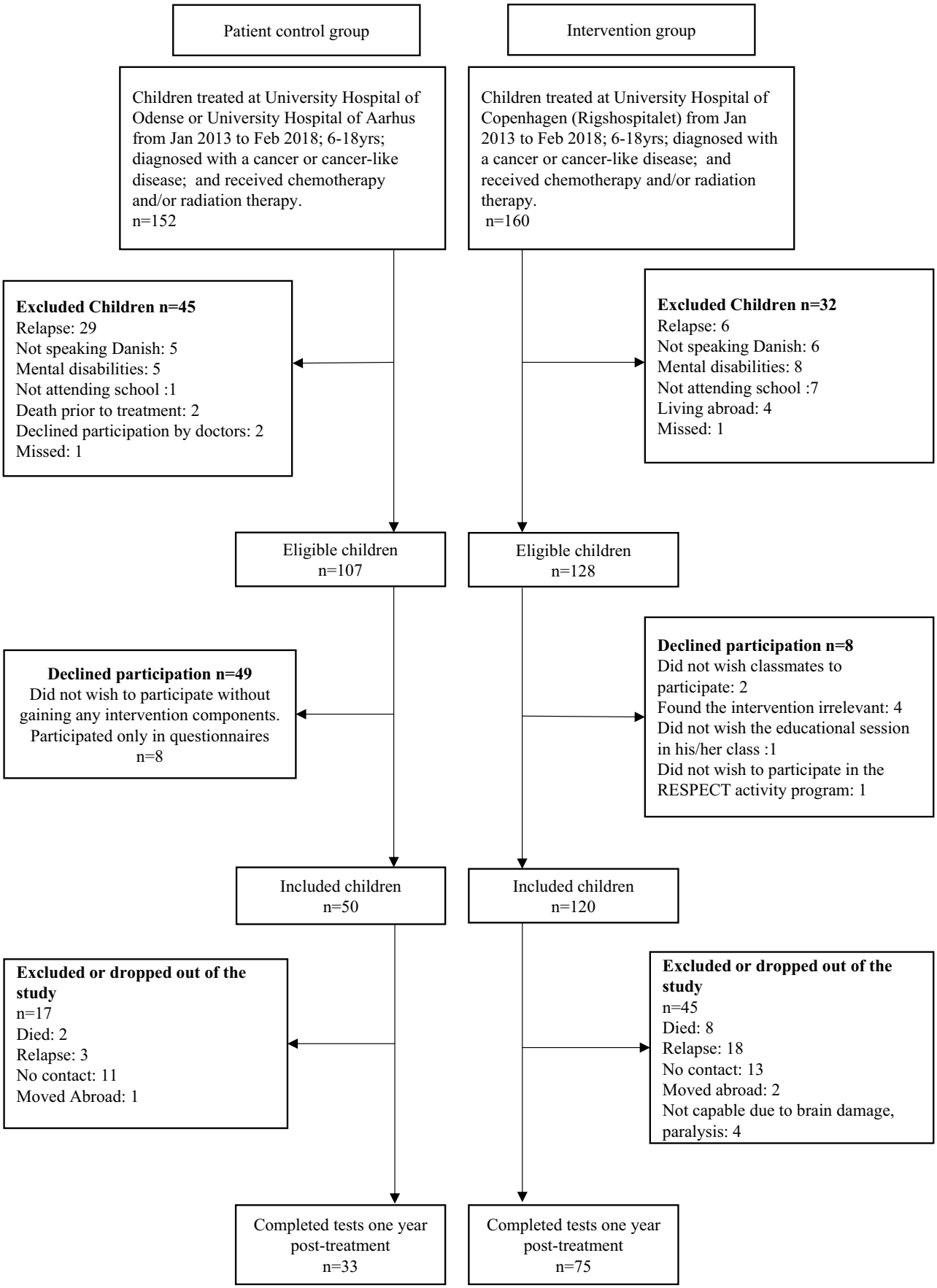
Patient control group
Intervention group
Children treated at University Hospital of Odense or University Hospital of Aarhus from Jan 2013 to Feb 2018; 6-18yrs; diagnosed with a cancer or cancer-like disease; and received chemotherapy and/or radiation therapy.
n=152
Children treated at University Hospital of Copenhagen (Rigshospitalet) from Jan 2013 to Feb 2018; 6-18yrs; diagnosed with a cancer or cancer-like disease; and received chemotherapy and/or radiation therapy.
n=160
Excluded Children n=45
Relapse: 29
Not speaking Danish: 5
Mental disabilities: 5
Not attending school :1
Death prior to treatment: 2
Declined participation by doctors: 2
Missed: 1
Excluded Children n=32
Relapse: 6
Not speaking Danish: 6
Mental disabilities: 8
Not attending school :7
Living abroad: 4
Missed: 1
Eligible children
n=107
Eligible children
n=128
Declined participation n=49
Did not wish to participate without gaining any intervention components.
Participated only in questionnaires
n=8
Declined participation n=8
Did not wish classmates to participate: 2
Found the intervention irrelevant: 4
Did not wish the educational session in his/her class :1
Did not wish to participate in the RESPECT activity program: 1
Included children
n=50
Included children
n=120
Excluded or dropped out of the study
n=17
Died: 2
Relapse: 3
No contact: 11
Moved Abroad: 1
Excluded or dropped out of the study
n=45
Died: 8
Relapse: 18
No contact: 13
Moved abroad: 2
Not capable due to brain damage, paralysis: 4
Completed tests one year post-treatment
n=33
Completed tests one year post-treatment
n=75

◂**Fig. 1** Flowchart of the enrollment process and reasons for dropouts in the RESPECT (Rehabilitation including Social and Physical Activity and Education in Children and Teenagers with Cancer) study

Abbreviations

RESPECT	Rehabilitation including Social and Physical Activity and Education in Children and Teenagers with Cancer
LCH	Langerhans cell histiocytosis
MDS	Myelodysplastic syndrome
CPET	Cardiopulmonary exercise test
CI	Confidence interval
SD	Standard deviation

Background

The improvements in childhood cancer survival rates create a need to lessen long-term treatment-related late effects to promote the best possible return to everyday life, including social, academic, and physical activities [1, 2]. Childhood survivors of cancer (CCS) experience prolonged absence from school, sports, and leisure activities during treatment, reducing their peer interaction and disrupting their development of social skills [3–5]. Impaired cardiorespiratory fitness [6–10], muscle strength [11, 12], and physical performance [11, 13] are common long-term physiological consequences of anti-cancer treatment, affecting CCS' ability to perform activities of daily living and their self-perception [14, 15] and reducing their ability to fully participate in social activities and education [16, 17]. Consequently, the CCS are vulnerable to social exclusion [3], which further diminishes their incentive to be physically active [18, 19]. Taken together, the impairments in physical and social functioning impact their health-related quality of life [20, 21]. Accordingly, there is an urgent call for interventions to address these aspects to ensure the children's optimal return to everyday life after treatment.

At diagnosis, we initiated a multimodal intervention entitled "Rehabilitation including Social and Physical Activity and Education in Children and Teenagers with Cancer" (RESPECT), which included hospital "co-admission" of healthy classmates as *ambassadors* to support the children with cancer and to promote the social network between hospital, school, and peers. This was combined with a supervised in-hospital physical activity program [22, 23]. The intervention was initiated at diagnosis to maintain both social relationships and physical functioning because ambassadors can increase the motivation of the child with cancer to engage in physical activity [24–26]. The overall aim of the RESPECT study is to facilitate children with cancer's reentry into everyday life after treatment, including adequate physical performance. We have previously shown that this intervention can maintain the children's cardiorespiratory fitness and physical function during the first six months of treatment, whereas children receiving usual care experienced a decline in cardiorespiratory fitness and physical function [27]. Therefore, the primary objective of the present study was to investigate the effects of a multimodal social and physical activity intervention on cardiorespiratory fitness, muscle strength, and physical function 1-year post-treatment when compared with both CCS controls and children not previously diagnosed with cancer.

Methods

Design and setting

This study is a multicenter, prospective, non-randomized controlled multicomponent study entitled "Rehabilitation including Social and Physical Activity and Education in Children and Teenagers with Cancer" (RESPECT) (Clinical Trial registration NCT01772849 and NCT01772862) and is part of the work of the Center for Integrated Rehabilitation (CIRE) [28].

Participants

We included participants during January 2013–February 2018. Inclusion criteria were age 6–18 years; any cancer diagnosis or myelodysplastic syndrome (MDS) or Langerhans cell histiocytosis (LCH); treatment with chemotherapy and/or radiation therapy; enrolled in school at diagnosis; and able to communicate in Danish. Exclusion criteria were mental disability (e.g., Down syndrome) and severe co-morbidity. We included children treated at the University Hospital of Copenhagen, Rigshospitalet, in the intervention group, and children treated at Odense University Hospital and Aarhus University Hospital in the patient control group. The patient control group received standard institutional, guided care. We excluded participants if they had experienced a recurrence of their primary diagnosis or were diagnosed with a secondary cancer. Further, we included age- and sex-matched children without a cancer history and/or chemotherapy/radiation as a community control group. The community control group consisted of a subgroup of ambassadors (n = 64) and a subgroup of participants without a history of cancer from the Acute Lymphoblastic Leukemia Survivor Toxicity and Rehabilitation (ALL-STAR) study (n = 30) assessed at the University Hospital of Copenhagen [29]. Figure 1 shows the enrollment process.

Intervention components

The intervention consisted of three components. (1) We conducted a 90-min educational session for the child with cancer's school class on cancer treatment and its side effects, everyday life at the hospital, supportive care, the benefits of physical activity, and the RESPECT study. (2) We selected two classmates as "*ambassadors*" in collaboration with the teachers, the classmates' parents, and the child with cancer [30]. The ambassadors were invited to be co-admitted every 14th in- and outpatient day throughout the entire treatment period. The ambassadors were co-admitted to the hospital for the day (i.e., 9 a.m. to 3 p.m.) and were present during the daily routines at the department and participated in school, social, and physical activities. The primary role of the ambassadors was to provide peer support, maintain social inclusion, and increase the motivation of the child with cancer to engage in school and physical activities. The planning of an ambassador co-admission has been presented previously [27]. (3) We conducted an in-hospital supervised physical activity intervention (the RESPECT physical activity program) carried out during admissions to the Department of Pediatric Oncology. The RESPECT physical activity program consisted of individually designed activities (duration 5–30 min) offered three times per week (Monday, Wednesday, and Friday) and group sessions (duration 30–120 min) including all eligible children with cancer and their ambassadors on Tuesdays and Thursdays, as shown in Table 1. Daily, we designed each physical activity session to accommodate the wellbeing (e.g., presence of nausea, pain, and dizziness), training category (able to walk/not in isolation, able to walk/ in isolation, and bedbound), and physical capacity of the child with cancer (Table 1). We had not predefined a targeted intensity of the physical activity program before study initiation. The aim of the physical activity sessions was to mobilize the children and accomplish as high an intensity as possible on a given day. Each session started with cardiorespiratory fitness exercises spanning simple mobilization to targeted aerobic exercises (provided the child's wellbeing permitted) followed by activities and/or games designed to improve muscle strength and balance [31]. Key equipment consisted of stationary cycle-ergometers, treadmills, dumbbells, balls, and various other items to facilitate games. We previously reported the intensity during group sessions elsewhere [6]. We measured the intensity of the individual and group physical activity program in a subgroup of CCS ($n = 50$) from September 2013 to September 2015. The mean heart rate was 145 beats/min [95% CI 142 to 149] or 69.3% [68.1 to 70.4%] of age-specific predicted maximal heart rate. The maximal heart rate was 185 beats/min [95% CI 174 to 184] or 89% [95% CI 87.7% to 90.4%] of age-specific predicted maximal heart rate [6]. Training frequency was calculated by dividing the number of days with physical activity by the number of weekdays admitted to the pediatric oncology department (excluding weekends and holidays).

Anthropometry, body composition, and medical characteristics

We weighed the participants to the nearest 0.1 kg and measured height to the nearest 0.1 cm. Body mass index (BMI) was calculated by dividing weight by height^2.

Physical outcome evaluation

The primary outcome was VO_2peak measured with the cardiopulmonary exercise test (CPET). The secondary

Table 1 The in-hospital RESPECT activity program

Training category/ weekday	Monday	Tuesday	Wednesday	Thursday	Friday	Weekend
Able to walk/not in isolation	Individual session 5–30 min Cardiorespiratory fitness Muscle strength Balance	Group session 30–120 min Cardiorespiratory fitness Muscle strength Balance	Individual session 5–30 min Cardiorespiratory fitness Muscle strength Balance	Group session 30–120 min Cardiorespiratory fitness Muscle strength Balance	Individual session 5–30 min Cardiorespiratory fitness Muscle strength Balance	No training
Able to walk/in isolation	Individual session 5–30 min Cardiorespiratory fitness Muscle strength Balance	Individual session 5–30 min Cardiorespiratory fitness Muscle strength Balance	Individual session 5–30 min Cardiorespiratory fitness Muscle strength Balance	Individual session 5–30 min Cardiorespiratory fitness Muscle strength Balance	Individual session 5–30 min Cardiorespiratory fitness Muscle strength Balance	No training
Bedbound	Individual session 5–30 min Muscle strength	Individual session 5–30 min Muscle strength	Individual session 5–30 min Muscle strength	Individual session 5–30 min Muscle strength	Individual session 5–30 min Muscle strength	No training

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outcomes were Sit-to-Stand, Timed Up and Go, and Handgrip Strength. We carried out the tests 1-year post-treatment ± 180 days. The treating physician permitted the tests providing the child's thrombocyte count was > 10 billion/L, hemoglobin count was > 5 mmol/L, and the temperature was < 38°. Exclusion criteria (for testing) included active diarrhea, cough or a cold, and side effects preventing testing. We held annual meetings with all centers to ensure comparability, and we distributed instruction videos to all members of the test teams. The tests are described in detail elsewhere [22]. All children in the age- and sex-matched control group were tested at Copenhagen University Hospital, Rigshospitalet, using the same equipment as the intervention group.

Following a modified Godfrey protocol, we performed the CPET on an electronically braked cycle ergometer (Lode Corival Pediatric or Monark Ergomedic 839 E) [22, 32]. We determined breath-by-breath ventilation and gas exchange data (INNOCOR ergo-spirometry-system, INNO00010, Innovision, DK-5260 Odense, Denmark, or Jaeger Master Screen® CPX System (MS-CPX) and JLAB Software Package™). VO_2peak was defined as the highest mean over 60 s and expressed in mL/kg/min. The maximal watt of the test was recorded. Heart rate and oxygen saturation were measured every 30 s (Polar FT2 sport tester Polar Electro, Kemple, Finland). Following consultation with experts on CPET testing in healthy children [33], we considered the CPET to be valid if one subjective criterion and two objective criteria were fulfilled. The subjective criteria were signs of intense effort. The objective criteria were heart rate > 180 beats/min and respiratory exchange ratio > 1.05 [33]. We stopped the test if oxygen saturation was under 90 or the child could not maintain the minimum required tempo (70 rpm).

Physical function tests

The children performed the Sit-to-Stand test [34] using a chair that allowed the child to flex the legs at a 90° angle. The child was instructed to fold his/her arms across the chest or to let them hang to the side, stand straight, and then touch the chair with their bottom while returning to a seated position. Strong verbal encouragement was given during the test. The test score equated the number of repetitions during a 30 second period.

The children performed the Timed Up and Go 3-m test [35] using a chair that allowed the child to flex the legs at a 90° angle. From the start position, with the back resting against the chair and arms on knees, we instructed the child to stand up, walk 3 m as fast as possible, turn around, and return to the start position. Completion time was recorded in seconds to the nearest two decimals. Strong verbal encouragement was given during the test. The last score of three tries was used in the analysis.

Handgrip Strength was measured using a Saehan hand dynamometer (Glanford Electronics, Scunthorpe, UK) and measured in kilograms. Two attempts per arm were performed either standing or sitting and without use of the elbow or the dynamometer touching anything. Strong verbal encouragement was given during the test and the highest score was used in the analysis [36].

Ethics approval and consent to participate

All participants and their parents gave written informed consent to participate in the educational sessions, to the inclusion of ambassadors, and to participation in the RESPECT activity program. The study was approved by the Regional Ethics Committee for the Capital Region (file. H 3-2012-105) and the Danish Data Protection Agency (file. 2007-58-0015/nr.30-0734) and complies with the Helsinki II Declaration.

Statistical method

The power calculation is based on the primary endpoint 1-year post-treatment being VO_2peak, and the power calculation is based on an anticipated 10% higher VO_2peak in the intervention group compared with the control group. We based the power calculation on a pilot that found a baseline VO_2peak of 24.3 (SD 5.9) [37]. The significance level 1 year after treatment end was 0.025, and the power was 0.90, resulting in 120 children in each group of children with cancer [22].

We analyzed VO_2peak (mL/kg/min), VO_2peak (L/min), max watt, Sit-to-Stand, Timed Up and Go, and Handgrip Strength using analysis of covariance (ANCOVA) models with the residual variance depending on the group (intervention group, patient control group, and community control group). VO_2peak (L/min), Sit-to-Stand, Timed Up and Go, and Handgrip Strength were log-transformed before analyses, and the back-transformed relative effects were presented as percentage difference to the reference level. To investigate whether the impact of adjusting for the differences between the three groups could result from differences in sex, age, cancer diagnosis, and time since diagnosis, the groups were compared in three different models: (1) a raw model without any adjustments, (2) a model adjusted for the sex-dependent effects of relative age differences (10% increase in age), and (3) a model further adjusted for cancer-type-dependent effects of time since diagnosis. We categorized the types of cancers in three groups: (1) hematological cancers receiving maintenance therapy (i.e., acute lymphoblastic leukemia (ALL), acute promyelocytic leukemia, t-cell non-Hodgkin's lymphoma); (2) other hematological cancers (i.e., Hodgkin's lymphoma, Burkitt non-Hodgkin lymphoma, acute myeloblastic leukemia, myelodysplastic syndrome, Langerhans

cell histiocytosis and children with acute lymphoblastic leukemia who were treated with hematopoietic stem cell transplantation); and (3) other oncological diseases (extracranial solid tumors and tumors located in the central nervous system).

We categorized the types of cancers in these three groups based on two previous observations. Firstly, we previously showed that children with acute lymphoblastic leukemia responded differently to physical activity than other oncological diseases (extracranial solid tumors and tumors located in the central nervous system) but not between children with extracranial solid tumors and children with tumors located in the central nervous system [38]. Secondly, we decided to account for the time since the diagnosis, as length of treatment could affect the results. In addition, we evaluated whether the difference between the three groups (intervention group, patient control group, and community control group) depended on sex or age by adding two-factor interactions as well as three-factor interactions between group, sex, and relative age difference to Model 3. The three-factor interaction was insignificant for all outcomes (all $p > 0.18$), and the two-factor interaction between group and sex was insignificant for all outcomes (all $p > 0.20$). However, for some outcomes, the differences between the groups appeared to depend on age. Therefore, estimated group differences for age 8 years and age 18 years are presented for all outcomes. We performed all analyses in R (version 3.6.0) and R-studio.

Results

Participant characteristics

We included 120 of 128 (94%) eligible children in the intervention group and 58 of 107 (54%) eligible children in the control group. In the intervention group, two children did not wish classmates to participate, four children found the intervention irrelevant, one child did not wish the educational session in his/her class, and one child did not wish to participate in the RESPECTS activity program. In the patient control group, the children declined participation because they did not gain any intervention components. One-year post-treatment, 45 children had been excluded or had dropped out of the intervention group, and 17 had been excluded or had dropped out of the patient control group (Fig. 1). Thus, the intervention group consists of 75 CCS and the patient control group consisted of 33 CCS at 1-year post-treatment. We observed no difference between groups in age, sex, height, weight, BMI, or diagnosis distribution. Anthropometric and clinical characteristics are shown in Table 2. The treatment protocols of the included children are presented in Supplementary 1.

Training frequency, harms, and feasibility

The median number of physical activity sessions attended per child was 34 [interquartile range: 19 to 50], corresponding to a participation rate of median 64% [interquartile range 50 to 82%] or three sessions per 5 days of in-hospital admission (excluding weekends and holidays). Overall, the children's participation was spread over a total of 3364 individual and 726 group physical activity sessions. No additional adverse events occurred during the physical activity sessions apart from the six minor events reported in earlier publications: four children experienced minor bruising, one child had a nosebleed during warm-up, and one child fainted shortly after exercise but had no further complications [22, 23].

Effect of the RESPECT activity program

One-year post-treatment, VO_2peak tended to be higher in the intervention group compared with the patient control group with a mean difference of 4.7 mL/kg/min [95% CI 0.4 to 9.1 mL/kg/min]. This mean difference remained similar when we adjusted sex-dependent age and for diagnosis-dependent time since diagnosis (Table 3). Watt max and VO_2 (L/min) during the CPET test were similar between the intervention- and the patient control group. The intervention group had a higher Sit-to-Stand score than that of the patient control group, with a mean difference of 7 repetitions [95% CI 4 to 10]. Moreover, the intervention group completed the Timed Up and Go test faster than the patient control group with a mean difference of − 20% [95% CI − 26 to − 13]. The intervention group was stronger in Handgrip Strength compared with the patient control group in both hands (see Table 3). In Sit-to-Stand, Timed Up and Go, and Handgrip Strength, the mean difference remained similar when we adjusted for sex-dependent age and for diagnosis-dependent time since diagnosis (Table 3). The mean and standard deviations and median and 10th to 90th percentile of cardiorespiratory fitness, muscle strength and physical function are presented in supplementary 2.

Cardiorespiratory fitness, muscle strength, and physical function compared with age- and sex-matched community control group

One-year post-treatment, both the intervention- and patient control group had lower cardiorespiratory fitness than the community control group (mean difference − 4.7 [95% CI − 7.1 to − 4.7]) (Table 4). The intervention group and community control group performed similarly in Sit-to-Stand (mean difference 0 repetitions [95% CI − 2 to 2]), Timed Up and Go (mean difference − 3% [95% CI − 7 to 1]), and Handgrip Strength (right hand: mean difference − 4% [95% CI − 17 to

Table 2 Anthropometric and clinical characteristics

Anthropometric characteristics	Intervention group ($n = 75$)	Patient control group ($n = 33$)	p value between intervention and patient control	Community control group ($n = 94$)	p value between intervention and community control group	p value between patient control group and community control group
Sex (males/females)	45/30 (61%/39%)	19/14 (58%/42%)	0.59	55/39 (59%/41%)	0.56	0.95
Age (years)	13.4 ± 3.1	13.5 ± 2.5	0.78	12.9 ±3.0	0.28	0.42
Height (m)	1.58 ± 0.16	1.63 ± 0.16	0.13	1.6 ± 0.16	0.27	0.54
Weight (kg)	51.87 ± 16.18	53.9 ± 15.29	0.54	51.3 ± 16.2	0.82	0.43
BMI (kg/m^2)	20.4 ± 4.5	19.9 ± 3.3	0.52	19.4 ±3.5	0.10	0.51
Diagnosis			0.69			
Leukemia	37 (49%)	16 (48%)				
Lymphoma	16 (21%)	7 (21%)				
Extracranial solid tumors	16 (21%)	9 (27%)				
Central nervous system tumor	4 (5%)	1 (3%)				
Other hematological disease	3 (4%)	0 (0%)				
Days since diagnosis (median, 10th to 90th percentile)	710 [486 to 1307]	644 [504 to 1314]	0.96			
Physical capacity at diagnosis						
VO_2peak (mL/min/kg)	27.8 ± 7.2	29.3 ±7.3	0.98			
VO_2 (mL/min)	1.4 ± 0.5	1.5 ± 0.8	0.25			
Max watt	108 ± 35	119 ± 70	0.17			
Sit-To-Stand (reps)	26 ± 7	18 ± 5	0.01			
Timed-Up-and-Go	3.9 ± 0.8	5.3 ± 1.6	< 0.001			
Right Handgrip Strength (kg)	21 ± 11	18 ± 11	0.19			
Left Handgrip Strength (kg)	19 ± 10	17 ± 12	0.5			

10], left hand: mean difference − 5% [95% CI − 18 to 10]). However, the patient control group had a lower Sit-to-Stand score (mean difference − 6.29 [− 9.29 to -3.27] repetitions), was slower to complete the Timed Up and Go test (mean 21 [12 to 32] %) and had lower Handgrip Strength (right hand: mean difference − 23 [− 41 to − 1] %, left hand: − 24 [− 40 to − 4] %) than did the community control group (Table 4). The mean differences remained similar when we adjust for sex-dependent age (Table 4).

Discussion

In this multicenter, prospective, non-randomized, controlled, multimodal study, we showed that children who received a peer-supported, supervised in-hospital physical activity program during treatment had higher cardiorespiratory fitness, muscle strength, and physical function than children who received usual care 1-year

Table 3 RESPECT activity program: cardiorespiratory fitness, muscle strength, and physical function 1-year post-treatment: comparison of the intervention group with the patient control group

	Unadjusted analysis estimate [95% CI]	*p*	Demographic-adjusted* estimate [95% CI]	*p*	Demographic- and diagnosis-adjusted** estimate [95% CI]	*p*	Comparison at age 8 years in a demographic- and diagnosis-adjusted model with age-dependent difference between groups*** estimate [95% CI]	*p*	Comparison at age 18 years in a demographic- and diagnosis-adjusted model with age-dependent difference between groups*** estimate [95% CI]	*p*
VO_2peak (mL/kg/min)	4.7 [0.4 to 9.1]	0.034	4.7 [0.5 to 8.8]	0.028	4.3 [0.4 to 8.2]	0.033	9.8 [0.4 to 19.2]	0.042	0.6 [− 6.3 to 7.5]	0.86
VO_2 (L/min) (% of level among patient controls)	14 [− 11 to 47]	0.30	15 [− 3 to 35]	0.09	12 [− 5 to 33]	0.16	27 [− 15 to 90]	0.24	3 [− 23 to 39]	0.82
Watt max (W)	9 [− 20 to 37]	0.55	7 [− 11 to 26]	0.43	3 [− 16 to 21]	0.77	7 [− 37 to 52]	0.74	1 [− 32 to 33]	0.97
Sit-to-Stand (repetitions)	67 [4 to 10]	< 0.001	7 [4 to 10]	< 0.001	7 [4 to 10]	< 0.001	− 1 [− 8 to 6]	0.78	12 [7 to 17]	< 0.001
Timed Up and Go (% of level among patient controls)	− 20 [− 26 to − 13]	< 0.001	− 21 [− 27 to − 14]	< 0.001	− 21 [− 28 to − 14]	< 0.001	− 7 [− 25 to 16]	0.50	− 29 [− 39 to − 18]	< 0.001
Right Handgrip Strength (% of level among patient controls)	24 [− 4 to 61]	0.095	29 [12 to 49]	0.001	31 [12 to 53]	0.001	35 [− 12 to 106]	0.15	29 [− 3 to 70]	0.074
Left Handgrip Strength (% of level among patient controls)	25 [− 1 to 59]	0.065	31 [15 to 48]	< 0.001	32 [16 to 52]	< 0.001	24 [− 14 to 77]	0.23	38 [8 to 77]	0.012

CI, confidence interval

*Adjusted for sex-dependent associations with relative age

**Adjusted for sex-dependent associations with relative age and diagnosis-dependent time since diagnosis

***Estimated in a model including sex-dependent associations with relative age, diagnosis-dependent time since diagnosis, and group-dependent associations with relative age

VO_2 (L/min), Timed Up and Go, Right Handgrip Strength, and Left Handgrip Strength were log-transformed; results are therefore presented as % difference from the level in the patient control group

Table 4 RESPECT activity program: cardiorespiratory fitness, muscle strength, and physical function 1-year post-treatment: comparison of the intervention group and the patient control group with the community control group

	Unadjusted analysis estimate [95% CI]	*p*	Demographic-adjusted* estimate [95% CI]	*p*	Estimated value at age 8 years in a model with age-dependent difference between groups** estimate [95% CI]	*p*	Estimated value at age 18 years in a model with age-dependent difference between groups** estimate [95% CI]	*p*
VO_2 peak (mL/kg/min)								
Intervention group	− 4.7 [− 7.1 to − 4.7]	< 0.001	− 5.4 [− 8.0 to − 2.8]	< 0.001	− 6.7 [− 14.3 to 0.9]	0.081	− 5.0 [− 9.2 to − 0.8]	0.019
Patient control group	− 9.3 [− 13.8 to − 4.7]	< 0.001	− 10.1 [− 14.4 to − 5.7]	< 0.001	− 18.2 [− 29.3 to − 7.2]	0.002	5.1 [− 12.5 to 2.3]	0.17
VO_2 (L/min) (% of level among Community controls)								
Intervention group	− 16 [− 26 to − 3]	0.016	− 10 [− 17 to − 3]	0.008	− 16 [− 32 to 5]	0.12	− 8 [− 19 to 5]	0.21
Patient control group	− 26 [− 42 to − 5]	0.021	− 22 [− 33 to − 8]	0.004	− 38 [− 58 to − 8]	0.02	− 10 [− 32 to 19]	0.45
Max watt (W)								
Intervention group	− 48 [− 73 to − 23]	< 0.001	− 39 [− 55 to − 23]	< 0.001	9 [− 35 to 53]	0.68	− 61 [− 86 to − 37]	< 0.001
Patient control group	− 56 [− 88 to − 24]	0.001	− 46 [− 66 to − 27]	< 0.001	− 10 [− 61 to 42]	0.70	− 62 [− 95 to − 29]	< 0.001
Sit-to-Stand (repetitions)								
Intervention group	0 [− 2 to 2]	0.78	0 [− 2 to 2]	0.87	− 4 [− 7 to 0]	0.058	3 [0 to 6]	0.058
Patient control group	− 6 [− 9 to − 3]	< 0.001	− 6 [− 9 to − 3]	< 0.001	− 4 [− 12 to 3]	0.26	− 8 [− 13 to − 2]	0.007
Timed Up and Go (% of level among community controls)								
Intervention group	− 3 [− 7 to 1]	0.14	− 4 [− 9 to 1]	0.083	8 [− 1 to 18]	0.083	− 12 [− 18 to − 5]	< 0.001
Patient control group	21 [12 to 32]	< 0.001	22 [12 to 32]	< 0.001	17 [− 5 to 46]	0.14	23 [6 to 43]	0.009
Right Handgrip Strength (% of level among Community controls)								
Intervention group	− 4 [− 17 to 10]	0.53	− 4 [− 11 to 4]	0.31	− 4 [− 19 to 13]	0.60	− 4 [− 16 to 10]	0.59
Patient control group	− 23 [− 41 to − 1]	0.043	− 26 [− 35 to − 14]	< 0.001	− 30 [− 53 to 3]	0.068	− 23 [− 40 to 0]	0.051
Left Handgrip Strength (% of level among Community controls)								
Intervention group	− 5 [− 18 to 10]	0.49	− 5 [− 12 to 3]	0.24	− 8 [− 23 to 9]	0.32	− 2 [− 14 to 12]	0.78
Patient control group	− 24 [− 40 to − 4]	0.022	− 27 [− 35 to − 18]	< 0.001	− 25 [− 45 to 2]	0.061	− 28 [− 41 to − 11]	0.004

CI, confidence interval

*Adjusted for sex-dependent associations with relative age

**Estimated in a model including, sex-dependent associations with relative age, and group-dependent associations with relative age

VO_2 (L/min), Timed Up and Go, Right Handgrip Strength and Left Handgrip Strength were log-transformed; results are therefore presented as % difference from the level in the community control group

after ended treatment. Moreover, we showed that children with cancer in the intervention group had similar muscle strength and physical function to children with no history of cancer (i.e., community controls); however, the children with cancer still displayed lower cardiorespiratory fitness than community controls. Our previous study showed that the intervention and patient control groups were comparable in anthropometric and diagnosis distribution prior to inclusion [27]. Our study suggested that children in the intervention group could maintain their

cardiorespiratory fitness, muscle strength, and physical function during treatment. In contrast, the control group experienced a further decline in cardiorespiratory fitness [27]. Furthermore, the intervention group and patient control group were comparable in cardiorespiratory fitness and handgrip strength but not in Sit-To-Stand and Timed-Up-and-Go at baseline (Table 2). Collectively, this suggests that a peer-supported, supervised in-hospital physical activity program during treatment may have long-lasting benefits for CCS regarding cardiorespiratory fitness, muscle strength, and physical function. However, the observed differences between the intervention- and patient control groups in physical function may be due to baseline differences. This indicate that children with cancer could benefit from early in-hospital physical activity programs, also in their everyday life after treatment.

It is possible that the improved physical function supported the children's educational and social rehabilitation as they may have fewer difficulties in matching the physical functioning of peers [39]. These results suggest that physically active children during treatment require less rehabilitation post-treatment to regain age-matched physical function but still require targeted interventions to improve their cardiorespiratory fitness. Conflicting evidence on the effects of physical activity during treatment exists. Several studies show benefits for cardiorespiratory fitness [23, 40–42], muscle strength [43–45], and physical function [46, 47], whereas others show no effect [48, 49]. Collectively, data have been synthesized in two meta-analyses, showing that physical activity during treatment can improve muscle strength [50] and physical function [51]. In agreement with the present study, CCS have lower cardiorespiratory fitness and muscle strength several years post-treatment [8, 9, 11, 52]. Factors that can contribute to lower cardiorespiratory fitness and muscle strength include cardiac, pulmonary, and vascular limitations, as well as peripheral neuropathy and altered body composition [9, 52]. The present study showed that physical activity during treatment has both an immediate effect and a long-term effect manifesting a year after intervention end. The effects of the intervention might reduce the children's risk of developing cardiorespiratory fitness-related medical conditions for years after their treatment has ended. In adults, studies have shown that a change in VO_2peak of 1 mL/kg/min corresponds to a 9–10% reduction in the incidence of cardiac mortality [53, 54] and a 5% cardiovascular disease risk reduction [55]. This is further supported by a recent study showing that exercise during childhood cancer treatment maintained left ventricular function post-treatment, whereas this was not the case in a control group with no exercise [56].

The RESPECT project is the first to include healthy classmates as ambassadors during cancer treatment and in a physical activity program [22]. Through semi-structured interviews, we previously explored children with cancer's motivation to engage in physical activity while admitted to the hospital [57, 58]. The children with cancer described how their motivation to be physically active increased during treatment because their ambassadors participated in the physical activity sessions [57, 58]: the ambassadors' presence provided distractions from common side effects (i.e., nausea, pain) and everyday hospital life, motivating them to get out of bed. Qualitatively, parents and children have described how the intervention supported the children in re-entering everyday life post-treatment, including physical activities, social interactions, and school attendance [57, 58]. The ambassadors provided an opportunity to receive support from peers when performing physical activities [57]. Moreover, they represented a unique opportunity to incorporate the child's everyday life into the hospital setting and increase the child's willingness to engage in rehabilitation offers [57]. However, involving healthy classmates as ambassadors may be more difficult in other settings. Thus, exploring alternative approaches to including healthy children in physical activity programs for children with cancer is critical. Through semi-structured interviews, we previously investigated the experience of being part of the RESPECT study [58]. The parents described how participating in the RESPECT intervention increased their understanding of how anti-cancer treatment and sedentary behavior affected their child's physical capacity [58]. They expressed that they learnt the importance of physical activity both during and after treatment and that this enabled them to support their child's physical activity post-treatment [58]. Throughout the study, one exercise professional or physical therapist conducted the physical activity program at a given time. Thus, achieving the physical activity program in other settings requires few additional human resources.

Taken together, the findings show that children with cancer need physical rehabilitation. Without physical rehabilitation the children risk long-term impairments in cardiorespiratory fitness, muscle strength, and physical function. Further, this study indicates that physical activity is beneficial for children with cancer, thus supporting the recommendations from the international Pediatric Oncology Exercise Guidelines (iPOEG) stating that children with cancer should be physically active and do what they can, when they can [59]. Building on the iPOEG guidelines, we recommend that clinicians emphasize physical activity during treatment, when side effects (i.e., nausea, pain) are most common. Targeted exercise interventions including cardiorespiratory fitness may be more suitable later in the treatment trajectory when treatment is less intense (e.g., maintenance phase of ALL treatment) or after treatment end. This remains to be investigated.

Strengths and limitations

The strength of this study is the high inclusion rate in the intervention group, with 94% of eligible children completing the intervention. Prior to the initiation of the RESPECT study, we expected some selection bias, given the study design. However, the limited participation rate in the control group (47%) introduced the possibility of further selection bias. The number of dropouts and excluded patients at 1-year post-treatment is a limitation of the study. We, therefore, suspected attrition bias because of poor retention one-year post-treatment. Thus, we performed post hoc analyses and tested for systematic dropouts or excluded patients concerning diagnosis distribution, sex, age, socioeconomic status, and ethnicity. Further, we tested whether these variables were comparable at baseline between the intervention and patient control groups. None of these variables were associated with dropout or exclusion in this study. No differences were observed in any of these variables at baseline or one-year post treatment. We observed more relapse cases in the intervention group compared to the patient control group. We expected this as the treatment of most rare and high-risk cancers is centralized at The University Hospital of Copenhagen. This discrepancy in eligible patients between the centers, combined with the high number of non-responders in the control group, limits the generalizability and certainty of the study results.

There is a possible geographical difference between The University Hospital of Copenhagen and the rest of the country concerning the testing personnel and differences in standard institutional guided care unrelated to treatment protocols. Nevertheless, all institutions are subject to the same regulations and have the same financial resources available to treat children. We included all children who received chemotherapy and/or radiation therapy. Consequently, the study consists of a heterogeneous group; therefore, we cannot conclude on the effects of the intervention for children with a specific diagnosis. Parents declining participation in the patient control group explained that the requirements to their children were excessive, as there were no benefits from participating in the study (i.e., no physical activity or ambassador visits). It can be speculated that the children in the patient control group consisted of children with an interest in exercise, consequently resulting in an underestimation of the effects.

Moreover, it can be speculated that children with the most severe long-term adverse effects declined participation or dropped out of the study, limiting the generalizability and certainty of the study results. Further, the study is limited by the few completed CPET. The missing data indicate that the children with the best physical capacity completed the CPET, thus limiting the generalizability and certainty of the effects of the intervention.

Conclusion

This study indicates that a peer-supported and supervised in-hospital physical activity intervention initiated from diagnosis may be beneficial on cardiorespiratory fitness and muscle strength in children with cancer post-treatment. The study also indicates that physical activity during treatment may improve muscle strength and physical function to a level similar to that of children without a history of cancer, although cardiorespiratory fitness requires a more targeted approach. However, the results should be interpreted with caution because of the limitations present in the study. Overall, improved physical function might not only improve the children's long-term physical performance but may also be a core element in their social and educational rehabilitation.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11764-023-01499-7.

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Author contribution HBL and KS designed the RESPECT study. MKF and HBL designed the current study. HBL, TT, PSA, and MKF were responsible for the data collection in the intervention group. HBL, HH, and PSW were responsible for the data collection in the control group. MKF, PSA, and LAJ were responsible for the data from the healthy age- and sex-matched control group. MKF, PSA, and TT carried out the intervention and performed all physical tests in the intervention group. MKF performed all statistical analyses. MKF wrote the first draft of the manuscript. All authors contributed to the final draft of the manuscript.

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Data availability The datasets used during the current study are available from the corresponding author on reasonable request after the last follow-up data have been collected and published.

Declarations

Ethics approval and consent to participate All participants and their parents received oral and written information, and the parents gave written informed consent. The Regional Ethics Committee for the Capital Region (file. H 3-2012-105) and the Danish Data Protection Agency (file. 2007-58-0015/nr.30-0734) approved the study and the data protection structure.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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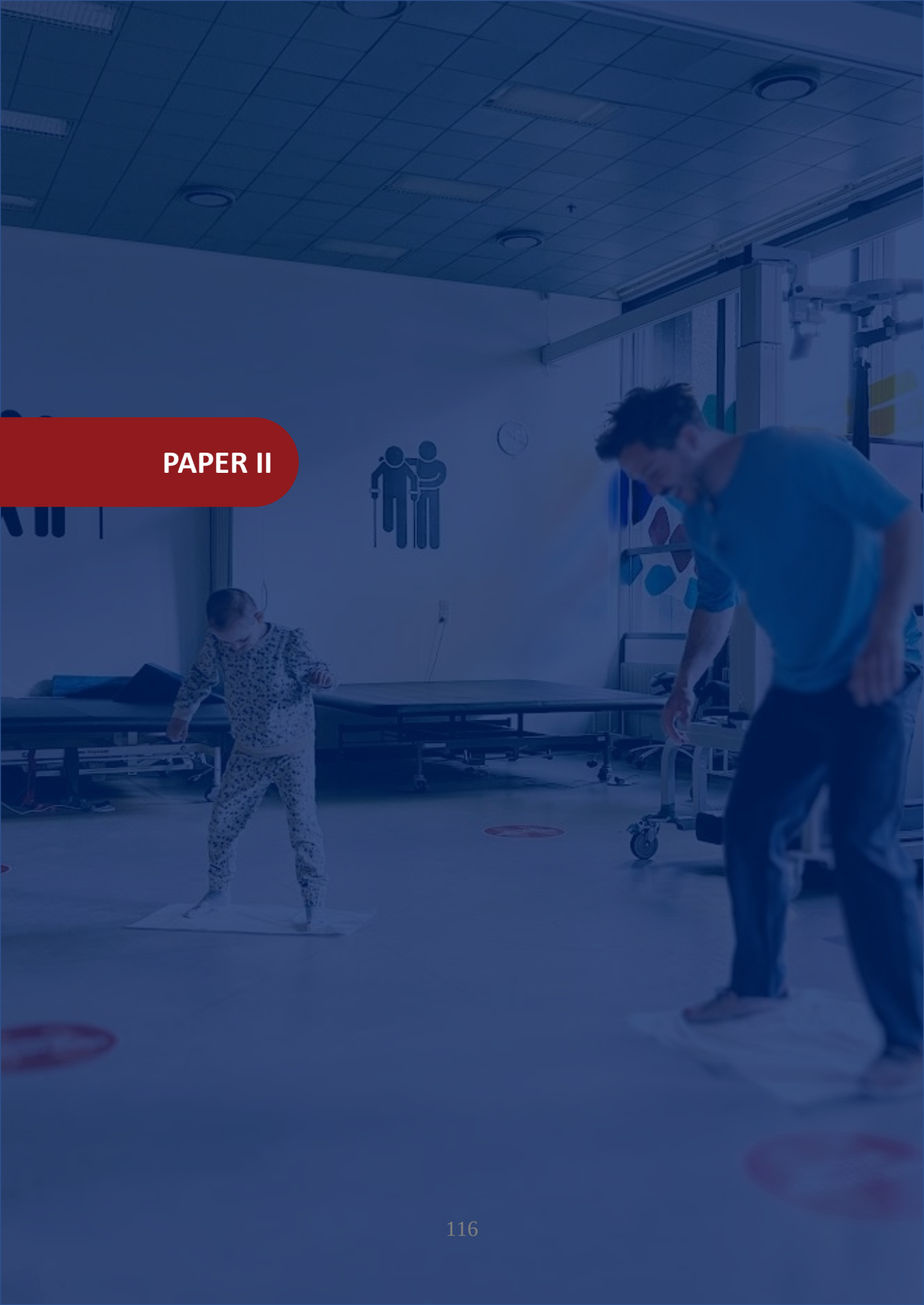
Supplementary 1: Treatment protocols and modalities for the included childhood cancer survivors

Treatment protocols	Intervention Group	Patient Control Group
NOPHO ALL 2008	27	13
NOPHO-DBH-AML 2012	8	3
ICC APL 01	2	0
Euro-LB-02	3	0
Euro NET PHL-C1 interrim	4	0
Euro NET PHL-C2	1	4
BFM NHL 2004	5	0
BFM NHL 2013	3	3
Euro-Ewing 99	5	2
EURAMOS-1	4	1
CCLG interim	1	0
EpSSG RMS 2005	3	2
EpSSG-NRSTS 2005	1	0
UKSSG	0	1
SIOPEL. high risk-PLADO	1	0
Neoadjuvant docetaxel/cisplatin/fluorouracil	1	0
SIOP-CNS GCT 2	2	1
SIOP 2001	0	1
SIOP ependynoma 2	1	0
SIOP PNET 5	1	1
SIOP- LGG 2004	0	1
LCH-III	1	0
Allogeneic transplantation	2	0
Treatment modalities		
Chemotherapy	75	33
Radiation therapy	10	4
Surgery	19	9
Tumor location		
Central nervous system	4	1
Head	2	1
Torso	5	4
Upper extremity	1	0
Lower extremity	8	3

Supplementary 2: Descriptive data on cardiorespiratory fitness, muscle strength and physical function one- year after ended treatment.

	n	Mean (SD)	Median [10^{th} to 90^{th} percentile]
VO_2peak (mL/kg/min)			
Intervention group	52	37.0 ± 6.0	37.5 [29.1 to 45.3]
Patient control group	25	32.3 ± 9.7	30.9 [22.7 to 44.5]
Community control group	38	41.5 ± 6.6	40.6 [33.5 to 50.4]
VO_2peak (L/min)			
Intervention group	52	1.95 ± 0.65	1.9 [1.2 to 3.0]
Patient control group	25	1.83 ± 0.86	1.6 [0.9 to 2.9]
Community control group	38	2.23 ± 0.66	2.14 [1.5 to 3.2]
Max Watt (W)			
Intervention group	52	148 ± 50	140 [90 to 210]
Patient control group	25	139± 59	130 [68 to 224]
Community control group	38	195 ± 62	180 [120 to 277]
Sit-to-Stand (reps)			
Intervention group	74	30 ± 5	30 [23 to 36]
Patient control group	18	23 ± 6	24 [16 to 30]
Community control group	90	29.±6	30 [21 to 35]
Timed Up and Go (s)			
Intervention group	75	3.4 ± 0.4	3.4 [2.9 to 4.0]
Patient control group	18	4.3 ± 0.6	4.3 [3.4 to 5.1]
Community control group	91	3.6 ± 0.6	3.4 [2.9 to 4.3]
Right Handgrip Strength (kg)			
Intervention group	75	27 ± 12	24[14to 44]
Patient control group	17	22 ± 10	18.0 [12 to 37]
Community control group	93	28 ±13	25 [14 to 48]
Left Handgrip Strength (kg)			
Intervention group	75	25 ± 12	22[12 to 43]
Patient control group	16	19 ± 8	18 [12 to 31]
Community control group	92	26 ± 12	23 [14 to 46]

PAPER II



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REVIEW

Physical capacity in children and adolescents with newly diagnosed cancer: A systematic review and meta-analysis

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Abstract

Objective: To review the body of evidence on cardiorespiratory fitness, muscle strength, and physical performance in children with newly diagnosed cancer, five databases (MEDLINE, Embase, CINAHL, CENTRAL, and Web of Science) were searched on December 19, 2022.

Methods: Thirteen studies, embodying 594 participants within 1 month of cancer diagnosis and 3674 healthy controls were included. Eighteen different outcomes on cardiorespiratory fitness ($n = 2$), muscle strength ($n = 5$), physical performance ($n = 10$), and adverse events ($n = 1$) were analyzed.

Results: Fifteen out of 17 outcomes on physical capacity showed severe impairments compared with healthy controls. Where possible, random-effects meta-analysis was conducted to synthesize the results. No adverse events were reported related to testing.

Conclusion: Children with cancer have impaired cardiorespiratory fitness, muscle strength, and physical performance within the first month after diagnosis. However, the evidence is based on a small number of studies with large clinical heterogeneity, limiting the certainty of evidence.

Abbreviation: ALL, acute lymphoblastic leukemia.

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KEYWORDS
cardiorespiratory fitness, muscle strength, pediatric exercise oncology, physical performance

1 | INTRODUCTION

The negative consequences of childhood cancer treatment on physical capacity (i.e., cardiorespiratory fitness, muscle strength, and physical performance) become evident[1-4] during treatment. Children diagnosed with cancer will experience multiple repeating or persisting side effects, including peripheral neuropathy, altered body composition, and impaired physical capacity throughout the cancer treatment trajectory.[1,4-9] Post treatment, childhood cancer survivors are expected to regain physical capacity, albeit to a varying degree. However, almost 80% of adult childhood extremity sarcoma survivors report musculoskeletal complications, and more than 15% have severe muscle strength impairments.[2] Loss of capacity induces fatigue and limited ability to carry out daily activities independently and to partake in social activities, eventually impacting health-related quality of life.[2,10-12]

Considering the direct impact of cancer treatment on physical capacity throughout the cancer trajectory and its link to reduced physical independence and health-related quality of life, it is crucial to understand the magnitude of these impairments in the early stages of cancer treatment. Within the body of evidence in pediatric exercise oncology, no study has summarized the current literature regarding these potential impairments. Such an overview can be used to support early evidence-based intervention strategies (e.g., physical rehabilitation).

This systematic review and meta-analysis, therefore, aims to summarize the body of evidence on cardiorespiratory fitness, muscle strength, and physical performance status of children (ages 1–18) with newly diagnosed cancer.

2 | METHODS

This systematic review followed the PRISMA guidelines,[13] and was registered in the PROSPERO database (CRD42022378696).

2.1 | Eligibility criteria

Inclusion criteria were: (i) children under age 18, newly diagnosed with cancer; (ii) objectively measured cardiorespiratory fitness, muscle strength, and physical performance using standardized methods; and (iii) assessment performed 31 days or less after cancer diagnosis/treatment initiation. We excluded studies that reported data on less than 10 patients or included patients with another index disease involving neuromuscular pathology and poor physical development. Studies including children undergoing hematopoietic stem cell transplantation and children with relapse of primary cancer disease were excluded.

2.2 | Information sources

The MEDLINE electronic database, CINAHL, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science were searched on December 19, 2022.

2.3 | Search strategy

The search string consisted of three blocks of keywords and MeSH/Thesaurus terms related to population, outcomes, and study type (Supporting File S1).

Two reviewers (Peter Schmidt-Andersen, Martin Kaj Fridh) independently used citation pearl growing to hand-search references of eligible studies and reviews identified in the search process.

To identify ongoing trials, the International Clinical Trials Registry platform was searched.

2.4 | Selection process

At least two reviewers (Peter Schmidt-Andersen, Anna Stage, Louise H. Bastholm, Jan Christensen, Martin Kaj Fridh) independently screened all titles and abstracts of identified studies. Further, at least two reviewers (Peter Schmidt-Andersen, Anna Stage, Martin Kaj Fridh) independently assessed studies included for full text. Disagreements in any of these processes were solved by discussion or a third reviewer (Jan Christensen).

2.5 | Data collection process

Corresponding authors of unobtainable studies, with missing data, or where assessment timing was inadequately reported, were contacted to obtain the missing data.

Data extractions were conducted independently by two reviewers (Peter Schmidt-Andersen, Anna Stage), and disagreements were solved by discussion or a third reviewer (Martin Kaj Fridh). The online Covidence software screening tool (Covidence systematic review software

2023, Veritas Health Innovation) was used to screen studies and data extraction.

2.6 | Data items

For each study, the following information was extracted: design; year of publication; number of patients; age at treatment initiation; time since treatment initiation; primary cancer disease; sex; adverse events related to testing; cardiorespiratory fitness (VO_{2max}, VO_{2peak}, aerobic effect, or maximal exercise tolerance); muscle strength (concentric, isometric, or eccentric muscle strength of any muscle group); physical performance (walking ability or distance, balance, muscle endurance, mobility, functional capacity, or motor development); and funding.

2.7 | Synthesis methods

To summarize the results, we conducted inverse variance random effects meta-analysis adjusted to Hedges' G and reported the results as weighted mean difference. For studies reporting data as median and range or interquartile range, the mean and standard deviation were estimated using methods described by Wan et al.[14] and Lou et al.[15] If studies did not report within study-comparisons to either matched or age-specific references, the reported data for children diagnosed with cancer were compared to the following published data containing age-specific reference values: cardiorespiratory fitness (VO_{2peak}—from the European Heart Study and the Copenhagen School Child Intervention Study)[16–20]; muscle strength (handgrip strength—from the McQuiddy Cohort),[21] and physical performance (Timed Up and Go Test—from the RESPECT study cohort[22]; Timed Up and Down Stairs Test—The Corral Cohort[23]; Six-Minute Walk Test—the Geiger Cohort[24]; and Functional Mobility Assessment Scale—the Marchese Cohort),[25] as described in Supporting File S2. If studies contained two groups within 31 days after diagnosis (e.g., in intervention trials), both groups were included in the meta-analysis and reported separately. If the reference material presented data in multiple groups divided by sex and age, a weighted mean and standard deviation within these strata were calculated to match the two compared groups.

When possible, mean differences, including 95% confidence intervals and *p*-values, were calculated using either a two-sample *t*-test[26] or a Wilcoxon rank-sum test (nonparametric data).[27] If a meta-analysis could not be conducted due to clinical heterogeneity, data were reported narratively. The risk ratio of adverse events related to testing in children newly diagnosed with cancer compared with healthy controls was calculated.

The heterogeneity of results was assessed, quantified, and interpreted using I^2 statistics. Between-study variance was quantified using τ^2.[28] All analyses and visual presentations were conducted using Review Manager (RevMan, version 5.4, The Cochrane Collaboration, 2020). Several sensitivity and meta-regression analyses were planned (CRD42022378696).

2.8 | Assessment of the quality of included studies and risk of bias

Based on the research question, the included studies were all scored as cross-sectional studies; hence, quality assessment was conducted using the Newcastle-Ottawa Scale for cross-sectional studies.[29] Two reviewers (Peter Schmidt-Andersen, Anna Pouplier) independently assessed the quality of each study; disagreements were solved by discussion or a third reviewer (Martin Kaj Fridh). Risk of bias for each outcome was assessed with the same scale using the summarized score: less than or equal to 4 = low quality—very serious risk of bias; 5–6 = moderate quality—serious risk of bias; and 7 or higher = high quality—no serious risk of bias.[29,30]

2.9 | Certainty assessment

Two authors (Peter Schmidt-Andersen, Martin Kaj Fridh) scored each outcome independently using the Grading of Recommendations Assessment and Evaluation (GRADE)[31] within the domains: risk of bias, inconsistency, indirectness, imprecision, and other considerations. Where applicable, indirectness was evaluated according to the rule-of-thumb, as described by Cochrane, describing statistical heterogeneity (<40% = low, 30%–60% = moderate, 50%–90% = substantial, 75%–100% = considerable).[32] Other considerations, that is large effect or if plausible confounding were accounted for, could upgrade evidence quality if no serious concerns were identified in other domains.[33] Data are presented in an evidence profile (Table 1).[32]

3 | RESULTS

Thirteen studies[22,34–45] with 14 patient groups were compared to healthy controls, including 594 children diagnosed with cancer, and 3674 unique healthy controls were included. Figure 1 shows a PRISMA flow diagram illustrating the study identification and selection process.

Additionally, eight ongoing trials that may fit the inclusion criteria were identified (Supporting File S3). None of these studies had published data available; however, three had published protocols, according to which the results would be relevant for this study.[46–48]

3.1 | Study characteristics

A summary of study characteristics, including references used for comparison, is presented in Supporting File S2. Nine studies reported comparisons with a healthy reference population.[22] We used imputed data for four studies[35,36,44,49] to conduct the analysis. Baseline assessment was performed 7–31 days after treatment initiation or date of diagnosis. A detailed description of the included studies can be found in Supporting File S4.

TABLE 1 Evidence profile.

Outcome	Measure	Certainty assessment						No. of patients		Relative deficit (mean difference) in children with cancer compared to healthy controls [95% CI]	Certainty
		No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Children with cancer	Healthy reference		
Cardiorespiratory fitness											
Exercise tolerance	Adapted Yo-yo and CPET	3 (4 patient groups)	Not serious	Not serious	Serious[a]	Serious[b]	Large effect	78	783	−2.55 SMD [−2.82, −2.27]	⨁◯◯◯ Very low
VO_{2peak}	CPET	2 (3 patient groups)	Not serious	Not serious	Serious[a]	Very serious[b]	Large effect	67	765	−19.63 mL/kg/min [−21.43, −17.83]	⨁◯◯◯ Very low
Muscle strength											
Hand grip, R	Hand dynamometer	5	Not serious	Very serious[c]	Serious[a]	Not serious	None	321	1667	−6.42 kg [−12.16, −0.69]	⨁◯◯◯ Very low
Lower body strength	Iso. Knee ext	2	Serious[d]	Very serious[c]	Serious[f]	Not serious	None	132	378	−62.29 N [−124.32, −0.26]	⨁◯◯◯ Very low
Lower leg strength	Iso. Ankle dorsi flex	2	Serious[d]	Very serious[c]	Serious[f]	Not serious	None	132	378	−17.86 N [−63.77, 28.04]	⨁◯◯◯ Very low
Explosive lower limb muscle strength	Med. Ball throw	1	Serious[d]	N/A[e]	Serious[g]	Very serious[b]	Large effect	24	28	−1.85 m [−2.85, −0.70]	⨁◯◯◯ Very low
Leg strength	STS (5 rep)	1	Serious[d]	N/A[e]	Serious[g]	Serious[b]	None	32	28	1.49 seconds (slower) [0.68, 2.29]	⨁◯◯◯ Very low
Physical performance											
Walking distance	6MWT	4	Very serious[h]	Serious[i]	Serious[a]	Not serious	Large effect	168	1971	−226.71 [−255.26, −198.16]	⨁◯◯◯ Very low
Functional capacity	TUG	3 (4 patient groups)	Serious[d]	Very serious[c]	Serious[a]	Not serious	None	133	198	0.92 seconds (slower) [0.47, 1.36]	⨁◯◯◯ Very low
Functional capacity 2	TUDS	2	Serious[j]	Serious[a]	Serious[a]	Serious[b]	None	43	774	2.19 [1.49, 2.90]	⨁◯◯◯ Very low
Functional mobility	FMA	1	Serious[d]	Serious[e]	Serious[g]	Very serious[b]	None	49	503	−30.34 [−36.15, −24.53]	⨁◯◯◯ Very low

(Continues)

TABLE 1 (Continued)

Outcome	Measure	Certainty assessment						No. of patients		Relative deficit (mean difference) in children with cancer compared to healthy controls [95% CI]	Certainty
		No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Children with cancer	Healthy reference		
Muscle endurance	STS (30 seconds)	1	Not serious	N/A[e]	Not serious	Serious[k]	None	90	62	−7.5 repetitions [−9.48, −5.52]	⨁◯◯◯ Very low
Static balance	Static stand	1	Serious[d]	N/A[e]	Serious[g]	Serious[b]	None	32	33	3.6 ground contacts [−2.16, 8.44]	⨁◯◯◯ Very low
Balance (sway)	Ultrasound-based motion analysis	1	Very serious[l]	N/A[e]	Serious[g]	Very serious[b]	None	12	11	N/A[m]	⨁◯◯◯ Very low
Motor skill development	BOT2-SF	1	Not serious	N/A[e]	Serious[g]	Not serious	None	109	N/A[n]	(23.2 ± 2.5 vs. 50.0 ± 3.4, $p < .001$)	⨁◯◯◯ Very low
Motor skill development	Bayley and Movement ABC	1	Serious[d]	N/A[e]	Serious[g]	Not serious	None	51	51	N/A[m]	⨁◯◯◯ Very low
Motor skill development	Movement ABC	1	Not serious	N/A[e]	Serious[g]	Serious[b]	None	14	17	N/A[m]	⨁◯◯◯ Very low
Adverse events	–	5	Serious[d]	Not serious	Not serious	Not serious	Very large effect	327/0	1717/0	RR = 1 [1, 1]	⨁⨁⨁◯ Moderate

Abbreviations: 6MWT, Six-Minute Walk Test; BOT2-SF, The Bruininks–Oseretsky Test of Motor Development; CPET, cardiopulmonary exercise test; FMA, Functional Mobility Assesment Scale; Iso., isometric; Med., Medicine; STS, Sit-to-Stand Test; TUDS, Timed-Up-and-Down-Stairs Test; TUG, Timed-Up-and-Go Test.

[a] Different cancer diagnosis between studies.

[b] Low power.

[c] I^2 = 75%–100% (considerable).

[d] Some concerns regarding selection, comparability, and assessment of outcome.

[e] NA—single study.

[f] Only ALL.

[g] Single study—not all cancer diagnoses.

[h] Some concerns regarding selection (representativeness and description of non-responders), comparability, and assessment of outcome.

[i] I^2 = 50%–90% (substantial).

[j] Some concerns regarding selection (description of non-responders), comparability, and assessment of outcome.

[k] Outcome is a surrogate measure of physical performance and not directly transferable.

[l] Some concerns regarding selection (representativeness, description of non-responders, and ascertainment of exposure), comparability, and assessment of outcome.

[m] Not applicable (data presented in SDs).

[n] Not applicable (age-specific percentile ranks were used for comparison).

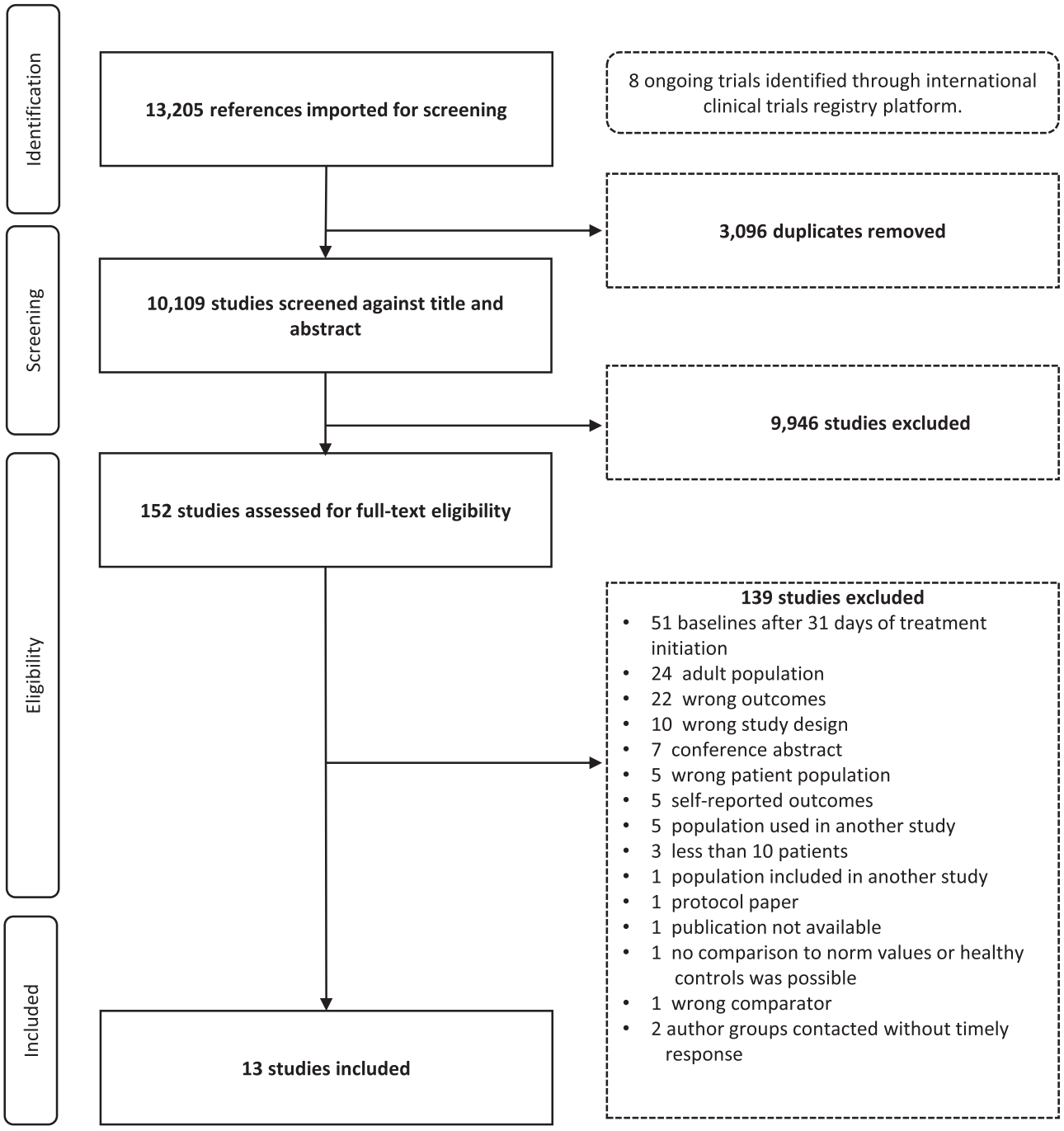

FIGURE 1 PRISMA flowchart. Study selection and PRISMA flowchart of the systematic review process.

3.2 | Certainty of evidence and risk of bias

The certainty of evidence was very low for all outcomes except for adverse events, which were of moderate certainty (Table 1).

Five outcomes (exercise tolerance, VO_{2peak}, explosive strength, walking distance, and adverse events) were considered large effect sizes.

The quality assessment used for the risk of bias of each included study is listed in Supporting File S5.

3.3 | Cardiorespiratory fitness

Three studies (four patient groups compared to healthy controls), including a total of 78 children with extracranial solid tumors,[35] any hematological cancer,[44] all types of cancer,[22] reported cardiorespiratory fitness, and were included in the meta-analysis illustrated in Figure 2A,B.

The meta-analysis showed that children with newly diagnosed cancer had a significantly lower exercise tolerance (standard mean

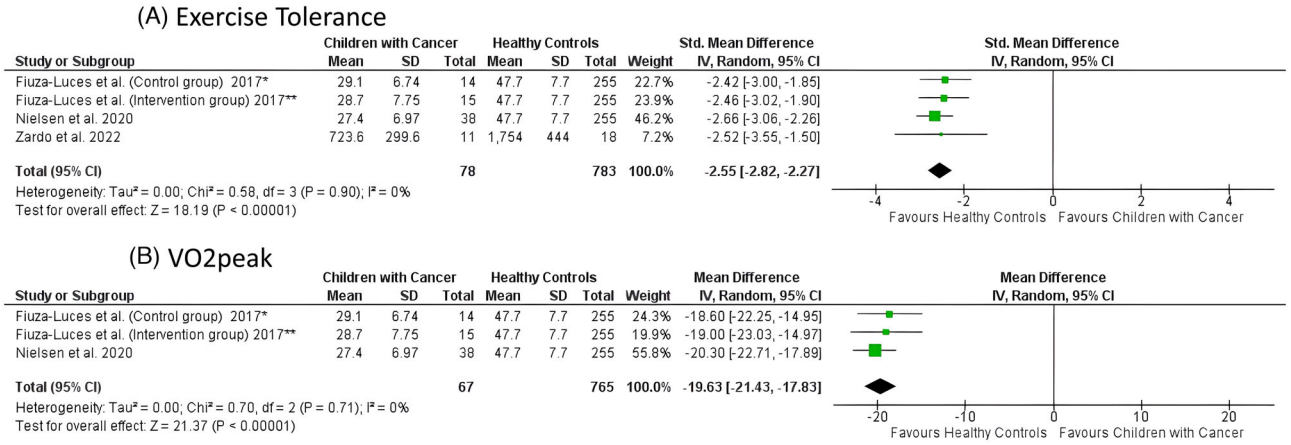

FIGURE 2 (A and B) Meta-analysis of cardiorespiratory fitness. (A) Meta-analysis of exercise tolerance. (B) Meta-analysis of VO_{2peak}. * = Within-study intervention group used as a patient group for comparison; ** = Within-study control group used as a patient group for comparison. Both patient groups from Fiuza-Luces et al.[35] were compared with imputed normative values from the European Heart Study and the Copenhagen School Child Intervention Study.[16–20] These are the same data used by Nielsen et al.[22].

difference of −2.55 [95% CI: −2.82 to −2.27], I^2 = 0%) and VO_{2peak} (mean difference of −19.63 mL/min/kg [95% CI: −21.43 to −17.83], I^2 = 0%), compared with healthy controls.

3.4 | Muscle strength

Five studies (five patient groups compared to healthy controls), including 321 children with acute lymphoblastic leukemia (ALL),[34,40] children with all types of cancers,[22,49] or a combined population of leukemia or non-Hodgkin lymphomas,[43] reported isometric handgrip strength and were included in the meta-analysis (Figure 3A–C).

Children with newly diagnosed cancer had a significantly lower handgrip strength compared with healthy controls (mean difference: −6.42 kg [95% CI: −12.16 to −0.69], I^2 = 96%).

A subanalysis of studies including only children with ALL[34,49] was performed and showed no difference in the interpretation of the results between children diagnosed with ALL and those diagnosed with other cancer diseases (Supporting File S6A).

Furthermore, no difference in the interpretation of the results was found between studies with and without imputed data[22,34,40,50] and studies without normative data[22,40,43] (Supporting File S6B,C).

Two studies that included data on 132 children with ALL and lymphoblastic lymphoma[34,45] reported isometric leg and ankle strength and were included in the meta-analysis illustrated in Figure 3B,C. Children with newly diagnosed cancer had a significantly lower isometric knee strength compared with healthy controls (−62.29 N [95% CI: −124.32 to −0.26], I^2 = 94%). However, no difference was found in ankle dorsiflexion strength (−17.86 N [95% CI: −63.77 to 28.04], I^2 = 88%).

Another study of 34 children with leukemia or non-Hodgkin lymphoma reported significantly reduced explosive lower-limb muscle strength (medicine ball throw) and muscle power (five repetitions, sit-to stand) compared with healthy children (respectively, mean difference = −1.85 m [95% CI: −2.85 to −0.70], and 1.49 seconds, [95% CI: 0.68 to 2.29]).[43]

3.5 | Physical performance

Twelve studies (13 patient groups compared to healthy controls), including 517 children diagnosed with all types of cancer, described different aspects of physical performance,[22,34–37,40–45,51] including: walking distance (6-Minute Walk Test),[34,39,44,45] two different measures of functional capacity (the Timed Up and Go Test[22,35,40] and Timed Up and Down Stairs),[35,44] functional mobility (Functional Mobility Assessment Scale),[36] muscle endurance (30-second Sit-to-Stand Test),[22] balance (ultrasound-based motion analysis[37] and static stand),[43] and motor skill development (Movement Assessment Battery for Children,[41,42] Bayley Scales of Infant Development,[41] and the Bruininks–Oseretsky Test of Motor Development).[34]

Children diagnosed with cancer had a significantly shorter walking distance compared with healthy controls (mean difference: −226.71 m [95% CI: −255.26 to −198.16], I^2 = 42%),[34,39,44,45] illustrated in Figure 4A. A sensitivity analysis without imputed data made no difference to the interpretation of the results (Supporting File S7A).

Children diagnosed with cancer had a significantly lower functional capacity (measured with Timed Up and Go) compared with healthy children (mean difference: 0.92 seconds [95% CI: 0.47 to 1.36], I^2 = 79%)[22,35,40] (Figure 4B). A sensitivity analysis without imputed data made no difference to the interpretation of the results (Supporting File S7B).

Two studies reported another measure of functional capacity, using the Timed Up and Down Stairs Test, and showed that children diagnosed with cancer had significantly lower values compared with healthy children (mean difference: 2.19 seconds [95% CI: 1.49 to 2.90], I^2 = 8%)[35,44] (Figure 4C).

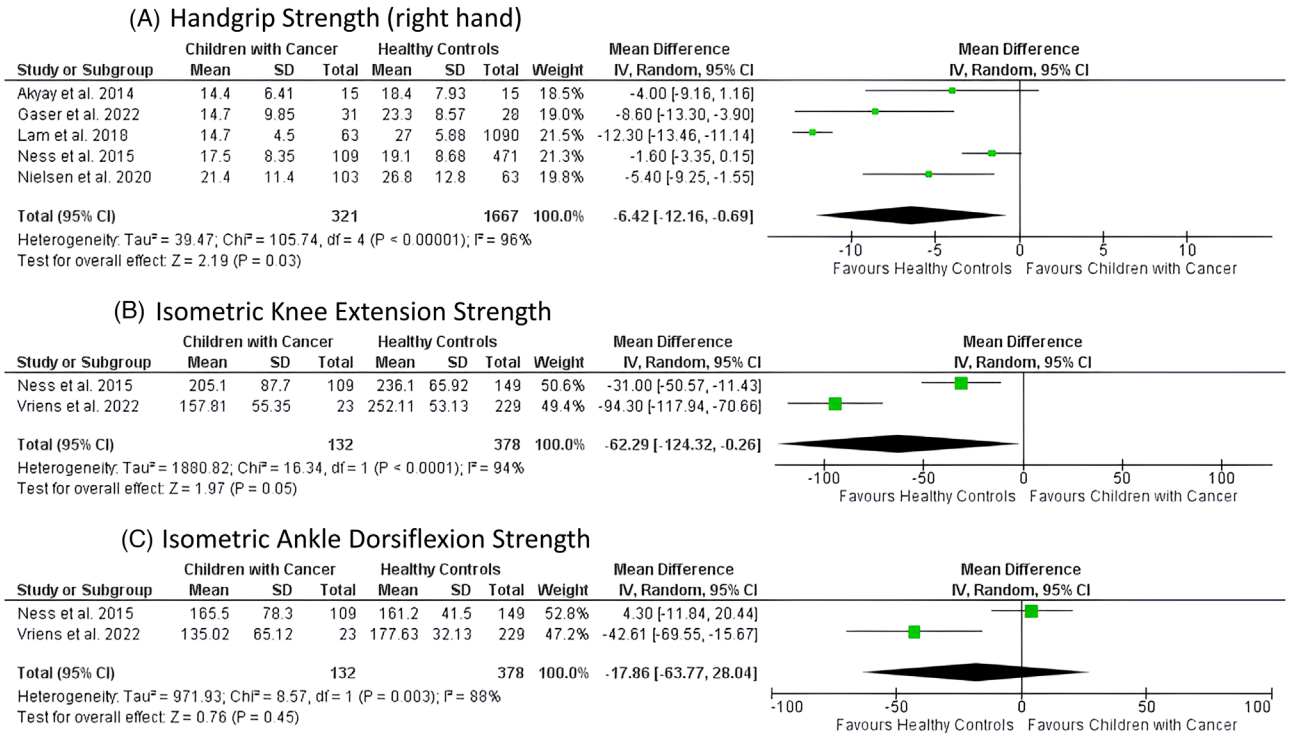

FIGURE 3 (A–C) Meta-analysis of muscle strength. (A) Meta-analysis of handgrip strength (right hand). Three studies did within-study comparisons to either age- and sex-matched controls[22,40,43] or normative data.[34] Lam et al.[49] study was compared with imputed normative handgrip strength values from the McQuiddy Cincinnati cohort.[21] (B) Meta-analysis of isometric knee extension strength: Both studies made within-study comparisons to normative data. (C) Meta-analysis of isometric ankle dorsiflexion strength: Both studies made within-study comparisons to normative data.

Children undergoing preoperative chemotherapy prior to a limb-sparing procedure or amputation[36] had significantly lower functional mobility compared with healthy controls (mean difference: –30.34 Functional Mobility Assesment Scale [FMA] scores [95% CI: –36.15 to –24.53], $I^2 = 74\%$)[36] (Supporting File S8).

Due to clinical heterogeneity between outcomes, it was not possible to conduct a meta-analysis of muscle endurance, balance, or motor skill development.

Nevertheless, one study[22] showed that children diagnosed with cancer ($n = 90$) had significantly reduced lower-limb muscle endurance compared with age- and sex-matched children (30 seconds Sit-to-Stand): mean difference = –7.5 repetitions [95% CI: –9.48 to –5.52].

Three studies[34,41,42] ($n = 174$) showed that children with newly diagnosed ALL had compromised motor skill development. Two studies reported that the average performance was in the lower 23rd ($p < .001$)[34] or 16th percentile ($p < .001$),[41] and one study reported that 36% of children with newly diagnosed cancer were below the 15th percentile[42] compared with healthy controls. All three studies used different outcome measures for motor performance (as presented in Supporting File S2).

One[37] of two studies[37,43] showed that 83% (10 out of 12) children diagnosed with cancer ($n = 45$) had compromised balance (being below 2 standard deviations) compared with normative data. The other study[43] found no significant between-group difference in a static balance test (mean difference = 3.6 ground contacts [95% CI: –2.16 to 8.44], $p = .22$) between children diagnosed with cancer ($n = 32$) and healthy controls ($n = 33$).

One study[37] reported that immediately after tumor removal, 10 of 12 children with cerebellar tumors had abnormal sway using ultrasound-based motion analysis. Two (17%) children had abnormal sway (>2 standard deviations lower than controls) in sitting, six (50%) had abnormal sway during standing, seven (58%) when standing with eyes closed, and 10 (83%) for tandem stance.

3.6 | Adverse events

Five studies ($n = 327$)[22,35,43,44,49] reported no adverse events relating to testing. The remaining studies did not report information regarding adverse events.

3.7 | Deviations from protocol

Due to the limited number of studies, we were unable to perform sensitivity analysis based on diagnostic groups and comorbidities. Further, heterogeneity analyses in continuous data by univariate meta-regressions on mean age and sex distribution were limited to those reported in Supporting Files S6–S8.

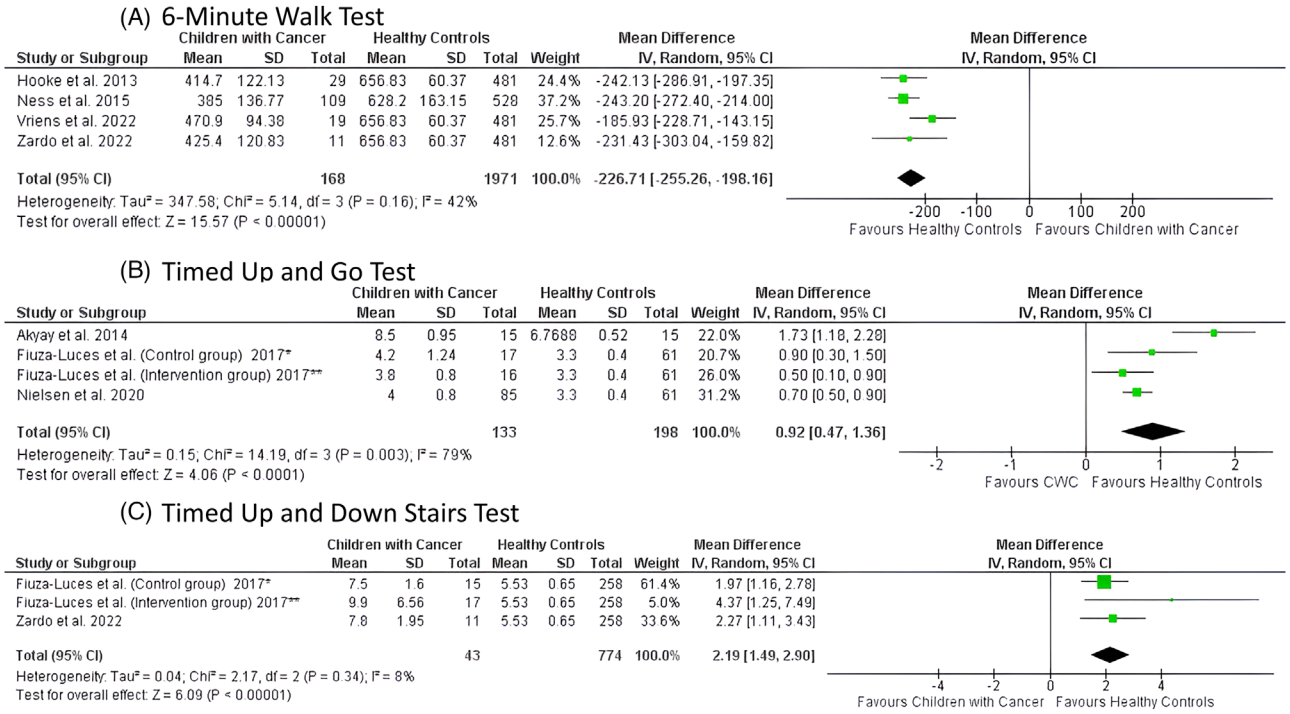

FIGURE 4 (A–C) Meta-analysis of physical performance. (A) Meta-analysis of the 6-Minute Walk Test. Three studies made within-study comparisons to normative data.[34,39,45] Zardo et al.[44] made comparisons to imputed data from the Geiger Cohort.[24] (B) Meta-analysis of the Timed Up and Go Test. Two studies did within-study comparisons to age- and sex-matched controls[22,40] or normative data.[35] Lam et al.[49] study was compared with imputed normative TUG scores from the RESPECT study cohort (Timed Up and Go Test).[22] (C) Meta-analysis of the Timed Up and Down Stairs Test. All studies were compared with imputed normative TUDS scores from the Corral Cohort.[23] * = Within-study intervention group used as patient group for comparison; ** = Within-study control group used as patient group for comparison.

4 | DISCUSSION

The body of evidence shows that children with newly diagnosed cancer have markedly impaired cardiorespiratory fitness, muscle strength, and physical performance compared with healthy children shortly after diagnosis.[22,34–37,39–45,52] Despite the relatively consistent findings across outcomes, the certainty in the evidence is rated very low, meaning that the true effects can be markedly different from the estimated effects. Hence, additional studies exploring specific physical outcome measures within specific diagnostic groups to describe the extent of the impairments are needed.

The physical impairments described in this study are likely due to sedentary behavior[53,54] and treatment-related deficiencies, such as chemotherapy-induced peripheral neuropathy and muscle atrophy,[8,9] and surgical procedures.[37] Because of large heterogeneity in cancer diagnosis as well as in the timing of physical assessment from cancer diagnosis in the included studies (i.e., within 1 month after diagnosis), we are not able to pinpoint if changes in physical capacity are primarily related to diagnosis or a specific treatment modality. From a clinical perspective, we would expect that children with central nervous system (CNS) tumors would present severe deficits compared to other diagnoses due to an often, complex clinical presentation with physical neurological symptoms before treatment and diagnosis[55]; however, we were not able to compare any outcomes within specific diagnosis. Only one of the included studies reports findings before the first administration of chemotherapy.[42] Thus, we cannot infer the impact of cancer diagnosis on children's physical capacity.

Because the literature indicates further deterioration of physical capacity over the course of cancer treatment,[4,22,35,44,56,57] our findings suggest that early initiation of interventions to promote physical activity and exercise in children with cancer are important.

Five of the included studies specifically reported no adverse events related to physical capacity testing; however, most studies did not report data on adverse events. Reporting bias, therefore, undermines our confidence that physical capacity testing is risk-free. Thus, the quality of evidence suggesting that it is safe to participate in testing physical capacity at the time of diagnosis is moderate. Nevertheless, most studies report that participation was approved by the treating physicians or that precautions were taken prior to and during testing regarding potential issues (e.g., history of thrombosis, bleeding, or fractures).[22,35–37,39,41,43,44,49] We recommend that future studies report adverse events and detail the precautions used when testing physical function to provide transparency about safety.

Children newly diagnosed with cancer had, on average, a 25% lower exercise tolerance, 40% lower VO_{2peak}, 27.9% lower handgrip strength, 20% lower knee extension strength, 38% lower walking distance, and 27%–35% lower functional capacity compared with healthy children. Similar degrees of deficits in cardiorespiratory fitness, muscle strength, and physical performance have been found to significantly impact daily-living activities and health-related quality of life.[34,50] Conversely,

ankle dorsiflexion strength[45] and static balance[37,50] were comparable between children with newly diagnosed cancer and healthy children. As these impairments contradict all other findings in this review, including similar outcomes of strength and balance, we do not regard these two findings as evidence that balance and lower leg strength have a later onset. However, the development of chemotherapy-induced neurological deficiencies early in the cancer treatment trajectory, including neuronal firing, sensory regulation, posture, and vestibular impairments, is sparsely investigated.[6] Ideally, the timing of the neurotoxic treatments should be considered when measuring physical capacity in clinical trials. One study tested according to time from vincristine dose (0–5 weeks after treatment initiation) showed that motor performance was affected at baseline and deteriorated further 5 weeks later.[42] This illustrates how the serial collection of data, including baseline assessment and later time points, may be important.

Collectively, multiple physical parameters are affected at the time of diagnosis, triggering limitations in both daily living and potentially social participation, creating unfavorable circumstances for further physical deterioration.

Testing children physically within the first months of treatment is multifaceted and leads to low test adherence. A feasibility study found that 27% of children with different types of cancers could perform cardiopulmonary exercise tests within the first 3 months of cancer treatment.[58] However, tests with lower demands (e.g., handgrip strength, Sit-to-Stand tests) had substantially higher completion rates (83% and 75%, respectively).[58] In line with this, in the quality assessment, most studies included[22,34,36,39,40,42] were rated to be suboptimal in relation to sample representativeness as a consequence of low acceptance and completion of tests. Reasons for not participating in physical testing included lack of permission from the treating physician, conflicting medical appointments, and refusal to participate due to side effects or insufficient motivation, suggesting that the results presented in this review underestimate the prevalence and magnitude of impairments in children newly diagnosed with cancer.

Differences in study population participants and non-participants, as well as risk factors (e.g., body mass index [BMI], pre-diagnosis activity level, or presence of side effects) also introduce bias. Just four studies provided data on non-participants.[34,41,42,49] with no between-group differences, again introducing uncertainty of our estimates.

4.1 | Strengths and limitations

Using imputed normative data can be considered both a strength and limitation. We strived to be transparent when employing these data and used the best-matched normative data as reference values for studies that did not include a matched population or reported an analysis using normative values. Hence, all relevant data were included. However, as only aggregate data were reported (and not individual participant data), a possible bias related to matched data persists. The normative material was therefore chosen first, emphasizing comparability, and second, on population size (power). In one example (Timed Up and Go Test), several large normative datasets (ranging: 176–1481 participants) were available within different age spans; 3–9,[59] 5–13,[60] and 10–21 years.[61] However, because the age span was too narrow in these groups, these datasets were not comparable with the studies included in the review. We, therefore, chose a smaller norm dataset ($n = 61$) that included comparably aged children (age 6–18 years).[22] To account for between-group variance, we used a conservative approach and employed an inverse variance random effects model. Further, to assess the influence of imputations on results, sensitivity analysis was conducted without imputed data. These did not change the interpretation of our results.

We carefully discussed the clinical heterogeneity between studies before conducting the meta-analysis. However, a limitation of this study is that the results are based on studies with various types of cancer. Therefore, the observed acute treatment-related toxicity and physical capacity may be different within each diagnostic group. Again, sensitivity analysis was planned to investigate this indirectness, which was often impossible due to the limited number of studies. One sensitivity analysis of handgrip strength showed no differences in interpreting the results between children diagnosed with ALL and children with various cancer diagnoses.

4.2 | Implications for practice and research

Several controlled trials[22,35,43,57] have investigated the effectiveness of physical activity interventions during cancer treatment, with promising results. To fully describe and understand the immediate deterioration of physical capacity at cancer diagnosis, larger studies with high test-completion rates stratified by diagnosis, treatment duration, and descriptions of individual risk and prognostic factors are needed.

To assess physical capacity sufficiently with a minimum of treatment-related toxicities and to screen for early-onset physical deficiencies, we consider standardized testing in the early assessment of children with cancer highly relevant. Early detection of physical capacity deficiencies would allow risk assessments: detecting and clarifying the severity of deficiencies, which may otherwise be overlooked, as children with cancers onset of sedentary behavior may be downplayed as being a temporary consequence of the logistics of being hospitalized and receiving treatment than physical deficiencies. Further, this would guide healthcare facilities in allocating resources effectively, providing tailored treatment plans regarding exercise and physical activity, ensuring that patients receive the appropriate level of care and support. Ideally, assessment should be conducted using outcome measures with known and acceptable measurement properties for children. However, strenuous assessment methods (e.g., cardiopulmonary exercise tests) are a barrier to testing physical capacity in the early stages of cancer treatment.[58] Assessment procedures should, therefore, place emphasis on being practical, quick, and validated for children with cancer or, at the very least, be appropriate for children.[24,62–64] Based on our and previous studies, outcome measures (e.g., Six-Minute Walk Test, handgrip strength, Timed Up and Go, and Sit to Stand) have been found to have acceptable

measurement properties and should, hence, be considered feasible in a clinical setting. If these tests are routinely obtained in clinical practice and documented in medical records, this could allow larger pro- and retrospective studies.

5 | CONCLUSION

This review indicates that physical capacity is markedly impaired among children with cancer within the first month after diagnosis. However, the certainty of the evidence was very low for all outcomes, limiting our confidence in the outcome estimates. Importantly, our results indicate that physical capacity testing appears to be safe, as no adverse effects were reported.

We therefore recommend early initiatives to promote physical activity and exercise to mitigate these effects. As some uncertainty persists, we recommend an individual-based combined exercise intervention.

To understand these mechanisms further and ensure adequate rehabilitation, early and ongoing screening for impaired physical capacity should be implemented into clinical practice.

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CONFLICT OF INTEREST STATEMENT

The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The views expressed in the submitted article are the authors own and not an official position of the institution or funder. None of the funders had any role in the design of this study, in the collection of data, the analysis, the interpretation of data, or the dissemination of data.

DATA AVAILABILITY STATEMETNT

All data generated or analyzed during this study are included in this published article and its Supporting Information files.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Supplementary file 1: Search string

POPULATION	OUTCOME	STUDY TYPE
#1 Neoplasms[mh] OR cancer*[tiab] OR carcinom*[tiab] OR leucaemia*[tiab] OR leucemia*[tiab] OR leukaemia*[tiab] OR leukemia*[tiab] #2 Adolescent[mh] OR Adolescen*[tiab] OR Child[mh] OR Child*[tiab] OR Paediatric*[tiab] OR Pediatric*[tiab] OR Pediatrics[mh:noexp] OR Young*[tiab] OR Youth[tiab] OR Teen*[tiab] #4 Animals[mh] NOT humans[mh]	#3 1RM[tiab] OR "6-minute walk test"[tiab] OR "6 minute walking test"[tiab] OR 6MWD[tiab] OR 6MWT[tiab] OR "Aerobic capacity"[tiab] OR "Bruininks-Oseretsky"[tiab] OR "Cardiopulmonary function"[tiab] OR "Cardiopulmonary performance"[tiab] OR Cardiorespiratory Fitness[mh] OR "Cardiorespiratory fitness"[tiab] OR "Cardiorespiratory function"[tiab] OR "Cardiorespiratory performance"[tiab] OR Exercise Test[mh] OR Exercise Tolerance[mh] OR "Exercise tolerance"[tiab] OR "Fitness level"[tiab] OR "Functional assessment"[tiab] OR "Functional capacity"[tiab] OR "Functional evaluation"[tiab] OR "Functional mobility"[tiab] OR "Functional status"[tiab] OR Gait[mh] OR Gait[tiab] OR "Grip strength"[tiab] OR "Gross motor function"[tiab] OR Hand Strength[mh] OR "Handgrip dynamometry"[tiab] OR "Muscle force"[tiab] OR "Muscle power"[tiab] OR Muscle Strength[mh] OR "Muscle strength"[tiab] OR	#5 Case Reports[pt] OR Case report*[ti] OR Case report*[ot] OR Case stud*[ti] OR Case stud*[ot] OR Meta-Analysis[pt] OR Meta-analysis[ti] OR Meta-analysis[ot] OR Review[pt] OR Review[ti] OR Review[ot] OR Systematic Review[pt] #6 Journal article[pt]

	"Muscular force"[tiab] OR "Muscular power"[tiab] OR "Muscular strength"[tiab] OR "O2 consumption"[tiab] OR "O2 uptake"[tiab] OR "Oxygen consumption"[mh] OR "Oxygen consumption"[tiab] OR "Oxygen uptake"[tiab] OR "One-repetition maximum"[tiab] OR Peabody Developmental Motor Scale*[tiab] OR "Peak oxygen"[tiab] OR "Physical capacity"[tiab] OR Physical Endurance[mh] OR "Physical endurance"[tiab] OR Physical Fitness[mh] OR "Physical fitness"[tiab] OR "Physical function"[tiab] OR "Physical performance"[tiab] OR Postural Balance[mh] OR "Postural balance"[tiab] OR "Shuttle walk"[tiab] OR "Six-minute walk test"[tiab] OR "Six-minute walking test"[tiab] OR Stair climb*[tiab] OR Stair Climbing[mh] OR Strength[tiab] OR VO2max[tiab] OR VO2peak[tiab] OR Walk Test[mh] OR "Walk test"[tiab] OR Walking capacit*[tiab]	
Search used: ((#1 AND #2 AND #3) NOT (#4 OR #5)) AND #6		
Search used in **International Clinical Trials Registry Platform (ICTRP):** ((#1 AND #2 AND #3) NOT #4)		

SUPPLEMENTARY FILE 2 Summary of study characteristics

Study, (year), country, design	Study sample	Sample used in SR (n) within each outcome	Diagnosis	Age at diagnosis (years)	Time since diagnosis	Control group: *healthy age- and sex-matched children or normative (imputed or non-imputed) data from other studies*	Adverse events related to testing	Summary of reported outcomes (children with cancer vs. healthy ref.)
Gaser et al. (2022), Germany, RCT (36)	41 of 70 eligible participants (71%)	34 (67 % males) **Handgrip strength** n = 31 **Medicine ball shot** n = 24 **Sit-to-stand n** = 32 **Static stand n** = 32	ALL, AML, or NHL	Mean age 9.8 years (range 5-17 years)	Within 31 days of diagnosis	***Age and sex-matched Children:*** **Handgrip strength** n = 28 **Medicine ball shot** n = 28 **Sit-to-stand n** = 33 **Static stand n** = 33	Reported: No adverse events	**Handgrip strength ↓** **Medicine ball shot ↓** **Sit-to-stand ↓** **Static stand ↓**
Vriens et al. (2022), Belgium, prospective cohort study (38)	62 of 95 eligible participants (60% male)	23 (57% males) **Isometric ankle and knee strength** n = 23 **6MWT** n = 19	ALL and LBL	Mean age 7.6 ± 4.3 years, For this review (10.3 ± 3.9) [Range 6-18 years]	Within 7 days of diagnosis (pre-phase)	***Normative data from the Beenakker Cohort*** **Isometric ankle and knee strength** n = 229 ***Normative data from the Geiger Cohort*** **6MWT** n = 481	Not reported	**Isometric ankle strength →** **Isometric knee strength ↓** **6MWT ↓**
Zardo et al. (2022), Italy, prospective cohort study (and case-control study) (37)	97 of 255 eligible participants (54% male)	11 (72% males) **Adapted Yo-Yo Intermittent Recovery Test** n = 11 **6MWT** n = 11 **Timed-up-and-down-stairs** n= 11	Any hematological malignancy	Mean age 10.58 ± 4.5 years (range 7-19 years) For this review 12.7 years (range: 8-17 years)	Within 30 days of diagnosis	***Healthy age- and sex-matched Children:*** **Adapted Yo-Yo Intermittent Recovery Test** n = 18 ***Imputed normative data from the Geiger Cohort (No normative data within study comparisons)*** **6MWT** n = 481 ***Imputed normative data from the Corral Cohort (No normative data within study comparisons)*** **Timed up and down stairs** n= 258	Reported: No adverse events	**Adapted Yo-Yo Intermittent Recovery Test ↓** **6MWT ↓** **Timed-up-and-down-stairs ↓**
Nielsen et al. (2020), Denmark, Quasi-experimental (22)	170 of 235 eligible participants (63% male)	170 (62,5% males) **Peak oxygen uptake (VO2peak)**: n = 38	All diagnoses (any cancer diagnosis or Langerhans cell histiocytosis (LCH) or myelodysplastic syndrome (MDS))	Mean age11.1 years old [range 6-17.9 years]	Within 31 days of diagnosis	***Age and sex-matched reference values:*** **Sit-to-stand**: n = 62 **Timed-up-and-go** n = 61 **Handgrip strength** n = 63	Reported: No adverse events	**VO2peak ↓** **Sit-to-stand ↓** **Timed-up-and-go ↓** **Handgrip strength ↓**

ALL = Acute Lymphoblastic Leukemia, AML = Acute Myeloid Leukemia, NHL = Non-Hodgkin's Lymphoma, LBL = Lymphoblastic lymphoma, 6MWT = Six-minute-walk test

→ = similar values in healthy references, ↓= impaired values compared to healthy reference

		Sit-to-stand: n = 90 **Timed-up-and-go** n = 85 **Handgrip strength** n = 103				***Normative data from the European Heart Study and the Copenhagen School Child Intervention Study*** **Peak oxygen uptake (VO2peak)**: n = 255		
Lam et al. (2018) China, RCT (42)	63 (50 % male)	**Handgrip strength** n = 63	All types of cancer	Mean age 12.7 years old [range 9-18 years]	Within 31 days of diagnosis	***Imputed Normative data from the McQuiddy Cincinnati Cohort (No normative data within study comparisons)*** **Handgrip strength***:* n = 1,090	Reported: No adverse events "Throughout the study period, no adverse events or serious adverse events were reported by participants"	**Handgrip strength ↓**
Corr et al. (2017) USA, Quasi-experimental (40)	49 (71 % male) Divided into two within study intervention (n=14 and control (n=35) group	**Functional mobility assessment** n = 49	lower extremity malignancies	Mean age13.5 years old [range 8-20 years]	1-2 weeks after treatment initiation	***Imputed Normative data from the Marchese Cohort (No normative data within study comparisons)*** **Functional mobility assessment** n = 503	Not reported	**Functional mobility assessment ↓**
Fiuza-Luces et al. (2017) Spain, RCT (39)	49 (71% male) Divided into two within-study intervention (n=24 and control (n=25) group	49 (71% males) **Peak oxygen uptake (VO2peak)** n = 29 **Timed-up-and-go, n** = 33 **Timed-up-and down-stairs** n= 32	Extracranial solid tumor	Mean age 10.0 years old [range 4-16 years]	Within 31 days of diagnosis	***Imputed Normative data from the European Heart Study and the Copenhagen School Child Intervention Study (No normative data within study comparisons)*** **Peak oxygen uptake (VO2peak)** n = 255 ***Imputed Normative data from the RESPECT study cohort:*** **Timed-up-and-go, n** = 61 ***Imputed normative data from the Corral Cohort (No normative data within study comparisons)*** **Timed up and down stairs** n= 258	Reported: No adverse events "no major adverse events or health-related issues attributable to the testing sessions or prescribed training sessions were noted"	**VO2peak ↓** **Timed-up-and-go ↓** **Timed up and down stairs ↓**
Ness et al. (2015) USA, Cross-sectional study (35)	109 of 211 eligible participants (65% male)	**Isometric ankle and knee strength** n = 109 **Handgrip strength** *n = 109* **6MWT** n = 109 **Bruininks-Oseretsky Test of Motor**	ALL	Median age 10 years old [range 4-18 years]	Within 7-10 days of diagnosis	***Normative data from the Nyström Eek Cohort*** **Isometric Muscle Torque** n= 149 ***Normative data from the Mathiowetz Cohort*** **Handgrip strength** *n = 471* ***Normative data from the Geiger Cohort***	Not reported	**Isometric ankle and knee strength ↓** **Handgrip strength ↓** **6MWT ↓** **Bruininks-Oseretsky Test of Motor Proficiency ↓**

ALL = Acute Lymphoblastic Leukemia, AML = Acute Myeloid Leukemia, NHL = Non-Hodgkin's Lymphoma, LBL = Lymphoblastic lymphoma, 6MWT = Six-minute-walk test

→ = similar values in healthy references, ↓= impaired values compared to healthy reference

		Proficiency n= 109				**6MWT** n = 528 ***Normative data from the Bruininks-Oseretsky Test cohort*** **Bruininks-Oseretsky Test of Motor Proficiency** (Age-specific percentile ranks were used for analysis)		
Akyay et al. (2014), Cohorte study (44)	15 (60% male)	**Handgrip strength** n = 15	ALL	Mean 9.7 years old [range: 4.5-17 years]	Within 31 days of diagnosis	***Healthy age- and sex-matched Children:*** **Handgrip strength:** n = 15	Not reported	**Handgrip strength ↓**
Hooke et al. (2013), USA, Quasi-experimental (43)	29 (65% male)	**6MWT = 29**	ALL (n= 9) Lymphoma (n=12), Solid Tumors (n=8)	Mean 10.6 years old [range: 6-17 years]	Between 15 and 29 days from treatment initiation	***Normative data from the Geiger Cohort*** **6MWT:** n=481	Not reported	**6MWT ↓**
Hartman et al. (2009), Netherlands, RCT (45)	51 of 67 eligible participants (56% male)	51 (56% males) **Movement-ABC and Bayley Scales of Infant Development** = 51	ALL	Median age: 5.4 years old [range 1.3-17.1 years old]	Within 31 days of diagnosis	***Normative values on motor performance based on the Bayley Scales of Infant Development (children <3.5 years) and the Movement Assessment Battery for Children (Movement-ABC)(children aged >4 years).***	Not reported	**Movement-ABC ↓** **Bayley Scales of Infant Development ↓**
Küper et al. (2013), Germany, prospective Cohorte study (41)	12 (50% male)	**Balance** n = 12	Cerebellar Tumor	Mean age11.1 years old [range 6–17 years]	Within 31 days of diagnosis(mean 14.8 days after surgery)	***Healthy age- and sex-matched Children:*** ***Balance: n=11***	Not reported	**Balance →**
Reinders-Messelink et al. (1999), the Netherlands, prospective Cohorte (46)	17 (64% male)	14 (no data characteristics available) **Movement ABC** *n = 14*	ALL	Median 5.8 years old [range 4.0 – 12.6]	Within one month of diagnosis (One week before first vincristine dose)	***Healthy age- and sex-matched Children:*** ***Motor Performance (Movement ABC)*** *n = 10*	Not reported	**Movement ABC ↓**

ALL = Acute Lymphoblastic Leukemia, AML = Acute Myeloid Leukemia, NHL = Non-Hodgkin's Lymphoma, LBL = Lymphoblastic lymphoma, 6MWT = Six-minute-walk test

→ = similar values in healthy references, ↓= impaired values compared to healthy reference

Supplementary file 3:

Characteristics of Future Studies

(Identified through World Health organization's International Clinical Trial Registry)

Public Title	Primary sponsor:	Main ID	Recruitment Status	Prospective registration	Date of Registration
Functional Capacity and Fatigue in Children and Adolescents in Cancer Treatment Performing Physical Activity	Universidade Federal de Santa Catarina, Brazil	RBR-7j4rkbz	Not Recruiting	No	2022-11-18
Effect of Dual-Task Training on Pediatric Oncology Patients	Afyonkarahisar Health Sciences University, Turkey	NCT05118464	Recruiting	Yes	2021-10-31
FiGHTING F!T: An exercise program for adolescents and young adults during cancer treatment in Western Australia	The University of Western Australia, Australia	ACTRN12620000663954	Not Recruiting	No	2020-06-10
Influence of different physiological exercise forms as well as a relaxation intervention on cancer-related fatigue, the current state of health and haematological / endocrinological parameters in paediatric oncological patients in acute therapy	Deutsche Sporthochschule Köln, Institut für Bewegungs- und Neurowissenschaft, Germany	DRKS00020902	Not Recruiting	Yes	2020-03-13
Quality of Life in Motion: A combined physical exercise and psychosocial training program to improve physical fitness in children with cancer.	VU university medical center Wilhelmina Children's Hospital, UMC Utrecht, Netherlands	NTR1531	Not Recruiting	Yes	2008-11-12
Integrative Neuromuscular Training in Adolescents and Children Treated for Cancer	Rigshospitalet, Denmark	RBR-7j4rkbz	Recruiting	Yes	2021-01-05
Rehabilitation Including Structured Active Play for Preschoolers With Cancer.	Rigshospitalet, Denmark	NCT05118464	Recruiting	Yes	2020-12-03
Exercise Training in Childhood Cancer FORTEe	Johannes Gutenberg University Mainz, Germany	NCT05289739	Recruiting	Yes	2022-01-18

Supplementary file 3: Characteristics off future studies identified through World Health organization's International Clinical Trial Registry.

SUPPLEMENTARY FILE 4

Characteristics of included studies

Gaser et al. (2022). Effects of strength exercise interventions on activities of daily living, motor performance, and physical activity in children and adolescents with leukemia or non-Hodgkin lymphoma: Results from the randomized controlled ActiveADL Study

Country	Germany
Design	Randomized Controlled Trial
Participants	41 children and adolescents with acute lymphoblastic leukemia, acute myeloid leukemia, or non-Hodgkin's lymphoma The author group was contacted and provided data on 34 participants that had participated in baseline assessment within one month of diagnosis Mean age 9.8 years (range 5-17 years)
Control	34 age and sex-matched children
Outcomes and assessment methods Children with cancer versus healthy reference (mean±SD)	Muscle strength: **Handgrip strength (right hand): Hand grip dynamometer (kg)** 14.7 ± 9.85(n=31) vs 23.3 ± 8.57 (n=28) **Explosive muscle strength: Medicine ball shot (meters)** 2.96± 1.00 (n=24) vs 4.90 ± 1.98 (n=28) **Muscle strength: Five repetitions sit-to-stand** 8.2± 2.56 (n=32) vs 6.6± 1.04 (n=28) Physical Performance: **Static Balance: Static stand (ground contact)** 13.75± 10.52 (n=32) vs 10.05± 5.93 (n=33) **Adverse Events:** No adverse events were reported Other Outcomes reported (but excluded from this review): **Handgrip strength (left hand): Hand grip dynamometer (kg)** **Eye-hand coordination: Inserting pins** **Reaction time on optical stimuli, eye-hand coordination: Reaction test** **Coordination with precision: Throwing at a target** **Flexibility: Stand-and-reach**
Funding source	Funded by German José Carreras Leukemia Foundation, grant number DJCLS 15R/2016.
Reference	Gaser D, Peters C, Oberhoffer-Fritz R, Götte M, Feuchtinger T, Schmid I, Haller B, von Luettichau I, Kesting S. Effects of strength exercise interventions on activities of daily living, motor performance, and physical activity in children and adolescents with leukemia or non-Hodgkin lymphoma: Results from the randomized controlled ActiveADL Study. Front Pediatr. 2022 Nov 8;10:982996. doi: 10.3389/fped.2022.982996. PMID: 36425395; PMCID: PMC9679409.

Vriens et al. (2022). Physical fitness throughout chemotherapy in children with acute lymphoblastic leukaemia and lymphoma

Country	Belgium
Design	Prospective Cohort Study
Participants	62 children and adolescents with acute lymphoblastic leukemia or lymphoblastic lymphoma The author group was contacted and provided data on 23 participants that had participated in baseline assessment within one month of diagnosis Mean age: 10.3 years, range 6-18 years
Control	229 and 481 normative values from the Beenakker Cohort (muscle torque) and Geiger Cohort (Six-minute walk test), respectively
Outcomes and assessment methods Children with cancer versus healthy reference (mean±SD)	Muscle strength: **Isometric knee extension strength (right): Hand-held dynamometer (newton) 157.81 ± 55.35 (n=23) vs 252.11 ± 53.13 (n=229)** **Isometric ankle dorsiflexion strength (right): Hand-held dynamometer (newton) 135.02 ± 65.12 (n=23) vs 177.63 ± 32.03 (n=229)** Physical performance: **Walking Distance: Six-minute-walk test (meters) 470.90 ± 94.38 (n=19) versus 656.832 ±60.37.15 (n=481)** **Adverse Events:** No adverse events were reported Other Outcomes reported (but excluded from this review): **Muscle strength: Standing broad jump** (no data available within the first month of diagnosis)
Funding source	None reported
Reference	Vriens A, Verschueren S, Vanrusselt D, Troosters T, Gielis M, Dirix V, Vanderhenst E, Sleurs C, Uyttebroeck A. Physical fitness throughout chemotherapy in children with acute lymphoblastic leukaemia and lymphoma. Eur J Pediatr. 2023 Feb;182(2):813-824. Doi: 10.1007/s00431-022-04741-z. Epub 2022 Dec 8. PMID: 36482087.

Zardo et al. (2022). The Impact of a Precision-Based Exercise Intervention in Childhood Hematological Malignancies Evaluated by an Adapted Yo-Yo Intermittent Recovery Test

Country	Italy
Design	Prospective Cohort Study (and Case-Control Study)
Participants	97 children and adolescents with any hematological malignancy. The author group was contacted and provided data on 11 participants that had participated in baseline assessment within one month of diagnosis Mean age: 12.7 years, range 8-17 years
Control	18 Healthy age- and sex-matched Children: Adapted Yo-Yo Intermittent Recovery Test Imputed normative data from the Geiger Cohort (No normative data within study comparisons): 6MWT n = 481 Imputed normative data from the Corral Cohort (No normative data within study comparisons): Timed up and down stairs n= 258
Outcomes and assessment methods Children with cancer versus healthy reference (mean±SD)	Cardiorespiratory fitness: **Adapted Yo-Yo Intermittent Recovery Test (meters): 723.6±299.6 (n=11) versus 1754 ± 444 (n=18)** Physical performance: **Six-min-walk test (meters): 425.4 ± 120.83 (n= 11) versus 656.83 ±60.37 (n=481)** **Timed-up-and down stairs (sec.): 7.8 ± 1.95 (n= 11) versus 5.53 ±0.65 (n=258)** **Adverse Events:** No adverse events were reported Other Outcomes reported (but excluded from this review): **Muscle strength: Five maximum repetitions test (5RM)** (no healthy reference available)
Funding source	Supported by the parents' charity association, "Comitato Maria Letizia Verga", "Fondazione Camerani and Pintaldi", and "Rolex Foundation" through private funds
Reference	Zardo W, Villa E, Corti E, Moriggi T, Radaelli G, Ferri A, Marzorati M, Eirale C, Vago P, Biondi A, Jankovic M, Balduzzi A, Lanfranconi F. The Impact of a Precision-Based Exercise Intervention in Childhood Hematological Malignancies Evaluated by an Adapted Yo-Yo Intermittent Recovery Test. Cancers (Basel). 2022 Feb 25;14(5):1187. doi: 10.3390/cancers14051187. PMID: 35267495; PMCID: PMC8909675.

Nielsen et al. (2020). Effects of a physical activity program from diagnosis on cardiorespiratory fitness in children with cancer: a national non-randomized controlled trial

Country	Denmark
Design	Quasi-Experimental/Non-Randomized Controlled Study
Participants	107 children and adolescents with any cancer diagnosis, Langerhans cell histiocytosis (LCH) or myelodysplastic syndrome (MDS)) malignancy. Mean age: 11.1 years, range 7-17.9 years
Control	63 Age and sex-matched reference values: Sit-to-stand: n = 62, Timed-up-and-go n = 61, Handgrip strength n = 63 Normative data from the European Heart Study and the Copenhagen School Child Intervention Study: Cardiopulmonary exercise test (VO2peak): n = 255
Outcomes and assessment methods Children with cancer versus healthy reference (mean±SD)	Cardiorespiratory fitness: **Peak oxygen uptake - VO2peak (ml/kg/min), Cardiopulmonary exercise test (CPET): 27.4±6.97 (n=38) versus 47.7 ± 7.7 (n=255)** Muscle strength: **Hand Grip strength (kg), Right: 21.4 ± 11.4 (n=103) vs. 26.8 ± 12.8 (n=63) **** Physical performance: **Sit-to-stand (repetitions): 25.1 ± 6.4 (n=90) vs. 31.8 ± 4.5 (n=62) **** **Timed-up-and-go (seconds: 4.0 ± 0.8 (n=85) vs. 3.3 ± 0.4 (n=61) **** **Adverse Events:** No adverse events were reported Other Outcomes reported (but excluded from this review): **Hand Grip strength (kg), Left: 20.0±10.8(n=104) vs. 24.3 ± 11.8 (n=63)**** **Max watt (watt) (no baseline comparisons to healthy reference)** **Flamingo balance (hits) (no baseline comparisons to healthy reference)**
Funding source	Supported by 106773/TrygFonden (DK)/ International, 201344/Børnecancerfonden/ International, 2956/ML Jørgensen og Gunnar Hansens Fond /International, KJ/BG 8871 H/ Toyota Foundation/International
Reference	Nielsen, M.K.F., Christensen, J.F., Frandsen, T.L. et al. Effects of a physical activity program from diagnosis on cardiorespiratory fitness in children with cancer: a national non-randomized controlled trial. BMC Med 18, 175 (2020). https://doi.org/10.1186/s12916-020-01634-6

Lam et al. (2018). An integrated experiential training programme with coaching to promote physical activity, and reduce fatigue among children with cancer: A randomised controlled trial

Country	China
Design	Randomized Controlled Study
Participants	63 children and adolescents with any cancer diagnosis Mean age: 12.7 years, range 9-18 years
Control	Imputed Normative data from the mcquiddy Cincinnati Cohort (No normative data within study comparisons): Handgrip strength: n = 1,090
Outcomes and assessment methods Children with cancer versus healthy reference (mean±SD)	Muscle strength: **Hand Grip strength (kg), Right: 14.7 ± 4.5 (n=63) vs. 19.1 ± 8.68 (n = 1,090)** **Adverse Events:** No adverse events were reported Other Outcomes reported (but excluded from this review): **Left-hand grip strength** **Self-reported Cancer-related fatigue** **Physical activity levels** **Self-reported Physical Activity Self-Efficacy** **Self-reported Quality of Life**
Funding source	None reported: "This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors"
Reference	Lam KKW, Li WHC, Chung OK, Ho KY, Chiu SY, Lam HS, Chan GCF. An integrated experiential training programme with coaching to promote physical activity, and reduce fatigue among children with cancer: A randomised controlled trial. Patient Educ Couns. 2018 Nov;101(11):1947-1956. doi: 10.1016/j.pec.2018.07.008. Epub 2018 Jul 7. PMID: 30007765.

Corr et al. (2017). Feasibility and functional outcomes of children and adolescents undergoing preoperative chemotherapy prior to a limb-sparing procedure or amputation

Country	USA
Design	Quasi-Experimental Study
Participants	49 children and adolescents with lower extremity malignancies (osteosarcoma, Ewing's sarcoma, and an undifferentiated sarcoma involving the soleus muscle) (71.4 % males) Divided into two within-study intervention (n=14) and control (n=35) groups Mean age: 13.5 years old, range 8-20 years
Control	Imputed Normative data from the Marchese Cohort (No normative data within study comparisons) Functional mobility assessment (FMA), n = 503
Outcomes and assessment methods Children with cancer versus healthy reference (mean±SD)	Physical Performance: **FMA total:** Within-study intervention group: **31.9 ±5.0 versus 59.57±5.39** Within-study control group: **25.9 ±16.0 versus 59.57±5.39** (FMA is a composite measure consisting of (1) pain; (2) function using timed up and down stairs (TUDS), time and timed up and go (TUG) time, heart rate (HR) and rate of perceived exertion (RPE) are also assessed during the TUDS and TUG; (3) use of assistive devices; (4) satisfaction with walking quality; (5) participation in work, school, sports; and (6) endurance measured by the 9-Minute Walk-Run (9MWR)) **Adverse Events:** No adverse events were reported
Funding source	This study was financially supported by a grant from the Tennessee Physical Therapy Association.
Reference	Corr AM, Liu W, Bishop M, Pappo A, Srivastava DK, Neel M, Rao B, Wilson T, Ness KK. Feasibility and functional outcomes of children and adolescents undergoing preoperative chemotherapy prior to a limb-sparing procedure or amputation. Rehabil Oncol. 2017 Jan;35(1):38-45. PMID: 28948112; PMCID: PMC5609724.

Fiuza-Luces et al. (2017). Exercise Intervention in Pediatric Patients with Solid Tumors: The Physical Activity in Pediatric Cancer Trial

Country	Spain
Design	Randomized Controlled Study
Participants	49 children and adolescents with extracranial solid tumors Divided into two within-study intervention (n=24) and control (n=25) groups Mean age: 10.0 years old, range 4-16 years
Control	Imputed Normative data from the European Heart Study and the Copenhagen School Child Intervention Study (No normative data within study comparisons) Peak oxygen uptake (VO2peak): n = 255 Imputed Normative data from the RESPECT study cohort: Timed-up-and-go: n = 61 Imputed normative data from the Corral Cohort (No normative data within study comparisons) Timed up and down stairs: n= 258
Outcomes and assessment methods Children with cancer versus healthy reference (mean±SD)	Cardiorespiratory Fitness (as reported in original study): **Peak oxygen uptake - VO2peak (ml/kg/min), Cardiopulmonary exercise test (CPET) (Treadmill tests only):** **Within-study Exercise group:** **1291 ± 167 (SEM) (n=15)** **Within-study control group:** **1167±206 (n=14)** Cardiorespiratory Fitness (as reported in Systematic review - author group was contacted to provide results in ml/kg/min): **Peak oxygen uptake - VO2peak (ml/kg/min), Cardiopulmonary exercise test, CPET:** Within-study Exercise group: **28.7 ± 7.75 (SD calculates from SEM=2.0) (n=15) versus 47.7 ± 7.7 (n=255) (from Nielsen 2020)** Within-study control group: **29.1±6.73 (SD calculated from SEM=1.8) (n=14) versus 47.7 ± 7.7 (n=255) (from Nielsen 2020)** Physical Performance: **Timed-up-and-go (sec.)** Within-study Exercise group: **3.8±0.8 (SD calculated from SEM = 0.2) (n=16) versus 3.3 ± 0.4 (n=61) (from Nielsen 2020)** Within-study control group: **4.2 ± 1.24 (SD calculated from SEM = 0.3) (n=17) versus 3.3 ± 0.4 (n=61) (from Nielsen 2020)** **Timed-up-and-down-stairs:** Within study Exercise group: **9.9 ± 6.56 (calculated from SEM =1.6) n= 17 versus 5.53 ±0.65 (n=258) (from Corral et al. 2021)**

	Within study control group: **7.5 ± 1.6 (calculated from SEM = 0.4) (n=15) versus 3.3 ± 0.4 (n=61) (from Nielsen 2020**) **Adverse Events:** "no major adverse events or health-related issues attributable to the testing sessions or prescribed training sessions were noted" Other Outcomes reported (but excluded from this review): **Physical Activity Levels** **Self-reported quality of life**
Funding source	Alejandro Lucia and Steven J. Fleck are supported by a grant from the National and Strength Conditioning Association (NSCA). A Lucı´a is also supported by a grant from Ca´ tedra Real Madrid-Universidad Europea (2015/UEM07) and Fondo de Investigaciones Sanitarias and Fondos Feder (FIS, grant PI12/00914 and PI15/00558). Luisa Soares-Miranda is supported by grant SFRH/BPD/76947/2011 funded by FCT (QREN-POPH-Type 4.1—Advanced training, subsidized by the European Social Fund and national funds of MEC), PTDC/DES/099018/2008 - FCT/FCOMP-01- 0124-FEDER-009573, and The Research Centre in Physical Activity Health and Leisure issupported by FCT: UID/DTP/00617/2013. Carmen Fiuza-Luces issupported by a research contract ''Sara Borrell'' (ISCIII-MINECOSpain/FEDER-EU, CD14/00005). Antonio Pe´ rez-Martı´nez is supported in part by National Health Service of Spain grant FIS (ISCIII-MINECOSpain/FEDER-EU PI12/01622) and CRIS Cancer Foundation (https://www.criscancer.org/en/index.php)
Reference	Fiuza-Luces C, Padilla JR, Soares-Miranda L, Santana-Sosa E, Quiroga JV, Santos-Lozano A, Pareja-Galeano H, Sanchis-Gomar F, Lorenzo-González R, Verde Z, López-Mojares LM, Lassaletta A, Fleck SJ, Pérez M, Pérez-Martínez A, Lucia A. Exercise Intervention in Pediatric Patients with Solid Tumors: The Physical Activity in Pediatric Cancer Trial. Med Sci Sports Exerc. 2017 Feb;49(2):223-230. doi: 10.1249/MSS.0000000000001094. PMID: 27631396.

Ness et al. (2015). Skeletal, neuromuscular and fitness impairments among children with newly diagnosed acute lymphoblastic leukemia.

Country	USA
Design	Cross-Sectional Study
Participants	109 children and adolescents with ALL Median age 10 years old, range 4-18 years
Control	Normative data from the Nyström Eek Cohort Isometric Muscle Torque n= 149 Normative data from the Mathiowetz Cohort Handgrip strength n = 471 Normative data from the Geiger Cohort 6MWT n = 528 Normative data from the Bruininks-Oseretsky Test of Motor Proficiency (Age-specific percentile ranks were used for analysis)
Outcomes and assessment methods Children with cancer versus healthy reference (mean±SD)	Muscle strength: **Isometric Lower extremity strength (Newtons) —Hand-Held Myometry - knee extension, "Break test":** **Right knee: 205.1 ± 87.70 (SD calculated from SEM = 8.4) (n=109) vs 236.1 ± 65.92 (SD calculated from SEM = 5.4)** **Isometric Lower extremity strength (n) —Hand-Held Myometry - ankle dorsiflexion, "Break test":** **Right Ankle: 165.5 ± 78.30 (SD calculated from SEM = 7.5) (n=109) vs 161.2 ± 41.50 (SD calculated from SEM = 3.4**) **Hand Grip strength (kg) – Jamar® hand held dynamometer:** **Handgrip (kg)** **Right hand: 17.5 ± 8.35 (SD calculated from SEM = 0.4) vs. 19.1 ± 8.68 (SD calculated from SEM = 0.8)** Physical performance: **Six-Minute Walk Test:** **385.0 ± 136.77 (SD calculated from SEM = 13.1)) vs. 628.2 ±163.15 (SD calculated from SEM = 7.1)** **Motor development (Percentile rank)** **The Bruininks-Oseretsky Test of Motor Proficiency Version 2 Short Form (BOT2-SF)** **23.2 ± 2.5 vs 50.0 ± 3.4** **Percentage of children with scores below 1.5 and 2.0 standard deviations:** **33.3 and 14.7 %** **Adverse Events:** No adverse events were reported Other Outcomes reported (but excluded from this review):

	Isometric Lower extremity strength (n) - knee extension: Left: 198.6 ± 87.70(n=109) vs 236.1 ± 65.92 Both: 201.9 ± 86.65(n=109) vs 236.1 ± 65.92 **Isometric Lower extremity strength (n) - ankle dorsiflexion:** Left: 163.1 ± 74.13 vs 161.2 ± 41.50 Both: 164.3 ± 75.17 vs 161.2 ± 41.50 **Hand Grip strength (kg) – Jamar® hand-held dynamometer:** Left: 15.9 ± 8.35 vs 19.1 ± 8.35 Both: 16.7 ± 8.35 vs 19.1 ± 8.35 **Bone Density and Body Composition** **Range of Motion** **Parent and child reported Health-Related Quality of Life**
Funding source	P30 CA021765/CA/NCI NIH HHS/United States R01 CA129384/CA/NCI NIH HHS/United States CA21765/CA/NCI NIH HHS/United States
Reference	Ness KK, Kaste SC, Zhu L, Pui CH, Jeha S, Nathan PC, Inaba H, Wasilewski-Masker K, Shah D, Wells RJ, Karlage RE, Robison LL, Cox CL. Skeletal, neuromuscular and fitness impairments among children with newly diagnosed acute lymphoblastic leukemia. Leuk Lymphoma. 2015 Apr;56(4):1004-11. doi: 10.3109/10428194.2014.944519. Epub 2014 Aug 20. PMID: 25030039; PMCID: PMC4336225.

Akyay et al. (2014). Muscle strength, motor performance, cardiac and muscle biomarkers in detection of muscle side effects during and after acute lymphoblastic leukemia treatment in children

Country	Turkey
Design	Prospective Cohort Study
Participants	15 children and adolescents with Acute lymphoblastic Leukemia Mean 9.7 years old, range: 4.5-17 years
Control	Healthy age- and sex-matched children: Handgrip strength: n = 15
Outcomes and assessment methods Children with cancer versus healthy reference (mean±SD)	Muscle strength: **Hand Grip strength (kg) – Nicolas Hand-Held Dynamometer, pediatric (Lafeyette Instruments, Lafayette, IN, model 78,011)** **Right hand: 13.48 ± 6.41 vs. 17.65 ± 7.93** (calculated from median 11.4 kg (range: 6.3-28.6) vs. 16.0 (7.0-34.6) Physical Performance: **Timed-up-and-go (sec.): 8.45± 0.95 versus 6.77 ± 0.52** (calculated from median 8.4 (range:.6.9-10.2) vs. 6.7 (range: 6.0-7.8)) **Adverse Events:** No adverse events were reported Other Outcomes reported (but excluded from this review): **Hand Grip strength (kg)** Left: 14.37± 8.28 vs. 16.99± 7.70 (Calculated from median 12.1 kg (range: 4.3-33.1) vs. 15.3 (6.8-33.6)) **Blood Samples**: Creatine phosphokinase (CPK), Magnesium (MG), Serum Electrolytes and corn trypsin inhibitors (Cti) **Echocardiography**:
Funding source	none reported
Reference	Akyay A, Olcay L, Sezer N, Atay Sönmez Ç. Muscle strength, motor performance, cardiac and muscle biomarkers in detection of muscle side effects during and after acute lymphoblastic leukemia treatment in children. J Pediatr Hematol Oncol. 2014 Nov;36(8):594-8. doi: 10.1097/MPH.0000000000000067. PMID: 25330012.

Hooke et al. (2013). Assessment of physical performance using the 6-minute walk test in children receiving treatment for cancer.

Country	USA
Design	Quasi-Experimental Study
Participants	29 children and adolescents with ALL, Lymphoma and solid tumors Mean 10.6 years old, range: 6-17 years
Control	Normative data from the Geiger Cohort 6MWT: n=481
Outcomes and assessment methods Children with cancer versus healthy reference (mean±SD)	Physical Performance: **Six-minute-walk test (meters): 414.71 ± 122.13 (n= 29) versus 656.83 ±60.37 (n=481)** **Adverse Events:** No adverse events were reported
Funding source	The American Cancer Society Doctoral Nursing Scholarship; The Center for Children with Special Health Care Needs, Leadership in Nursing grant number T80-MC00010, from the Maternal and Child Health Bureau, Health Resources and Services; The White Family Oncology Fellowship; The Oncology Nursing Society Foundation Doctoral Scholarship, and The Pine Tree Apple Tennis Classic Foundation (M.C. Hooke, principal investigator).
Reference	Hooke MC, Garwick AW, Neglia JP. Assessment of physical performance using the 6-minute walk test in children receiving treatment for cancer. Cancer Nurs. 2013 Sep-Oct;36(5):E9-E16. doi: 10.1097/NCC.0b013e31829f5510. PMID: 23963198.

Hartman et al. (2009). A randomized trial investigating an exercise program to prevent reduction of bone mineral density and impairment of motor performance during treatment for childhood acute lymphoblastic leukemia.

Country	Netherlands
Design	Randomized Controlled Study
Participants	51 children and adolescents with ALL Median age: 5.4 years old, range 1.3-17.1 years old
Control	Normative values on motor performance based on the Bayley Scales of Infant Development (BSID-II) (children <3.5 years) and the Movement Assessment Battery for Children (Movement-ABC) (children aged >4 years)
Outcomes and assessment methods Children with cancer versus healthy reference (mean±SD)	Physical Performance: **Motor Performance (BSID-II and movement-ABC): significantly Impaired compared to healthy peers: (-1.41 SD'S = 15.9 percentile)** **Adverse Events:** No adverse events were reported Other Outcomes reported (but excluded from this review): **Body Composition and BMD** Passive Ankle Dorsiflexion
Funding source	none reported
Reference	Hartman A, te Winkel ML, van Beek RD, de Muinck Keizer-Schrama SM, Kemper HC, Hop WC, van den Heuvel-Eibrink MM, Pieters R. A randomized trial investigating an exercise program to prevent reduction of bone mineral density and impairment of motor performance during treatment for childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2009 Jul;53(1):64-71. doi: 10.1002/pbc.21942. PMID: 19283791.

Küper et al. (2013). Location and restoration of function after cerebellar tumor removal-a longitudinal study of children and adolescents.

Country	Germany
Design	Prospective Cohort Study
Participants	12 children and adolescents with cerebellar tumors Mean age11.1 years old, range 6–17 years
Control	11 Healthy age- and sex-matched children
Outcomes and assessment methods Children with cancer versus healthy reference (mean±SD)	Physical Performance: **Balance (Abnormal sway (>2 SD): (ultrasound-based motion analysis):** **Sitting: 2 of 12 (16.7 %)** **Standing: 6 of 12 (50%)** **Standing, eyes closed: 7 of 12 (58.3 %)** **Tandem stance: 10 of 12 (83.3 %)** **Adverse Events:** No adverse events were reported Other Outcomes reported (but excluded from this review): **Upper limb motor function (Pegboard test)** **MR Imaging and Lesion Volume – Symptom Mapping**
Funding source	Deutsche Forschungsgemeinschaft (DFG TI 239/5-2).
Reference	Küper M, Döring K, Spangenberg C, Konczak J, Gizewski ER, Schoch B, Timmann D. Location and restoration of function after cerebellar tumor removal-a longitudinal study of children and adolescents. Cerebellum. 2013 Feb;12(1):48-58. doi: 10.1007/s12311-012-0389-z. PMID: 22562748.

Reinders-Messelink et al. (1999). Motor performance of children during treatment for acute lymphoblastic leukemia.

Country	The Netherlands
Design	Prospective Cohort Study
Participants	17 children and adolescents with ALL 14 children were available for baseline assessment Median 5.8 years old, range 4.0 – 12.6
Control	Healthy age- and sex-matched children: Motor Performance (Movement ABC) (4) n = 10
Outcomes and assessment methods Children with cancer versus healthy reference (mean±SD)	Physical Performance: **Movement ABC (Number of Children with Movement ABC <15th Centile)** **(n = 14 tested at baseline)** **Total score (%):** **5 (36)** **Manual dexterity (%):** **2 (14)** **Ball skills (%):** **1 (7)** **Balance (%):** **7 (50)** **Adverse Events:** No adverse events were reported
Funding source	The Groningen Foundation for Pediatric Oncology Research (SKOG)
Reference	Reinders-Messelink H, Schoemaker M, Snijders T, Göeken L, van Den Briel M, Bökkerink J, Kamps W. Motor performance of children during treatment for acute lymphoblastic leukemia. Med Pediatr Oncol. 1999 Dec;33(6):545-50. doi: 10.1002/(sici)1096-911x(199912)33:6<545::aid-mpo4>3.0.co;2-y. PMID: 10573577.

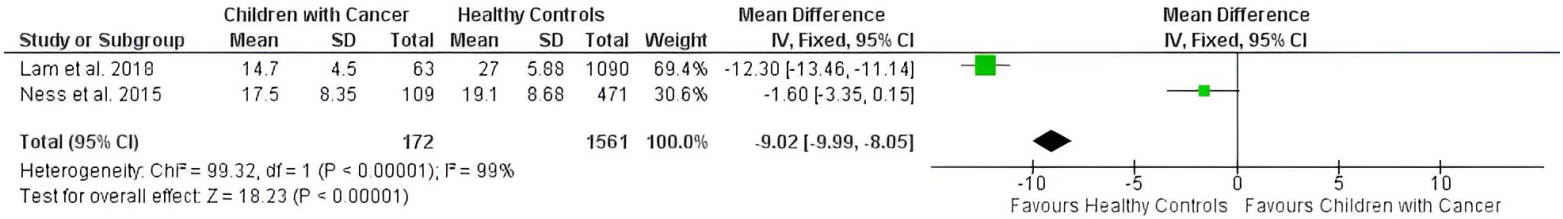
SUPPLEMENTARY FILE 5 Quality assessment in referred studies assessed by Newcastle-Ottawa Scale

Quality Indicators from Newcastle-Ottawa Scale for Cross-Sectional Studies

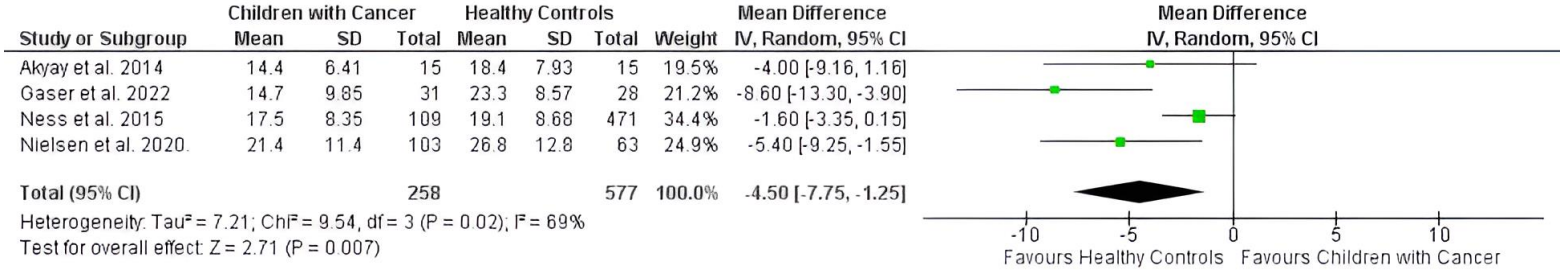
Studies	1	2	3	4	5	6	7	Total Score
Ness et al.	+	-	+	+	++	+	+	7
Akyay et al.	-	-	-	++	++	+	+	6
Corr et al.	+	-	-	+	+	+	+	5
Fiuza-Luces et al.	+	-	-	++	++	+	+	7
Hartman et al.	+	+	+	+	-	+	-	5
Hooke et al.	-	-	-	++	++	+	-	5
Lam et al.	+	+	+	++	-	++	-	7
Nielsen et al.	+	+	-	++	++	+	+	8
Reinders-Messelink et al.	+	-	+	++	+	+	+	7
Gaser et al.	+	+	-	+	+	+	+	6
Vriens et al.	+	-	-	+	-	+	+	4
Küper et al.	-	-	-	-	+	+	+	3

Table 3: 1: Representativeness of sample; 2: Sample size; 3: Non-respondents; 4: Ascertainment of the exposure; 5: Comparability; 6: Assessment of outcome 7: Statistical test.

SUPPLEMENTARY FILE 6A Sub-Analysis of Handgrip Strength (right hand) in children with ALL)



SUPPLEMENTARY FILE 6B Sensitivity Analysis of Handgrip Strength (right hand) without Imputed Data (using only studies conducting within-study comparisons)



SUPPLEMENTARY FILE 6C Sensitivity Analysis of Handgrip Strength (right hand) without Normative Data (using only sex-and age-matched controls as comparison)

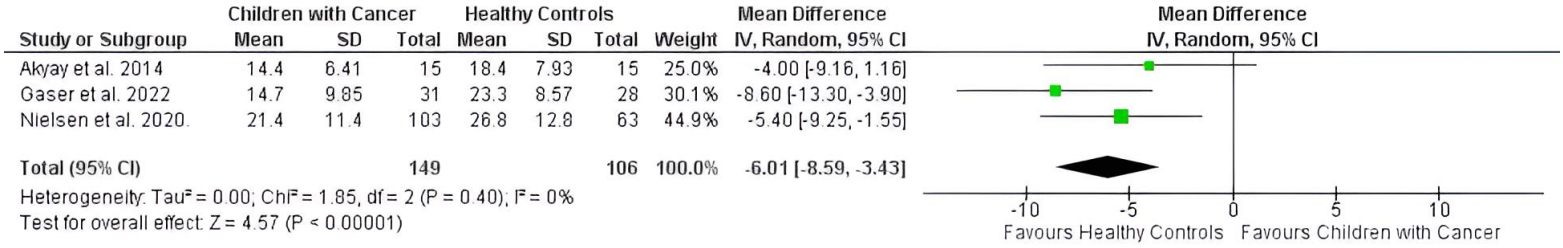
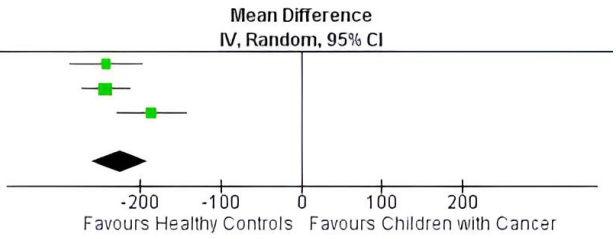


Figure legend: Supp. File 6A. Lam et al. (52) were compared with imputed normative handgrip strength values from the McQuiddy Cincinnati Cohort (22).

SUPPLEMENTARY FILE 7A Sensitivity Analysis of 6-Minute Walk Test without Imputed Data (using only studies conducting within-study comparisons)

Study or Subgroup	Children with Cancer Mean	SD	Total	Healthy Controls Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Hooke et al. 2013	414.7	122.13	29	656.83	60.37	481	29.4%	-242.13 [-286.91, -197.35]
Ness et al. 2015	385	136.77	109	628.2	163.15	528	40.0%	-243.20 [-272.40, -214.00]
Vriens et al. 2022	470.9	94.38	19	656.83	60.37	481	30.6%	-185.93 [-228.71, -143.15]
Total (95% CI)			**157**			**1490**	**100.0%**	**-225.36 [-260.99, -189.73]**

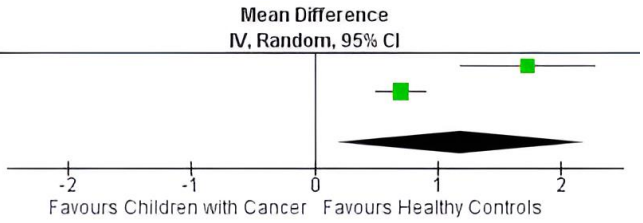
Heterogeneity: Tau² = 603.53; Chi² = 5.13, df = 2 (P = 0.08); I² = 61%
Test for overall effect: Z = 12.40 (P < 0.00001)



SUPPLEMENTARY FILE 7B Sensitivity Analysis of TUG without Imputed Data (using only studies conducting within-study comparisons).

Study or Subgroup	Children with Cancer Mean	SD	Total	Healthy Controls Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Akyay et al. 2014	8.5	0.95	15	6.7688	0.52	15	46.8%	1.73 [1.18, 2.28]
Nielsen et al. 2020	4	0.8	85	3.3	0.4	61	53.2%	0.70 [0.50, 0.90]
Total (95% CI)			**100**			**76**	**100.0%**	**1.18 [0.17, 2.19]**

Heterogeneity: Tau² = 0.49; Chi² = 12.04, df = 1 (P = 0.0005); I² = 92%
Test for overall effect: Z = 2.30 (P = 0.02)



SUPPLEMENTARY FILE 8 Meta-Analysis of Functional Mobility Assessment Scale (FMA)

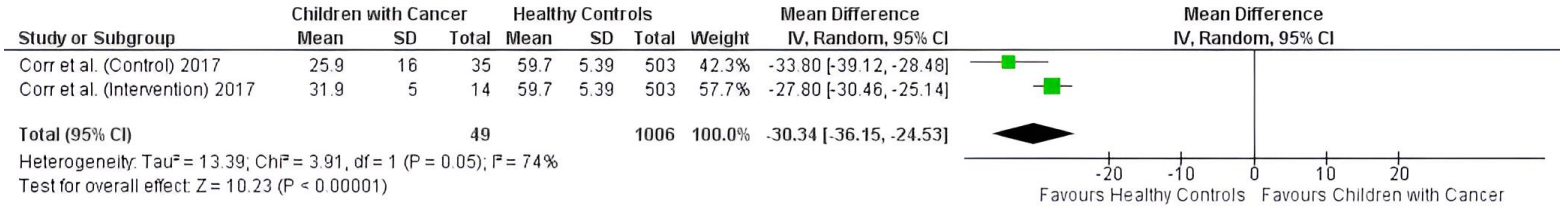


Figure legend: Supplementary File 8. The FMA is a composite tool measuring pain, Timed Up and Go, Timed Up and Down Stairs, the 9-Minute Walk/Run Test, heart rate, and rate of perceived exertion. This analysis was based on two subgroups: baseline measures of a within-study intervention group and a control group from Corr et al. (36) Both subgroups were compared to imputed normative data from the Marchese Cohort (25).

PAPER III

PAPER III

frontiers in Pediatrics

CLINICAL TRIAL
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Integrative Neuromuscular Training in Adolescents and Children Treated for Cancer (INTERACT): Study Protocol for a Multicenter, Two-Arm Parallel-Group Randomized Controlled Superiority Trial

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Background: Improved survival rates for children and adolescents diagnosed with cancer call for novel strategies for reducing short- and long-term treatment-related side effects. These include the physical and metabolic sequelae that are exacerbated by sedentary behavior and treatment-induced toxicities. We aim to investigate the effect of an integrative neuromuscular training intervention during the first 6 months of anti-cancer treatment primarily on muscle strength, and secondarily on exercise capacity, physical function, markers of metabolic syndrome, dysmetabolism, and health-related quality of life during and after ended treatment.

Methods: One hundred and twenty-seven children and adolescents, newly diagnosed with malignant and benign neoplasia, aged 6–17 years, and treated with chemotherapy or radiation will be randomized to either the intervention or the control arm of the study. The intervention group will, in addition to usual care, be offered a combination of 6 months of supervised physical exercise (integrative neuromuscular training) and home-based exercise. The active control group will, in addition to usual care, receive information along an unsupervised written home-based training program. All participants, including parents, will receive information about the importance of physical exercise during the course of cancer treatment, at the start of treatment, and in 5 monthly sessions. The primary outcome is measured in terms of isometric quadriceps muscle strength. Secondary outcomes include muscle strength and endurance, markers of metabolic syndrome and dysmetabolism, exercise capacity, physical function and activity, days of hospitalization, and health-related quality of life. Assessment will be conducted at

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treatment initiation (baseline), at 3 and 6 months after inclusion, and 1 month and 1 year after ended treatment. The primary endpoint for lower-body muscle strength is at 6 months after treatment initiation. The effects of the intervention will be evaluated through a constrained linear mixed model.

Discussion: This national randomized controlled study has the potential to provide new knowledge concerning the short- and long-term effects of a novel, inclusive approach for youth exercise programming (integrative neuromuscular exercise) in children and adolescents during anti-cancer treatment. Using a pragmatic, low-cost, and time-efficient training design, this intervention can be easily adapted to both hospital and home settings.

Clinical Trial Registration: ClinicalTrials.gov (NCT04706676), first released January 5, 2021.

Keywords: childhood cancer, integrative neuromuscular training, rehabilitation, during treatment, survivorship, muscle strength, metabolic syndrome

INTRODUCTION

In the Western world, the 5-year survival rate for children and adolescents diagnosed with cancer has improved progressively over the last 3 decades; from 72 in 1985 to above 85% in 2017 (1, 2). However, this improved rate is accompanied by an increase in both short- and long-term side effects (1, 2) and calls for novel strategies that work beyond sole survival as most children enter a negative loop where treatment-induced toxicities and a sedentary lifestyle exacerbate the physical deficits of cancer treatment (3–14).

Children and adolescents diagnosed with cancer are predominately treated with chemotherapy, radiotherapy, glucocorticoids, and surgery causing well-documented side effects, including damage to skeletal muscles, the central and peripheral nervous systems, and impaired cardiorespiratory fitness. This results in impaired gait (walking distance and reaction time) and balance, and it leads to fatigue and reduced physical activity (10, 15–18). Collectively, these factors have significant negative implications for physical health outcomes, including risk of muscle atrophy (10, 14, 19, 20), which persist into adulthood, as approximately two-thirds of cancer survivors have shown to have at least one chronic health condition 30 years after treatment initiation (8).

Skeletal muscles serve fundamental functions, ranging from generating mechanical force and mobility to regulating whole-body metabolic homeostasis (15). Hence, muscle atrophy and altered body composition with lower lean body mass and skeletal muscle index, seen after cancer treatment, threaten independent living due to reduced physical ability (15, 21–23). Muscle atrophy may also play an essential role in the development of dysmetabolism in long-term survivors, i.e., studies have reported increased prevalence of metabolic syndrome with physical inactivity being a predominant risk factor (OR, 1.7; 95% CI, 1.1–2.6) (24).

These severe physical and metabolic disturbances may be founded early during cancer treatment, as lower-body muscle strength and cardiorespiratory fitness are significantly decreased by 21 and 42%, respectively, within the first 30 days of treatment in children and adolescents compared to age- and sex-matched controls (10, 18), which highlights the need for early exercise interventions (13).

Previous studies in pediatric oncology patients indicate that exercise interventions are generally safe, feasible, and have beneficial preserving effects on muscle strength, cardiorespiratory fitness, and physical functioning during cancer treatment (18, 25–28). Furthermore, children are interested and can be motivated to engage in exercise and physical activity while hospitalized despite cancer disease and intensive chemotherapy (13, 18, 29).

In general, the body of evidence concerning the effectiveness of exercise interventions during anti-cancer treatment in children is based on studies with small sample sizes, heterogeneous aims, interventions, and outcomes; using either broadly defined or undefined exercise interventions with a low grade of reproducibility (9, 11, 13, 30–52).

An emerging, more inclusive, concept of exercise is integrative neuromuscular training; a conjunction of different types of physical exercise with potential neuromuscular output designed to enhance both health- and skill-related components of physical function (53). Moreover, it is time-efficient, can be adapted to both hospital and home settings, and is developmentally appropriate for both children and adolescents. Accordingly, this type of exercise is thought to counteract both lifestyle and potentially treatment-induced neuromuscular deficits and improve physical function, such as walking, running, lifting, and balance; fundamental movement skills for achieving a long-term physically active and healthy lifestyle (15, 32, 34, 37, 54, 55).

Abbreviations: CNS, Central Nervous System; DXA (scan), Whole-Body Dual-Energy X-Ray Absorptiometry; HDL, High-Density Lipoprotein (cholesterol); ICF, international classification of functioning, disability, and health; INT, Integrative Neuromuscular Training; INTERACT (study), Integrative neuromuscular training in adolescents and children treated for Cancer; OR, OddsRatio; RESPECT (project), REhabilitation including Social and Physical activity and Education in Children and Teenagers with cancer.

Quasi-experimental and controlled studies have underscored how 7–12 weeks of integrative neuromuscular training can improve muscular strength, fundamental movement skills, and selected measures of physical fitness compared to physical education classes and customary sports in healthy children and adolescents (5–14 years) (56–60).

Although no studies have been conducted on children and adolescents during prolonged periods of hospitalization nor during cancer treatment, integrative neuromuscular training appears as a feasible exercise modality due to its age- and skill-appropriate approach to progressive exercise targeting neuromuscular deficits. Furthermore, its challenging, motivational, play-and-game approach to exercise can potentially improve adherence and long-term lifestyle behavior in children surviving cancer.

The study is based on the overarching hypothesis that supervised structured integrative neuromuscular training initiated at the time of diagnosis effectively prevents deficits in muscle strength 6 months after initiated treatment.

The primary objective of this study is to investigate the effects of a 6-month integrative neuromuscular training intervention compared with unsupervised home-based exercise on isometric knee extension strength in children and adolescents (6–18 years) during anti-cancer treatment. Our secondary objectives are to investigate the effects of the intervention on markers of metabolic syndrome, days of hospitalization, health-related quality of life, upper-body muscle strength, exercise capacity, physical function, physical activity behavior, and body composition.

METHODS AND ANALYSIS

This protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (61).

Trial Design

The INTERACT study is a national multicenter, two-arm parallel-group, randomized controlled superiority trial based on empirical evidence within the research group (13, 18, 43, 62) and methodical recommendations from current evidence (27). The primary endpoint is at 6 months after inclusion, and follow-up will be 12 months after ended treatment.

Setting

The three of four centers for pediatric oncology in Denmark will functions as trial sites: Copenhagen University Hospital, Rigshospitalet; Aarhus University Hospital; and Odense University Hospital.

Eligibility Criteria

Children and adolescents with newly diagnosed malignant and benign neoplasia aged 6–17.9 years and admitted from January 2021 for treatment at the departments for pediatric oncology will be eligible for inclusion. Diagnoses include malignant and benign neoplasia treated with chemotherapy and/or irradiation. Children with a severe mental and/or physical disability (i.e., participants where all types of physical training and testing of physical function are contraindicated), terminal illness, and individuals unable to communicate in Danish will be excluded.

When answering patient-reported outcomes, the parent(s) will be used as informants to answer proxy questionnaires and provide sociodemographic data on behalf of their child.

Recruitment

All eligible participants and their parents will receive the information about the study within 2 weeks of treatment initiation by the treating physician at the clinical ward. If interested, a member of the research team, a project nurse or physiotherapist, will provide oral and written information about the study to the child and parents, in a quiet and undisturbed environment on the ward.

Participants who are willing to participate will sign the informed consent before any study-related procedures are initiated. When informed consent for participation is obtained, the recruitment staff will schedule the baseline assessments in the local occupational- and physiotherapy department, which will be conducted before randomization.

Integrative Neuromuscular Training

In addition to usual care, the intervention group will receive integrative neuromuscular training (INT) for 6 months. An overview of the components of the intervention (and active control group) can be found in **Table 1**.

All participants are encouraged to participate in a minimum of two training sessions per week for the first 7 weeks and three sessions per week in weeks 8–24. Usually, during the first 6 months of treatment, all participants indifferent of cancer type will either be hospitalized or have outpatient appointments every week. Hence, at least one supervised training will be planned every week. All remaining training sessions will therefore be conducted as either supervised or home-based training, depending on admission. If there are weeks without any hospital or outpatient clinic visits, the training sessions will all be conducted as home-based training, and the participants will receive a phone call or text message from the intervention physiotherapist concerning questions, exercise choice, and exercise intensity.

Based on individual needs and where applicable, parents will be instructed to conduct INT at home. When relevant participants will be provided with exercise equipment corresponding to the child's age and fitness level (e.g., fitness ropes, medicine ball, dumbbells).

Integrative neuromuscular training contains a range of developmentally appropriate activities that target general and specific strength and conditioning elements, such as strength, power, motor skills, dynamic stability, core-focused strength, and agility (53, 63). INT can be camouflaged as games and play or performed as a structured strength and conditioning program, depending on the participant's age, motor skill level, and daily variations in side-effects (nausea, fatigue, dizziness, pain). Unlike more traditional types of physical activity (e.g., walking, cycling), integrative neuromuscular training targets neuromuscular deficits by stimulating neural plasticity, alerting motor unit recruitment, firing frequency, and synchronization of

TABLE 1 | Overview of content in the intervention and active control group.

	Study interventions	
	(Experimental) integrative neuromuscular training	**(Comparator) active control group**
Description	Supervised neuromuscular exercise during admissions and visits to the outpatient clinic, containing elements of strength, motor skill, dynamic stability, core-focused strength, and agility exercises (prescribed according to age and training experience) Home-based exercise during weeks without visits to the hospital	Unsupervised home-based training program consisting of combined aerobic, strength, and stretching exercises (described in Additional file 1)
Duration	6 months of exercise initiated 2 weeks within start of cancer treatment	
Recommended frequency (minimum session/weekly)	2 training sessions/week for the first 7 weeks 3 sessions/week from weeks 8–24	2 sessions/week
Recommend time/session	15–35 min	15–20 min
Recommended no. of exercises	2–6	3
Usual care	Both groups will receive usual standardized hospital care, including physiotherapy if needed.	
Motivational counseling	Each child and their parents will participate in a monthly 15–30-min motivational counseling session.	

Description of content in the intervention (experimental) and active control (comparator) arms of the study.

motor unit activation (15, 32, 34, 37, 54, 55). The intervention is designed to enhance both health- and skill-related components of physical fitness.

To increase adherence, training intensities (load or level of difficulty) and length of training sessions (training volume and rest periods) will be periodized according to the participants' chemotherapy cycles, where applicable, to accommodate potential side effects, primarily treatment-related fatigue (64). An example of a training plan adjusted to a low-risk treatment protocol for acute lymphoblastic leukemia (ALLtogether 2018; ClinicalTrials.gov NCT04307576) can be seen in **Supplementary Figure 2**.

Training intensity (load or level of difficulty) and length of training sessions are adjusted throughout the treatment trajectory and expected to be considerably lower the first week following chemotherapy. The purpose of this pre-emptively reduced intensity and volume is to (1) encourage participants to attend exercise, even though physical symptom burden may be more extensive during these periods and (2) prescribe manageable exercise accommodating the symptom burden (64). Furthermore, to familiarize the participants with physical exercise, in a period of transition from everyday life to life with cancer, including treatment regimens and hospitalization, the initial weekly training frequency will be fixed to a minimum of two training sessions per week for the first 7 weeks, and a minimum of three sessions per week in weeks 8–24.

Health Counseling/Motivational Intervention

Due to the strain related to the anti-cancer treatment, motivation is paramount in this setting. Each child and their parents in both groups will participate in a monthly 20-min health counseling session to adjust the intervention according to the child's needs and preferences.

The sessions are based on self-determination theory (65), describing the interplay between external and internal motivation forces, defined within three innate psychological needs/parameters: autonomy, competence, and relatedness. Practically, these sessions will follow a semi-structured interview protocol involving: (1) autonomy: Each participant has the option to change the training program according to their needs, skill level, and presence of symptoms using cooperative planning (co-creation); (2) competence: It must be apparent for the participants that the training sessions maintain or develop their physical function by tracking progress in the exercise diaries (e.g., number of repeated exercises, loads, difficulty of exercise). Furthermore, if applicable, the participant sets a monthly goal for participation level within the international classification of functioning, disability, and health (ICF) (66); (3) relatedness is achieved by putting the potential effects of exercise into a social context; e.g., that through exercise, they can partake more easily in social relations on equal terms with peers.

The goal is to achieve internal motivation to engage in exercise and physical activities; that is, to design the exercise program so that the child engages in the exercises for the fun of it.

Home-Based Training Program

The active control group will receive a home-based training program consisting of strength and stretching exercises for lower and upper body (see **Supplementary Figure 1**). The participants can choose from two or three stretching, lower- and upper-body resistance exercises, respectively, and they are asked to perform three sets of 10 repetitions for each resistance exercise. All exercises use body weight as resistance but can be progressed in terms of level of difficulty. The use of the home-based training program will be monitored with an exercise diary.

Usual Care

Both groups will receive usual standardized hospital care, including physiotherapy, as needed. However, procedures for referrals to physiotherapy and staff resources are different in each center. At Copenhagen University Hospital, Rigshospitalet, children and adolescents are referred to physiotherapy when/if a physical deficit occurs (e.g., impaired gait and balance, drop feet, surgical operations). In contrast, at Aarhus and Odense University Hospital, all children are referred to physiotherapy at diagnosis. At all three centers, physiotherapy resources will be distributed according to the severity of illness and physical deficits.

Randomization

Following baseline assessment, participants will randomly be assigned to either the intervention group (integrative neuromuscular training + motivational-counseling sessions + usual care) or active control group (home-based training program + motivational-counseling sessions + usual care) by a blinded statistician using a computer-generated concealed allocation procedure to secure a proportionate stratified random sample with a (2:2) allocation. Participants will be stratified by sex, pubertal stage, and diagnosis as treatment for (1) solid tumors, (2) CNS-tumors, and (3) treatment for hematologic malignancy.

Baseline assessors and the statistician will be blinded to the allocation of participants; however, due to the nature of the intervention, neither participants nor intervention staff will be blinded throughout the intervention.

Fidelity

This research project is based on an international collaboration between specialists in metabolism, exercise, and physical activity in pediatric cancer patients. Further, it is based on several years of experience with exercising children and adolescents with cancer through the RESPECT project (REhabilitation including Social and Physical activity and Education in Children and Teenagers with cancer), based at Copenhagen University Hospital, Rigshospitalet. The RESPECT project has shown how children can and will perform safe, in-hospital exercise and how this counteracts side effects resulting from cancer treatment, including loss of fitness and muscle strength, compared with children in pediatric wards in other Danish hospitals (13, 18, 29, 43). Two key principles of RESPECT are early rehabilitation from treatment initiation and supervised exercise, hypothesizing that: (1) Maintaining children's physical function and fitness is easier during treatment than recovering deficits and developing new relationships post-treatment and (2) supervised exercise is more effective than unsupervised exercise.

These two principles will be continued in the INTERACT project. Moreover, the intervention will be evolved to a more structured design, as results from RESPECT suggest, and it will be able to explore potential effects because of its randomized controlled design.

To secure an aligned intervention and reliability of assessment within the three centers, a mandatory two-day workshop (2 × 4 h) is held at each site for the physiotherapist conducting the intervention. The workshop includes a practical introduction to the integrative neuromuscular training intervention, including pro- and regression of exercise intensity or difficulty, and a thorough run-through of all of the physical assessment protocols.

Outcomes

Assessment will be conducted within 14 days after treatment (chemotherapy and/or irradiation) initiation (baseline), at 3 and 6 months after inclusion, and at 1 month and 1 year after ended treatment. An overview of the overall study trajectory, outcomes, and assessment timing is presented in **Figure 1**.

A complete list of outcomes can be found at ClinicalTrials.gov.

Primary Outcome

Isometric Knee Extension Strength

Isometric knee extension is tested using a special-build strength ergometer (Gym 2000®, Vikersund, Norway) with a dynamometer (U2A100 kg, Hottinger, Germany) and amplifier. Data is collected using an AD-card (100 HZ) with customized software (LabVIEW ®, National Instruments, Texas, USA). Each participant receives detailed instructions on how to perform each test and is given time to familiarize before each test if needed.

The participant is sitting upright on the bench, with arms hanging alongside the body and hands grasping the bench. Hips and knees are kept in 90 degrees flexion. The height of the bench is adjusted to keep both feet off the ground.

The chain to the dynamometer is adjusted to keep the leg in 90 degrees flexion during muscle contraction. The test is performed unilaterally, primarily on the right leg, unless testing on the right leg is restricted (e.g., due to injury or solid tumors in lower extremity).

The participant is instructed to kick (forward) with maximal force and to keep maximal intensity for at least 5 s. Three attempts with a 2-min break are carried out; however, the participant can try as many attempts as possible if they keep showing improvements. The highest score represents the test score.

Primary Secondary Outcome

Markers of Metabolic Syndrome (Primary Secondary Outcome)

Metabolic syndrome is based on waist circumference, triglycerides, high-density lipoprotein (HDL) cholesterol, blood pressure, fasting blood sugar, and insulin. Age-based criteria for each parameter concerning metabolic syndrome is defined by the International Diabetes Foundation (67).

Waist circumference is measured in centimeters, after taking several consecutive natural breaths, at a level parallel to the floor, in a midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the midaxillary line following standards described by the World Health Organization (68).

Triglycerides, high-density lipoprotein (HDL) cholesterol, fasting blood sugar, and insulin will be analyzed in blood samples drawn from an antecubital vein or, when possible, through a central or peripheral venous catheter. Samples that have already been collected for routine clinical or research purposes (and

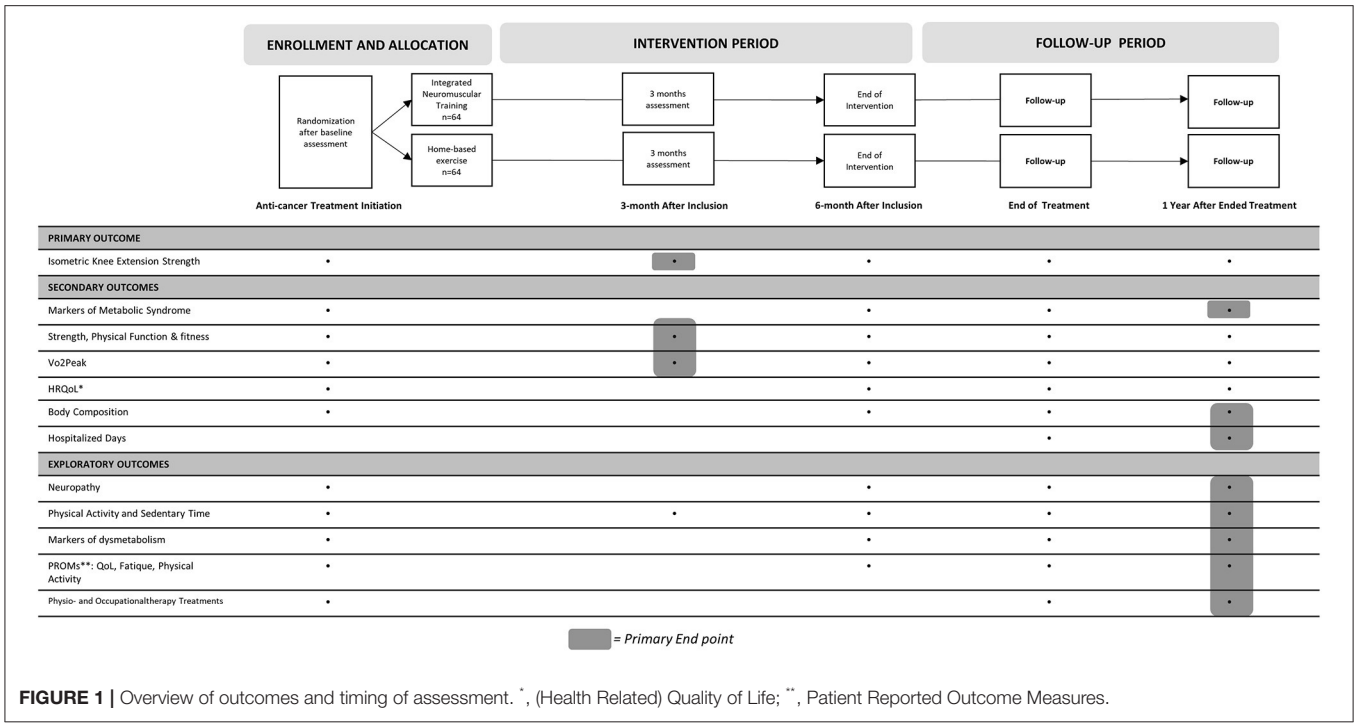

FIGURE 1 | Overview of outcomes and timing of assessment. *, (Health Related) Quality of Life; **, Patient Reported Outcome Measures.

stored in an authorized biobank) will also be used in the study to minimize the number of samples taken.

Blood pressure (mmHg) will be measured in the morning using the right arm with the subject sitting.

Although children younger than 10 years cannot be diagnosed with metabolic syndrome, the potential decline or increase in the biological markers (i.e., predisposition for metabolic syndrome) will be investigated in this study.

Secondary Outcomes

Secondary outcome measures will include assessment of upper-body muscle strength (measured through isometric bench press; same equipment used for primary outcome), handgrip strength (Jamar, Patterson Medical, Illinois, USA) (69), cardiopulmonary fitness/vo2 peak [through Cardiopulmonary Exercise Test (Cortex, Leipzig, Germany)], walking distance (6-min Walk Test) (70), lower extremity muscle strength and endurance (through 30-s and 1-min Sit-to-Stand Test, respectively) (71, 72), basic functional mobility (through Timed up-and-Go test) (73), body composition [through Whole-Body Dual-Energy X-ray Absorptiometry (DXA) Scan (Lunar, Lunar Corporation Madison, WI, USA)], and quality of life (through PedsQL Generic Core Scale) (74). These outcomes represent direct or surrogate measures of physical fitness, physical function, or quality of life. Each outcome is described in detail at the uploaded protocol at clinicaltrails.gov (NCT04706676).

Further, as a measure of the economic cost of hospitalization, total days of hospitalization will be measured and compared in the two groups after ended treatment.

Explorative Outcomes

On an explorative basis, this study will measure neuropathy (through Pediatric Modified Total Neuropathy Score) (75), balance (as Modified Clinical Test of Sensory Interaction in Balance) (76), physical activity and sedentary time through accelerometry (ActiGraph^{TM}, ActiGraph LLC, Pensacola FL, USA), muscle power through countermovement jump (FP4, HUR-Labs Oy, Tampere, Finland), markers of dysmetabolism (metabolomics, intestinal microbiota, inflammatory cytokines and mediators, growth and reproductive factors, and macro- and micronutrients collected through plasma, urine and feces samples, and dietary assessment), self- and proxy-reported general physical activity, health-related quality of life (PedsQL 3.0 Cancer Scale) (74), and fatigue (PedsQL Multidimensional Fatigue Scale) (74).

To further measure the potential cost of standard care/rehabilitation, the total number of physio- and occupational therapy treatments will be measured and compared between groups and centers.

Sample Size

A 10% increase in muscle strength due to physical exercise is regarded as a clinically relevant change (62). Based on a mean 41.4 ± 7.6 (lower body muscle strength, kg ± SEM) (44) and a 10% increase, an alpha level of 0.05, and power of 80%, 106 children are needed. We expect that approximately 60 children with cancer aged 6–17 will be diagnosed per year at Copenhagen University Hospital, Rigshospitalet, Aarhus University Hospital, and Odense University Hospital. Assuming a 20% dropout rate, 2.2 years will be required to include the needed number of children with cancer ($n = 127$).

Statistical Considerations

Constrained longitudinal data analysis is applied to evaluate the intervention effectiveness by using constrained (generalized) linear mixed models in two scenarios. In the first one, predictors will include follow-up time points categorized as 3 and 6 months to account for any non-linear effect and dummy variables representing the intervention group at 3- and 6-month follow-ups, respectively. In the second scenario, the time variable will be treated as a continuous variable and an interaction between treatments (binary-coded, 1 representing intervention group), and the time variable will be included instead. Normal distribution will be applied on continuous outcome muscle strength, while binomial distribution will be applied on binary outcome metabolic syndrome. Baseline characteristics, such as age (as a continuous variable), gender, and type of cancer (categorized as solid, CNS, and hematologic tumors), will be included additionally as covariates in both scenarios. Patient identity will serve as a random intercept. Likelihood ratio tests based on maximal likelihood will be applied for the model selection of the fixed effects to determine linear or non-linear associations. Benjamin-Hochberg procedure will be applied to reduce the false discovery rate due to multiple comparisons. The level of significance is 0.05.

Data Management

Questionnaire data will be directly uploaded and stored on a secured server for sensitive data (REDCap). All other assessed data will be uploaded to the same server by all collaborators.

General Data Protection Regulations (GDPR EU) will comply with national and international law.

A data processing agreement with all collaborators will be made before any samples are shared for analysis.

DISCUSSION

This national randomized controlled study has the potential to investigate the short- and long-term effects of structured exercise in children and adolescents during anti-cancer treatment with a follow-up time into survivorship, 1 year after ended cancer treatment.

This study is based on almost a decade of experience within the research group conducting physical activity interventions for children with cancer through the RESPECT project. This experience has been extensively incorporated in this study; the chosen intervention, design, and choice of comparators.

Intervention

The INTERACT study will use an exercise training intervention that may be complex due to the integrative design with individually targeted exercise prescriptions, i.e., we will not be able to present a generic exercise program that can accommodate all age groups, diagnosis, and logistical challenges. However, it does provide general guidelines for training modifications, exercise intensities, training accumulation, and suggestions for adequate rest and recovery during the first 6 months of cancer treatment. This will further provide a template for long-term exercise programming and long-term physical conservation (or even improvements) after ended cancer treatment. It will further provide evidence of the necessity of long-term exercise programming, appropriate testing, and monitoring to provide adequate physical exercise intervention, preserving strength and physical function during treatment. This will prepare children and adolescents for a normalized lifetime of exercise and active leisure activity after ended cancer treatment.

To maintain adherence and motivation throughout a 6-month training intervention, we expect weekly supervision of the training to be necessary. We therefore expect that exercise interventions with weekly supervision will have higher adherence rates, since participants will be more motivated, resulting in increased effects on muscle strength, markers of dysmetabolism, physical function, and levels of physical activity during and after treatment compared to unsupervised home-based training (active controls).

Design

We have chosen a randomized controlled design to provide evidence of the potential effectiveness of integrative neuromuscular training in children and adolescents during cancer treatment. This will allow us to minimize confounding factors, such as geographical differences in patient uptake and usual care at each center, which was considered a limitation to the previous RESPECT study (18).

This study includes all malignant diagnoses of pediatric cancer. Due to different treatment protocols, length of hospitalization, and the potential dysfunctions and side effects from the cancer disease itself, this creates heterogeneity within and between groups. We choose to include all diagnoses, firstly to secure sufficient power in the study population within a reasonable timeframe, thereby minimizing bias due to changes and development of treatment protocols. Secondly, and most importantly, by including all cancer diagnoses, which we have shown are both motivated and trainable (13, 18), we will increase the generalizability and external validity of this study. To minimize heterogeneity, the groups will be stratified by sex, pubertal stage, and diagnosis.

Choice of Comparators

A potential pitfall within the INTERACT study design may be the choice of using an active control group and performing a home-based intervention instead of using a passive comparator (i.e., usual care). Experiences from the two centers used as passive comparators within the RESPECT project showed that children or their parents are more likely to decline participation (up to 46%) or not adhere to scheduled assessment if placed in the passive control group (18). Furthermore, we found it ethically obligatory to be able to inform the participants and parents in the active control group, considering that they had accepted participation in an exercise intervention, about the potential benefits of physical activity and exercise during treatment, and to provide them with examples of body-weighted exercises.

The current evidence substantiates our hypothesis that adherence, and thereby potential effects, in a supervised exercise intervention will be higher than in home-based interventions.

The current intervention studies in hospitalized children with cancer are based on either home-based or supervised exercise. Adherence rates in these two types of interventions differ substantially from one another; home-based and supervised interventions report a weighted mean adherence of 64.3% (range 37–80) (35, 51, 52, 77) and 88.6% (range 85–100) (31, 32, 48, 49, 78), respectively. Logically, the studies with low adherence to exercise report either no effect or a small, non-significant effect on physical function or fitness, compared to usual care in current studies using home-based interventions. To be effective, physical intervention studies should therefore require a minimum degree of supervision and that non-supervised, home-based interventions correspond to usual care.

Accordingly, we believe that our active control group has close similarities to an adequate group receiving usual care. We also believe that this study will be able to demonstrate that information on physical exercise alone cannot be regarded as a sufficient alternative to supervised physical exercise.

In conclusion, physical activity and exercise interventions are regarded as a safe and feasible method to counteract treatment and inactivity-related side-effects in children and adolescents with cancer; nevertheless, large-scale studies are needed to draw definite conclusions regarding the effectiveness of physical exercise interventions (12, 18). An age-appropriate integrative exercise intervention started immediately after treatment initiation is a promising strategy to reduce the anti-cancer treatment-related side effects.

This research project can potentially change the pediatric exercise oncology and rehabilitation field. The project strives to document between-group changes in strength and physical function, thereby advancing from concluding safety and feasibility measures to report not only a preservation of physical function but significant improvements in children and adolescents' physical function after 24 weeks of treatment compared to treatment initiation. We will achieve our results using a pragmatic, low-cost, and time-efficient training intervention that is appropriately developed for both children and adolescents and can be adapted to both hospital and home settings. This intervention can therefore relatively easily be implemented into current clinical practice.

Ethics and Dissemination

The study will comply with the Helsinki II Declaration. The study has been peer-reviewed and approved by the Danish National Committee on Health Research Ethics (Approval Number: H-20040897), and data handling is approved by the Danish Data Protection Agency (jr. nr.: P-2021-14).

Consent to Participate

Written informed consent will be obtained before inclusion to the study by a member of the research staff (project nurse or physiotherapist) alongside information about the potential risks and benefits of participating in the study. This includes information concerning the child or adolescent's privacy rights and the investigator's disclosure obligations.

Adolescents (aged 15–17.9 years) will receive oral and written information specifically adapted to this age group. If a patient does not wish to participate, this is respected regardless of the parent's acceptance.

Risks and Adverse Reactions

The project is expected to cause limited risks, side effects and discomfort.

Integrative neuromuscular training and isometric muscle strength tests are associated with exertion and shortness of breath and may in some cases feel strenuous. If either the intervention staff or the participant-assigned physician assess that participation is unsafe, the training session or test will be canceled. Reasons for canceling an intervention training session or test include thrombocyte counts <10 billion/l, hemoglobin <5 mmol/l or systolic blood pressure <95 mm Hg.

Dissemination Policy

The results of this study will be presented in scientific peer-reviewed journals and at international conferences. Authorship eligibility follows the Vancouver Recommendation.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available due Danish and EU personal data legislation but are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Danish National Committee on Health Research Ethics. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

This protocol article was primarily drafted by HL, KM, PS-A, MF, and JC. HZ drafted the statistical considerations paragraph and is responsible for the statistical analysis. All authors (PS-A, MF, KM, AP, LH, AF, KS, HH, SL, HZ, JC, and HL) have substantially contributed to the study design and conception of the intervention and will be involved in data collection, analysis, and/or manuscript preparation as the study proceeds. All authors have revised and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.833850/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary figure 1: Home-based training program

Description of exercises (Active control group)

LOWER BODY EXERCISES:
Calf Raises (easy):
With a hip-width distance between the feet, stand on a mat or the floor. Lift your heels so that you are now standing on your toes. Lower yourself to the starting position and repeat.

Squat (intermediate/hard):
With a shoulder-width distance between the feet, bend down to an approx. 90-degree angle at the knees, then return to the starting position. Keep your back straight and look ahead.

Hip Thrust (intermediate):
Lie on your back, bend your legs and let your feet rest on the mattress/bed. Brace your stomach and buttocks. Lift your buttocks from the mat until there is a straight line between the shoulder and the knee.

UPPER BODY EXERCISES:
Pushups Against Wall (easy):
(As below, leaning against wall)

Pushups, Resting on Knees (intermediate):
Place the knees on the floor, keep your upper body fixed with outstretched arms and a shoulder-wide grip. Lower your body to the floor and push back.

Pushups (hard):
Stand on your toes, keep your upper body fixed with outstretched arms and a shoulder-wide grip. Lower the body to the floor and push back.

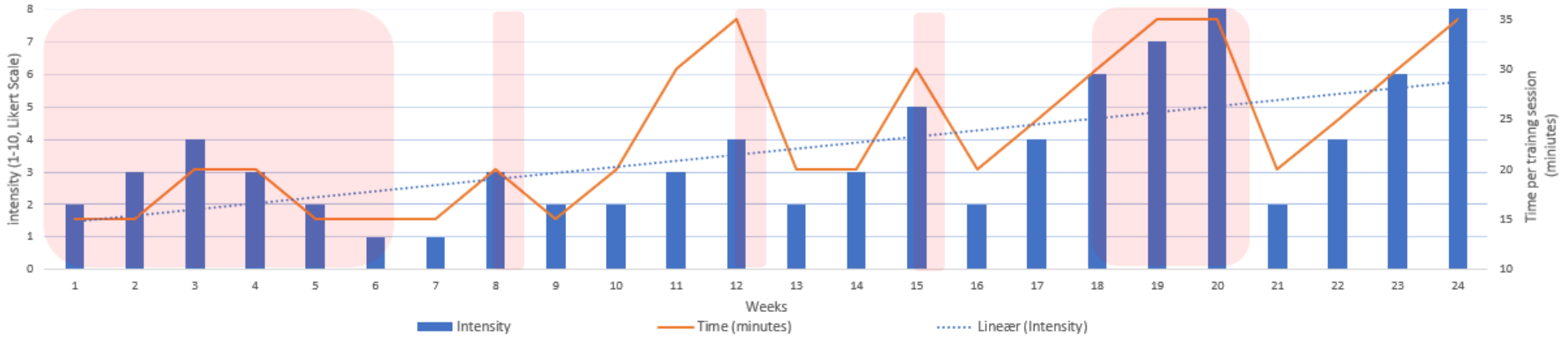
STRETCHING EXERCISES:
Calf stretch:
Support yourself against a wall and place one sole of the foot up against the wall, lowering the heel on the floor. Keep the knee fully extended/stretched. Gently press the hip forward until feeling a stretch on the back of the lower leg. Hold for 30 sec. and change leg.

Front thigh stretches:
Sit on the floor with legs outstretched. Try to lean your body forward and touch your toes. Hold for 30 sec.

Supplementary figure 1: Description and illustration of exercises in the active control group.

Supplementary figure 2: Treatment adjusted training plan, example

6 months of INT training, Acute Lymphocitic Leukemia, LOW-RISK																								
Month	1				2				3				4				5				6			
Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Chemo (cycle)	x	x	x	x	x	x		x				x			x			x	x	x				
Radiation																								
Surgery																								
Mesocycle (theme)	Adaption		Individualisation		Progressive overload 1				Progressive overload 2				Progressive overload 3				Progressive overload 4				Transition			
Contents	Warm up Introduction to equipment Matching of expectations		Warm Up (individualized) Motor Skills Strength exersices (BW) Incorporate own exercises		Motor Skill and Strength/Power				Strength/Power + Motor Skill				Strength/Power +Motor Skill +Endurance				Strength/Power +Motor Skill +Endurance +Agility				Strength/Power +Motor Skill +Endurance +Agility			
Training sessions/week	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Number of primary exercises	1 to 2				1 to 2				≥2				≥2				≥2				≥2			
Total number of exercises	1 to 3				1 to 3				2 to 4				3 to 5				3 to 5				4 to 6			
Time per training session	15	15	20	20	15	15	15	20	15	20	30	35	20	20	30	20	25	30	35	35	20	25	30	35
Pause between exercises	2 min	→																						30 sec
Workload (1-10)	2	3	4	3	2	1	1	3	2	2	3	4	2	3	5	2	4	6	7	8	2	4	6	8



Legend: 24-week example of a tentative individual training plan adjusted to a low-risk treatment protocol for acute lymphoblastic leukemia (ALLtogether 2018; ClinicalTrials.gov identifier: NCT04307576). The bottom diagram shows the inverse relationship between training intensity (blue pillars) and time per training session, including resting periods, (orange curve), according to chemotherapy treatment cycle. The dotted curve shows the linear progression in intensity throughout six months of intervention. The primary purpose in alternating the intensity and time per training session, is to accommodate the variation of treatment-related side effects. Therefore, the intensity of training will be low, and the total training time will be longer, when the burden of side effects will be high and vice versa.

PAPER IV

PAPER IV

Title: Feasibility of an exercise intervention and physical assessments during the first six months of cancer treatment in children and adolescents

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Brief running title: Feasibility of physical exercise and testing during acute cancer treatment in children and adolescents

Keywords: pediatric exercise oncology, physical assessment, exercise intervention, physical activity

Abstract

Purpose: The aim was to assess the feasibility of a randomized controlled exercise intervention, including physical assessments, in children and adolescents during the first six months of cancer treatment.

Materials and methods: A sample of children and adolescents (n = 84, 6–17.9 years) from an ongoing trial (INTERACT: NCT04706676) was randomly assigned to an integrative neuromuscular training (INT) intervention or active control intervention during treatment. The following inter-related feasibility domains were assessed: availability, acceptance, and attrition. Further, we assessed adherence to INT and physical assessments. Adverse events related to exercise and physical assessments were also reported.

Results: We found feasible rates within the availability and attrition domains. While the INT group demonstrated feasible group-level adherence rates, individual adherence to prescribed intervention demands was suboptimal. Physical assessments after six months of cancer treatment showed feasible rates.

Conclusion: This study offers insights into the feasibility of an early-initiated INT intervention designed for children and adolescents undergoing cancer treatment. To ensure an optimal frequency of exercise in future studies, a flexible approach to hospital-based INT and a structured strategy for

home-based exercise should be considered. Future trials should prioritize outcomes to minimize the length and timing of assessment.

Introduction

Children diagnosed with cancer typically experience a decline in physical activity levels during treatment [1–3] and frequently experience physical impairments, including reduced cardiorespiratory fitness, muscle strength, and balance, which subsequently affect their quality of life [1,4–7]. These impairments can persist into adulthood for childhood cancer survivors, elevating the risk of chronic medical conditions such as metabolic syndrome, diabetes, and cardiovascular disease [8–12].

Physical activity and exercise interventions in children and adolescents receiving cancer treatment have shown promise in maintaining physical capacity during cancer treatment, ultimately enhancing their quality of life and mitigating the risks of long-term health effects [1,4–7]. However, designing and administering safe, effective, and practical intervention studies in this population is challenging due to treatment-related side effects and motivational barriers [13]. Moreover, conducting physical assessments to evaluate physical capacity in the changeable nature of cancer treatment is complicated [7,13,14].

Key factors contributing to feasibility in intervention studies include participants accepting enrollment, adhering to the intervention without compromising the safety of the participants, and sustained engagement throughout the intervention period [15,16].

We therefore aimed to investigate the feasibility of a randomized controlled early initiated exercise intervention with physical assessments in children and adolescents during the first six months of cancer treatment.

Methods

Design

This explorative prospective feasibility study is based on data collected from an ongoing nationwide trial: Integrative Neuromuscular TRaining in Adolescents and Children Treated for cancer (INTERACT) [17]. This trial aims to investigate the effects of a supervised integrative neuromuscular training intervention (INT) in children and adolescents (6–18 years) during the first six months of cancer treatment.

Setting

INTERACT is a multicenter, two-arm parallel-group randomized controlled superiority trial (Clinical Trial registration NCT04706676) carried out at three of four main treatment centers in Denmark: Copenhagen University Hospital–Rigshospitalet, Odense University Hospital, and Aarhus University Hospital. Enrollment started in January 2021, and the inclusion of patients is expected to continue until October 2024.

Participants and recruitment procedure

The trial includes children with newly diagnosed cancer treated with chemotherapy and/or irradiation aged 6–17.9 years at diagnosis. Children with mental illness or physical disability, terminal illness, and children unable to speak Danish are excluded [17].

All children eligible for the INTERACT trial receive verbal and written information concerning the contents and trajectory of the trial within 14 days of treatment initiation.

Intervention and active control group

Participants were allocated to an active control group or an intervention group (1:1 ratio). A comprehensive description of both the intervention and active control interventions, including the rationale for the chosen methods, can be found in the trial protocol [17].

In addition to their usual care, the participants randomized to the intervention group received a 24-week integrative neuromuscular training (INT) intervention that incorporated general and specific strength and conditioning exercises designed to enhance both health- and skill-related components of

physical fitness [18,19]. A game and play-based approach for children and a more structured approach for adolescents was used for the INT intervention, which primarily targeted lower-body strength but also included exercises targeting other muscle groups and motor skills. Activities and exercises targeting lower-body strength were categorized as primary exercises, while exercises targeting upper-body strength and activities used for active recovery were categorized as secondary exercises.

The frequency and intensity (see Table 1) of the INT sessions were adjusted over the course of treatment. The frequency and intensity of training were lower in the first week after chemotherapy. During the first seven weeks, the participants were all advised to participate in a minimum of two non-consecutive training sessions per week, whereas three sessions per week were recommended during weeks eight through 24 (a total of 65 sessions). Of the 65 exercise sessions, the Intervention group was encouraged to partake in one weekly supervised exercise session.

Children and adolescents participated in supervised INT sessions when hospitalized, which included outpatient clinic visits. The INT sessions took place in the patient's room or a nearby hospital gym. During periods without hospitalization, the intervention group participants were encouraged to perform prescribed exercises at home. In addition to their usual care, the active control group participants received a booklet that functioned as a training log, with suggestions for upper-body, lower-body, and stretching exercises. The active control participants were encouraged to be physically active two or three times per week. The general program design of the INT intervention and the active control are outlined in Table 1.

Physical assessment

Assessment of physical capacity: Physical assessments of different aspects of physical capacity were conducted at baseline (treatment initiation—within 14 days of treatment initiation), three months after program initiation (±14 days), and six months after program initiation (±14 days). A detailed

description of each outcome for physical capacity can be found in the published protocol article [17] and at ClinicalTrial.gov (NCT04672681).

All assessments included measures of the primary outcome of lower-body muscle strength (measured with isometric knee extension strength (Gym 2000®, Vikersund, Norway and with a dynamometer – U2A100 kg, Hottinger, Germany)), and secondary outcomes of upper-body muscle strength (isometric bench press; Gym 2000®, Vikersund, Norway), handgrip strength (Jamar, Patterson Medical, Illinois, USA)[20], walking distance (6-minute walk test) [21], lower-extremity muscle strength, and endurance (30-second and 1-minute sit-to-stand tests, respectively) [22,23], basic functional mobility (timed up-and-go test) [24] (Lunar, Lunar Corporation Madison WI), balance (modified clinical test of sensory interaction in balance) [25] and physical activity and sedentary time (accelerometry (ActiGraph™, ActiGraph LLC, Pensacola FL).

Assessment of body composition, neuropathy, metabolic syndrome, and questionnaires: At baseline and six months after treatment initiation, the following outcomes were assessed: body composition (whole-body dual-energy x-ray absorptiometry (DXA) scan); neuropathy (pediatric modified total neuropathy score) [26]; and markers of metabolic syndrome (waist circumference, triglycerides, high-density lipoprotein (HDL) cholesterol, blood pressure, fasting blood sugar, and insulin). Patient- and proxy-reported general physical activity, health-related quality of life (PedsQL 3.0 cancer scale) [27], and fatigue (PedsQL multidimensional fatigue scale) [27] were also assessed.

Feasibility outcomes

Feasibility in the study was divided into two overall categories: 1) feasibility of early-initiated exercise encompassing various parameters relating to participation in the INTERACT trial intervention and active control group; and 2) feasibility of physical assessments, including adherence and safety of assessing the different trial outcomes.

The feasibility domains within these two categories (i.e., availability, acceptance, attrition, adherence, practicality, and safety, including calculations) are defined in Table 2. The table also contains acceptable (expected) cut-off values for each feasibility domain, defined a priori.

Regarding group-based adherence, it was expected from a practical perspective that each participant in the intervention group could attend, on average, one supervised in-hospital exercise session per week. At least one weekly visit to the hospital is scheduled so the child/adolescent could adhere to treatment procedures and protocols, including regular blood sampling. Depending on treatment and residence, however, participants were expected to have weeks without hospital visits or weeks with hospitalization and access to in-hospital exercise sessions. Participants being able to attend 24 supervised exercise sessions over the course of the 24-week intervention was therefore anticipated to be realistic. Based on two studies with similar populations and interventions, we expected the group-based adherence rate to be >65% [1,7].

For the safety domain, mild, moderate, and severe adverse events were defined according to the National Cancer Institute's common criteria [28].

Statistical methods

The INTERACT trial is expected to include 128 children with cancer [29]. To evaluate the feasibility outcomes of interest, 30–50 participants in each group are recommended for pilot studies [30,31]. Statistical considerations, including a priori considered acceptable cut-offs for all outcomes of interest, are presented in Table 2.

Group-based adherence: If participants attended more than the prescribed 24 supervised exercise sessions and 65 combined supervised and home-based sessions, these individual adherence rates were standardized to a maximum of 100% when calculating the group-based adherence. Since the INTERACT trial includes children and adolescents with different cancer diagnoses, we planned to conduct a sub-analysis of adherence rates, excluding participants who finalized their treatment before

the end of the intervention period or had periods where exercise was contraindicated and, therefore, were logistically or medically unable to attend all supervised exercise sessions.

Adherence—physical assessment: We expected the symptom burden of treatment to be more severe if participants were included at a later stage (and therefore assessed later), versus children who were included early in the trial. We therefore conducted a sub-analysis to investigate if the time from starting treatment until inclusion in the project would potentially interact with each participant's ability to complete baseline testing.

The Mann-Whitney U test [32] was used to compare the differences in completion of baseline testing (in primary and secondary physical capacity outcomes) based on the days enrolled in the trial from the start of treatment.

Ethics approval and consent to participate:

The participants and their parents all provided written, informed consent to participate in the INTERACT trial. The study was approved by the National Committee on Health Research Ethics (H-20040897) and the Danish Data Protection Agency (P-2021-14), and it complies with the Helsinki II Declaration.

Results

Of 110 eligible patients, 76% accepted participation; hence, 84 children were included in the study. Table 3 presents participant characteristics.

Children were included in the trial within a median of four days (IQR: 2–7) after treatment initiation and tested within a median of seven days (IQR: 5–10) after treatment initiation.

A visual presentation of the participant's process through the screening, inclusion, intervention period, and assessments—including reasons for declining participation and non-adherence within each feasibility domain—can be found in Figure 1. Selected feasibility outcomes and sub-analysis of the early initiated exercise intervention and of physical assessments are described below.

Feasibility of early initiated exercise

An overview of the results relating to the feasibility of early-initiated exercise can be found in Table 4.

Adherence—intervention group: Forty children participated in 685 supervised exercise sessions and logged 737 home-based sessions, thereby engaging in a total of 1,422 supervised and home-based exercise sessions in the course of the 24-week intervention period. Children participated in a median of 0.67 (IQR: 0.42–0.96) supervised exercise sessions or 1.65 (IQR: 0.78–2.00) total exercise sessions per week and a median of 16 sessions during the intervention period (IQR: 10–23).

When standardized to a maximum of 100% adherence, the intervention group participated in 638 supervised exercise sessions and logged 714 home-based exercise sessions, thereby engaging in a total of 1,352 supervised and home-based exercise sessions. The standardized data changed neither the median values for training sessions per week nor group-based adherence.

The primary reasons for not participating in supervised sessions were cancellations due to treatment-related procedures (31%), severe side effects (21%), lack of motivation for any physical activity (19%), physical restrictions (e.g., regimes after surgery, 12%), INT-related injury (9%), or fever (5%). Adherence varied between diagnoses: Children diagnosed with leukemia adhered to a median of 73% (IQR: 63–96%), children diagnosed with all other hematologic cancers adhered to a median of 57% (IQR: 39–67%), children diagnosed with extracranial solid tumors adhered to a median of 71% (IQR: 50–100%), and one child with a tumor within the central nervous system adhered to a median of 29%.

Adherence to intervention demands and practicality: Twenty percent (n = 8) of the participants adhered to the listed requirements (Table 1) of exercise frequency, participating in a minimum of 24 supervised exercise sessions. Regarding the practicality of exercise, we found that a median of 50% (IQR: 29–71) of the supervised sessions fulfilled the intensity requirements.

Adherence—active control group: Thirty-five children completed the active control intervention. Children in this group logged 607 registrations in the training logs, 349 of which were physical activities and 258 were registrations of non-adherence. The control-group children participated in a median of 0.04 (IQR: 0–0.75) training sessions per week or a median of 1 session (IQR: 0–19) during the entire active control intervention period (IQR25-75: 0–19).

Adherence to active control intervention requirements: Of the 35 children in the control group, only one participant adhered to the activity recommendations (i.e., performing two weekly exercise sessions, 48 in total).

From the training logs, the reasons for not participating in exercise included the following: lack of motivation for any physical activity (95%), physical restrictions (e.g., regimes after surgery) (2%), injury due to control intervention (2%), or fever (1%).

We noted that several training logs in the control group may be inexact, since 15 participants reported less than two registered activities (the first registered activity was usually when the training log was handed out and the participant was shown the suggested exercises). In these cases, the logs were either returned blank or not returned at all.

Feasibility of physical assessments

An overview of the results relating to the feasibility of physical assessment can be found in Table 5. Further, a visual presentation of adherence throughout the three assessment periods, including reasons for non-participation and abrupted assessments (i.e., assessments stopped by either participants or personnel), can be found in Figure 1. Reasons for stopping tests prematurely are specified within each outcome (see Supplementary File 1).

Physical capacity—baseline assessment of physical capacity: We found that 70% (n = 59) of the participants completed the isometric knee extension test (primary outcome), and 43% (n = 36) of the

participants were able to complete the entire physical assessment test battery within 14 days of treatment initiation.

A sub-analysis (Supplementary file 2) comparing the difference in inclusion time (days since treatment initiation) in participants who completed the entire test battery (median of 3 days, from treatment initiation IQR: 1.0–6.0) versus participants who did not complete (median of 5.5 days from treatment initiation, IQR: 2.25–8.75) showed that children not completing the entire test battery were generally tested later ($p = 0.0443$, $Z = 609$).

Safety—early initiated exercise and physical assessments: One participant (1%) experienced a severe adverse event (tibial tubercle avulsion fracture) during baseline assessment for isometric leg strength. In total, we conducted 184 isometric leg extension tests during the three assessment periods, corresponding to a rate of 0.005 adverse events per session.

No severe adverse events were registered during supervised or home-based exercise in the registered 1,422 sessions in the intervention group or 349 sessions in the control group.

During the supervised exercise sessions, seven minor events (events that led to interrupted training sessions, with temporary, transient symptoms) and four moderate adverse events (events that led to non-invasive interventions or caused limitations in daily living activities) occurred. These are described in Table 4.

Ten minor adverse events, causing interrupted (no-completion) assessment for parts of the test battery. These are described in Table 5.

Discussion

In this feasibility study of a randomized control superiority exercise trial, we found that several aspects of this early-initiated exercise intervention were feasible. Three-quarters of the eligible children accepted participation in the trial, which is slightly below our preset criteria (77% versus 80%, respectively); nevertheless, we regarded this as feasible, since parents and children experience

an immediate state of distress during the initial phases of cancer diagnosis and treatment. We also found that the attrition rate in the intervention control groups met the criteria for feasibility. The group-based adherence for supervised intervention was considered feasible, and we found that the collected data on either adherence or non-adherence during supervised sessions in the intervention group provided transparent reporting. In contrast, we found that the control group had a very low adherence rate to the self-administered intervention.

Overall, we found varying adherence rates to physical assessments throughout the six-month intervention period, which raised concerns regarding the feasibility of physical assessments during the early stages of cancer treatment. These rates were affected by symptom burden, treatment-related logistics, and the duration of the test battery. We found it feasible to measure isometric leg extension (primary outcome of the INTERACT trial) in the intervention group at six months, with slightly lower adherence (yet near feasible) rates in the control group. Physical assessments at baseline and three months may be biased due to selection bias, likely due to a higher treatment burden.

Twenty-four percent of the eligible children declined participation, which was above the preset cut-off value for success; hence, potential selection bias is a possibility. We set the 80% cut-off value based on previous experiences with a physical activity intervention on a similar population [33] with a 96% acceptance rate. This rate is considered very high compared to other pediatric oncology exercise interventions reporting acceptance rates ranging from 51–90% [3,5,6,33–35]. We lowered the acceptance rate to 80%, because we anticipated that the early inclusion in the trial would be a limiting factor, as parents and children report being in an immediate state of distress, acute stress, and elevated anxiety during the initial weeks of receiving a diagnosis and initiating treatment [5,36]. This was consistent with the declared reasons for declining participation. The un-adjusted group-based adherence was 67% in the intervention group, which is slightly above the preset criteria and comparable to similar trials reporting adherence rates of 65–68% [1,7]. In general, adherence or

attendance to research exercise interventions is either underreported or reported differently in the current body of evidence. We decided to provide several accounts of adherence, including individuals fulfilling criteria for intensity and exercise frequency, as the various aspects of adherence might be of interest when designing future studies.

A recent trial by Stössel et al. reported that children with all types of cancer could perform a mean of 2.7 ±1.2 (SD) supervised sessions per week of aerobic and strength training during intensive treatment [6]. In comparison, the children in our study reported a median of 0.67 (IQR: 0.42–0.96) supervised or 1.65 (IQR: 0.78–2.00) total training sessions per week. Of note, Stössel and colleagues offered supervised exercise in an in- and out-patient setting (58% of exercise sessions) as well as in patients' homes (25%). In the Stossel study, 17% of the sessions were conducted as self-administered exercises. Further, the duration of the intervention was shorter and adjusted individually to the individual participant's diagnosis (8 ±2.1 weeks). This highlights that a greater frequency of supervised sessions can be achieved, although doing so would require a higher degree of personalized exercise in combination with a flexible schedule and an adaptable exercise setting. During baseline testing of isometric leg extension, one participant suffered a tibial tubercle avulsion fracture. We did not find any deviations from test procedures in this patient, nor could we identify any markers that could have foreseen this event. No similar fracture has been reported previously under similar circumstances in the literature [5,37,38] nor from our international collaborators. As our research group has not experienced a similar event among more than 500 strength tests for ongoing trails [17,39], we consider the isometric leg extension test to be safe. We subsequently verified the testing procedures with the project staff at the center, and we did not find justification for altering test procedures or omitting the test from this or potential future studies.

We found that participants who completed the entire baseline test battery were included earlier in the project than children who could only participate in some or none of the assessments. As treatment

progressed, the occurrence and intensity of treatment-related side effects (e.g., pain, nausea, fatigue) increased, which could explain why children are less likely to participate in delayed physical assessment procedures. Of interest, a study reported that children with cancer were more likely to complete strenuous cardiopulmonary exercise testing if performed close to their last administration of chemotherapy [13]. Similarly, we found that children included later in the study—thus having received a longer duration of treatment—versus children who were included early were less likely to complete the entire test battery. In summary, we found that physical assessments conducted earliest in the test battery had the highest adherence rates (timed-up-and-go, handgrip strength, and isometric leg strength). We also found that tests conducted as the last part of the battery had the lowest completion rates at all points in time. These data suggest that timing, duration, and a prioritized order of the physical assessment battery are key variables to consider when planning assessments during acute cancer treatment in children and adolescents.

Strengths and limitations

The acceptance rate of 76% can be seen as a limitation of this feasibility study. As 24% declined participation, this may contribute to selection bias. Nevertheless, since this acceptance rate is above similar intervention studies, we consider the above findings viable.

Since this study included children and adolescents (6–17.9 years) with different types of cancer receiving different treatment protocols in three different centers coupled with a personalized integrative exercise intervention, the generalizability of our results may pose challenges when applied directly to specific diagnoses and settings. This complexity can be seen as a limitation; however, our aim was to present a broad array of feasibility parameters with a comprehensive report on adherence measures, as the various aspects of adherence might be of interest when designing future studies.

Implications for future research

In contrast to unsupervised self-administered interventions, supervised interventions are a determining factor in securing high adherence and transparency of the intervention [40]. Despite our interventions having a low frequency compared to the relatively long duration of the intervention (1 supervised session/weekly), two-thirds of the participants adhered to the prescribed frequency, and approximately half of the supervised interventions fulfilled the requirements of the prescribed intensity. We recommend aligning the anticipated frequency, intensity, and adherence with the available resources, as supervised exercise interventions must accommodate logistics and the changeable nature of cancer treatment [6,40,41]. We would further recommend that future studies explore the effectiveness of a more controlled approach to home-based interventions, which could include app-based exercise modalities or virtual (if not in-person), supervised approaches within the participants' homes.

Although this feasibility study had a high acceptance, 17 patients (16%) declined participation due to the parents and children lacking the mental clarity to make an informed decision about the trial during the early stages of cancer treatment. We nevertheless recommend early inclusion, as the treatment burden and side effects intensify, especially within the initial weeks of diagnosis. We also recommend that intervention studies prioritize the necessary resources and flexibility to give the children and parents well-informed instructions at a suitable time point, ideally coordinated in close cooperation with the nurse. The early initiation of exercise therapy appears critical, and early assessment is a crucial benchmark for targeted approaches.

Conclusion

This study offers valuable insights into the feasibility of an early-initiated exercise intervention for children and adolescents undergoing cancer treatment. Our findings indicate a high level of acceptance and adherence among children and adolescents, highlighting the feasibility of a strength training intervention and the assessment of physical capacity. To ensure a high frequency and

intensity of exercise in future studies, it is important to consider a flexible approach to supervised exercise and a more controlled strategy for home-based exercise.

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Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to Danish and EU personal data legislation but are available from the corresponding author upon reasonable request.

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https://doi.org/10.1016/j.ctrv.2018.08.012.

FIGURE AND TABLE LEGENDS:

Table title: TABLE 1 Overview of contents and requirements in the intervention and active control group.
[Table legend: Table 1: description of contents and requirements of prescribed exercise in intervention and active control group.
*Activities and exercises with a focus on lower-body strength were categorized as primary exercises. Other activities targeting other muscle groups or with a restitution purpose or diverting attention from treatment-related side effects were categorized as secondary activities.]

Table title: TABLE 2 Feasibility outcomes.
[Table legend: Overview of feasibility domains, measure, calculation, and pre-defined cut-off values for achieving feasibility. INT = exercise intervention group, CON = active control group]

Table title: TABLE 3 Participant characteristics.
[Table legend: participant characteristics. CNS = central nervous system, INT = Exercise intervention group, CON = Active control group]

Table title: TABLE 4 Results: feasibility of early initiated exercise.
[Table legend: Overview of feasibility results regarding early initiated exercise.
INT = exercise intervention group, CON = active control group
*Adjusted analysis without children who completed treatment 6 months before the end of the intervention period
**standardized to a maximum of 24 supervised sessions/participant
***standardized to a maximum of 48 home-based sessions/participant]

Table title: TABLE 5 Results: feasibility of physical assessment.
[Table legend: Overview of feasibility results regarding feasibility of physical assessment
INT = Exercise intervention group, CON = Active control group
Due to dropouts, 82 participants were eligible for 3-month assessments (42 INT, 40 Con), and 75 participants at 6 months (40 INT, 35 CON)
*for questionnaires: children were eligible for children aged 8–18 years (for baseline assessment, 67 children were eligible, and 70 were eligible for 6-month assessment (35 in intervention, 35 in control group)]

Figure title: FIGURE 1 Flowchart.
[Figure legend: Flowchart and overview of feasibility outcomes. ICU = Intensive Care Unit.]

Supplementary file title: Supplementary file 1 Reasons for not completing physical assessment
[Supplementary file legend: Assessment methods arranged by the order in test battery.]

Supplementary file title: Supplementary file 2 Boxplot of completed versus incomplete test at baseline

565 [Supplementary file legend: The influence of time since inclusions (from treatment initiation) on
566 completion rates of the entire physical capacity assessment battery at baseline.]

Table 1: Requirements of intervention and control group

	Intervention group (Integrative neuromuscular training)	Active control group
Description	24 weeks of supervised in-hospital exercise + unsupervised home-based exercise, initiated with two weeks of treatment initiation	24 weeks of unsupervised home-based exercise, initiated with two weeks of treatment initiation
Detailed description of unsupervised sessions	Week-to-week prescribed exercise based on in-hospital interventions. If the child participates in leisure time physical activities (e.g., soccer, gymnastics), these can replace prescribed exercise. If the child is not motivated, the participant is encouraged to do any physical activity (e.g., walking, jumping on a trampoline)	Control participants are recommended to follow an exercise plan (combined aerobic, strength, and stretching exercises) or be physically active
Registration of exercise	Supervised exercise: All sessions in logged by the exercise staff Unsupervised exercise: Participants/parents log activities in a printed exercise log	Unsupervised exercise: Participants/parents log activities in a printed exercise log
Requirements/Demands		
Frequency	Week 1-7: ≥2 exercise sessions per week Week 8-24: 3 exercise sessions per week (Total: 65 exercise sessions, of which 24 are expected to be supervised sessions)	Min. 2 Exercise sessions per week (Total: 48 exercise sessions)
Intensity	Week 1-7: ≥2 different exercises including ≥1 lower body exercise (primary exercises) * Week 8-24: ≥3 different exercises including ≥2 lower body exercises (primary exercises) *	-

Table legend: Table 1: description of contents and requirements of prescribed exercise in intervention and active control group.
*Activities and exercises with a focus on lower-body strength were categorized as primary exercises. Other activities targeting other muscle groups or with a restitution purpose or diverting attention from treatment-related side effects were categorized as secondary activities.

Table 2: feasibility outcomes

FEASIBILITY OUTCOMES			
Domain	**Measure**	**Calculation**	**Cut-off**
FEASIBILITY OF EARLY INITIATED EXERCISE			
Availability	Children within the target population fulfilling inclusion criteria	Participants fulfilling inclusion criteria/ Children diagnosed with cancer	>90%
Acceptance	Children approached who enrolled	Participants available for baseline assessment/ children eligible for trial	>80%
Attrition	Children who left study before completion	Participants dropped out during intervention period/ participants available for feasibility study	<10%
Adherence to demands (intervention)	Children in intervention group adhering to all supervised interventions	Participants adhering to prescribed frequency of exercise (24 supervised sessions)/ participants in intervention group at the end of intervention	>50%
Practicality (explorative)	Median supervised sessions fulfilling requirements for intensity	Supervised sessions** fulfilling requirements for intensity (prescribed number of primary and secondary exercises)/ participants in intervention group at the end of intervention	>40%
Adherence to demands (Control)	Children in control group adhering to all home-based interventions	Participants adhering to prescribed frequency of exercise (48 home-based sessions)/ participants in control group at the end of intervention	>50%
Group-based Adherence			>70%
- **INT (primary)**	Median adherence to intervention	Median of total supervised sessions per participant (INT)	-
- **CON**	Median adherence to control intervention	Median of total home-based sessions per participant (CON)	-
Safety early initiated exercise	Children reporting severe adverse events during exercise	Reported events/eligible children	<5%
FEASIBILITY OF PHYSICAL ASSESSMENT			
Adherence physical assessment	Children adhering to physical testing	Participants participating in physical assessment/ participants available for feasibility study	>80%
Safety physical assessment	Children reporting mild, moderate or severe adverse events during physical assessment	Reported events/eligible children	<5%
Safety physical assessment (subanalysis)	Adverse event rate per test sessions	Reported events/total number of test sessions	-

Table legend: Overview of feasibility domains, measure, calculation, and pre-defined cut-off values for achieving feasibility. INT = exercise intervention group, CON = active control group

Table 3: participant characteristics

Anthropometric characteristics			
	All participants (n=84)	INT (n=44)	CON (n=40)
Sex (males/females)	51 /33(64/36 %)	25/19 (57/43 %)	26/14 (65/35 %)
Age (mean±SD)	11.6 ±3.7 years	11.6 ± 3.9 years	11.6 ± 3.4 years
Diagnosis			
- Acute lymphoblastic leukemia	n= 24, 13 males (54 %)	n= 14, 8 males (57 %)	n= 10, 5 males (50 %)
- Other hematological cancers	n=30, 20 males (67 %)	n= 15, 10 males (67 %)	n= 15, 10 males (67 %)
- Extracranial solid tumors	n= 22, 12 males (55 %)	n= 12, 5 males (42 %)	n= 10, 7 males (70 %)
- CNS-tumors	n= 8, 6 males (75 %)	n= 3, 2 males (67 %)	n= 5, 4 males (80 %)
Height (mean±SD)	142.0± 44.5 cm	147.0 ± 39.3 cm	152.6±32.4 cm
Weight (mean±SD)	42.5±18.7 kg	44.6±19.1 kg	46.7±19.8 kg
BMI (mean±SD)	17.8 ±3.6	17.3±3.3	18.2±4.0

Table 3: participant characteristics. CNS=central nervous system, INT= Exercise intervention group, CON= Active control group

Figure 1: Flowchart

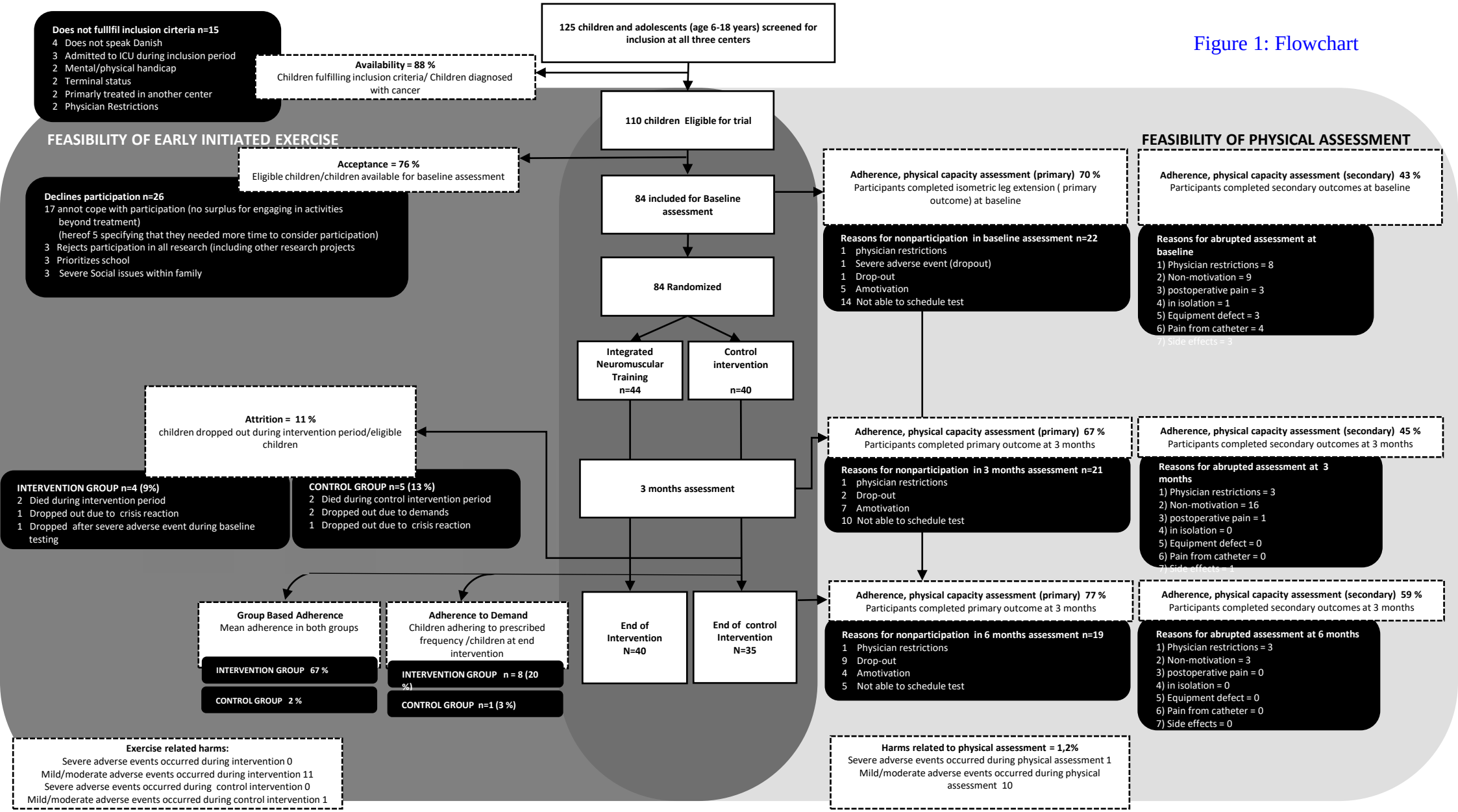


Table 4 Results: feasibility of early initiated exercise

RESULTS, FEASIBILITY OF EARLY INITIATED EXERCISE			
Domain	Calculation	**Reported results and subanalysis**	**Cut-off**
Availability	110 children eligible for trial / 125 children diagnosed with cancer	88%	>90%
Acceptance	84 children available for baseline assessment/ 110 children eligible for trial	77 %	>80%
Attrition	9 children dropped out during intervention period/ 84 children available for feasibility study	11 %	<10%
- **INT**	4 children dropped out intervention/ 44 children available for feasibility study (INT)	9 %	
- **CON**	5 children dropped out control intervention/ 40 children available for feasibility study (CON)	13 %	
Adherence to demand (frequency)			
- supervised sessions (primary)	8 children adhered to all supervised sessions/40 children available for feasibility study (intervention)	20 % (23 %*)	>50%
- supervised and home-based	3 children adhered to all supervised and home-based sessions/40 children available for feasibility study (intervention)	8 % (10%)	
- home-based (CON)	1 child adhered to all home-based sessions/35 children available for feasibility study (control)	3 %	
Practicality (intensity)	Median % 507 supervised sessions** fulfilling requirements for intensity/40 children available for feasibility study (intervention)	50 %, IQR: 29-71	-
Group-based Adherence			
- INT	Median % of 638** supervised sessions/40 children available for feasibility study (intervention)	67 %, IQR: 42-96 (75 %, IQR: 58-98*)	>65%
- CON	Median % 343*** home-based sessions/35 children available for feasibility study (intervention)	2 %, IQR: 0-40	>65%
Safety of early initiated exercise			
- Severe adverse events (primary)	0 severe adverse events reported during exercise or physical activity	-	<5%
- Minor/moderate adverse events	**Intervention group:** **7 minor adverse events** (3 acute nausea, 2 temporary distress /crying, 1 pain from stomach, 1 pain from back **4 moderate adverse events** (2 occasions of transient but notable delayed muscle soreness, 1 sprained fifth toe during home-based exercise (full recovery) 1 sprained ankle during home-based exercise (full recovery)) **Control Group:** **1 moderate adverse event** (1 sprained ankle during leisure time sport activity (full recovery))		

Table legend: Overview of feasibility results regarding early initiated exercise.
INT = exercise intervention group, CON = active control group
*Adjusted analysis without children who completed treatment 6 months before the end of the intervention period
**standardized to a maximum of 24 supervised sessions/participant
***standardized to a maximum of 48 home-based sessions/participant

TABLE 5 Results: feasibility of physical assessment

RESULTS, FEASIBILITY OF PHYSICAL ASSESSMENT					
DOMAIN	**TIMEPOINT**	**TEST PARAMETER**	**RESULTS GROUP**	**INT**	**CON**
Adherence physical testing	**BASELINE** 62 of 84 (74 %) were able to participate in baseline assessment	Iso.knee extension	n = 59 (70 %)		
		Iso. bench	n = 44 (52 %)		
		TUG	n = 59 (70 %)		
		Balance	n = 55 (66 %)		
		STS 30	n = 51 (61 %)		
		STS60	n = 51 (61 %)		
		Handgrip	n = 62 (74 %)		
		6MWT	n = 49 (58 %)	-	-
		TOTAL (all test)	n = 36 **(43 %)**		
		Physical Activity	n = 46 (55 %)		
		DEXA	n = 47 (56 %)		
		Metabolic syndrome	n = 58 (69%)		
		Neuropathy	n = 45 (54 %)		
		Questionnaire Child*	n = 41 (62 %)		
		Questionnaire proxy	n = 54 (64 %)		
	3 MONTHS 63 of 82 (78 %)	Iso.knee extension	n = 55 (67 %)	n = 29 (69 %)	n = 26 (65 %)
		Iso. bench	n = 48 (59 %)	n = 26 (62%)	n = 22 (55 %)
		TUG	n = 55 (67 %)	n = 29 (69 %)	n = 26(65 %)
		Balance	n = 56 (68 %)	n = 31 (74 %)	n = 25 (63 %)
		STS 30	n = 53 (65 %)	n = 28 (67 %)	n = 25 (63 %)
		STS60	n = 52 (63 %)	n = 28 (67 %)	n = 24 (60 %)
		Handgrip	n = 63 (77 %)	n = 34 (81 %)	n = 29 (73 %)
		6MWT	n = 46 (56 %)	n = 25 (60 %)	n = 21 (46 %)
		TOTAL (all test)	n = **37 (45 %)**	n = **19 (45 %)**	n = **18 (45 %)**
		Physical Activity	n = 34 (41%)	n = 11 (26 %)	n = 15 (38 %)
	6 MONTHS 66 of 75 (85 %)	Iso.knee extension	n = 58 (77 %)	n = 32 (80 %)	n = 26 (74 %)
		Iso. bench	n = 55 (73 %)	n = 31 (78 %)	n = 24 (69 %)
		TUG	n = 62 (83 %)	n = 38 (95 %)	n = 24 (69 %)
		Balance	n = 63 (84 %)	n = 37 (93 %)	n = 26 (74 %)
		STS 30	n = 61 (81 %)	n = 36 (90 %)	n = 25 (71 %)
		STS60	n = 61 (81 %)	n = 36 (90 %)	n = 25 (71 %)
		Handgrip strength	n = 66 (85 %)	n = 38 (95 %)	n = 27(77 %)
		6MWT	n = 56 (75 %)	n = 33 (83 %)	n = 23 (66 %)
		TOTAL (all test)	n = **44 (59 %)**	n = **24 (60 %)**	n = **20 (57 %)**
		Physical Activity	n = 34 (45 %)	n = 17 (43 %)	n = 17 (48 %)
		DEXA	n = 56 (75 %)	n = 30 (75 %)	n = 26 (74 %)
		Metabolic syndrome	n = 65 (87 %)	n = 32 (80 %)	n = 33 (94 %)
		Neuropathy	n = 51 (68 %)	n = 25 (63 %)	n = 26 (74 %)
		Questionnaire Child*	n = 48 (69 %)	n = 24 (69 %)	n = 24 (69 %)
		Questionnaire proxy	n = 53 (71 %)	n = 29 (73 %)	n = 24 (69 %)
Safety of physical assessment					
- Severe adverse events (primary)	**1 (1 %)**				
- Rate of severe adverse event	**0.005 adverse event/ test session.**				
- Minor adverse events	2 transient pain from patella during iso.leg ext. 6 transient pain from shoulder during bench pres 2 transient nausea (no fainting) during balance testing **Total 10 minor adverse events (8.4%)**				

Table legend: Overview of feasibility results regarding feasibility of physical assessment.
INT = Exercise intervention group, CON = Active control group, TUG= timed-up-and-go test, STS= Sit-to-stand test, 6MWT=6-minute-walk-test.
Due to drop-outs 82 participants were eligible for three-month assessments (42 INT and 40 Con), and 75 participants were eligible at 6 months (40 INT and 35 CON)
*for questionnaires: children were eligible for children aged 8-18 years. (for baseline assessment, 67 children were eligible, and 70 were eligible for 6-months assessment (35 I intervention and 35 in control group)

Implications of rehabilitation

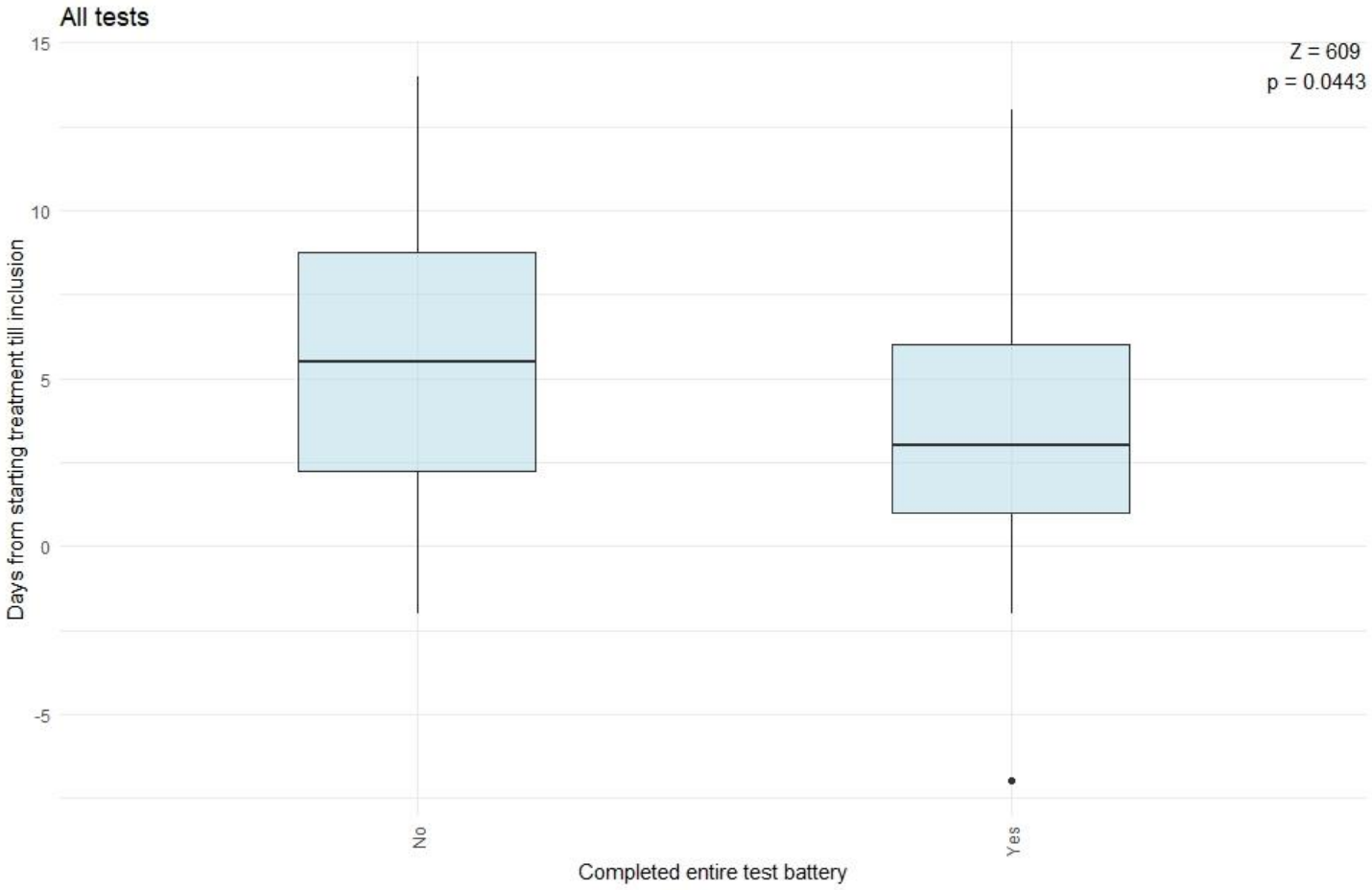
- To ensure a high frequency and intensity of exercise in future studies, it is important to consider a flexible approach to supervised exercise and a more controlled strategy for home-based exercise.
- Treatment duration affects children and adolescents with cancer's ability to perform physical performance assessments. Healthcare professionals should consider the timing of physical performance assessments and prioritize outcomes to minimize the length of assessment.

Supplementary file 1: Reasons for not completing physical assessment

	Baseline (76 participants available)	**3 months** (63 participants available)	**6 months** (65 participants available)
Timed-Up-and-Go			
1) Physician restrictions	n = 3	n = 1	
2) Non-motivation		n = 1	
Handgrip			
	No tests was abrupted by participant		
Isometric leg extension			
1) Physician restrictions	n = 1	n = 1	
2) Non-motivation		n = 2	n = 1
3) postoperative pain	n = 1		
4) in isolation	n = 1		
5) Equipment defekt	n = 3		
Isometric bench press			
1) Physician restrictions	n = 3	n = 1	n = 3
2) Non-motivation	n = 4	n = 2	n = 1
3) postoperative pain	n = 2	n = 1	
6) Pain from catheter	n = 4		
Sit-To-Stand			
1) Physician restrictions	n = 1		
2) Non-motivation	n = 1	n = 1	
Balance			
1) Physician restrictions			
2) Non-motivation	n = 2	n = 2	n = 1
7) Side effects	n = 1		
Six-minute-walk test			
2) Non-motivation	n = 4	n = 8	
7) Side effects	n = 3		

Assessment methods arranged by the order in test battery.

Supplementary File 2



Supplementary file title: Supplementary file 2 Boxplot of completed versus incomplete test at baseline

[Supplementary file Legend: The influence of time since inclusions (from treatment initiation) on completion rates of the entire physical capacity assessment battery at baseline.]

PAPER V

PAPER V

Title: **Exploring the motivation among children and adolescents for exercise during the first six months of cancer treatment: a qualitative study**

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Number of tables/figures: 2/1

Abstract

Purpose: To improve understanding of what influences motivation of children and adolescents diagnosed with cancer to engage in exercise during the first six months of treatment.

Materials and methods: Qualitative design using semi-structured interviews with children (6–17 years) diagnosed with cancer (n=12) and their parents (n=12). A deductive thematic analysis based on self-determination theory was applied.

Results: Three predefined themes described different aspects of motivation for exercise during treatment.

Amotivation: Treatment-related illness and fatigue causing amotivation was described as a dominant barrier. Exercise driven by negative reinforcements facilitated short-term exercise engagement but was perceived as amotivation.

Controlled regulation: Exercise regulated by exercise professionals could facilitate and introject positive experiences with exercise (i.e. ameliorated side effects) and create confidence in physical capabilities.

Autonomous self-regulation: An autonomy-supportive approach using co-creation and age-appropriate and treatment-regulated exercise, facilitated trust, and confidentiality with exercise professionals.

Conclusion: Motivation for exercise is a dynamic interplay that can be facilitated or negatively affected by treatment, parents, peers, and external regulation. Exercise interventions should use an individual and autonomy-supportive approach, encompassing treatment-related daily variations of physical capacity. Externally regulated motivation can facilitate exercise on a short-term basis when children are inactive or hesitant to engage in exercise.

Keywords: pediatric exercise oncology, motivation, self-determination theory

INTRODUCTION

Early initiation of physical exercise limits the physical deterioration caused by inactivity and treatment-induced toxicities, such as muscle wasting, altered body composition, balance deficiencies, and impaired gait during cancer treatment in children with cancer [1]. Motivation plays a crucial role in child engagement in exercise throughout the cancer treatment trajectory [2]. Cancer treatment is challenging for children; the physical and emotional toll of cancer and treatment (primarily chemotherapy, radiation, and steroids) severely impacts physical capacities (i.e., muscle strength, endurance, and physical competence) within weeks after treatment initiation alongside fluctuating periods of fatigue and lethargy throughout the treatment trajectory [1,3–5]. Further, being hospitalized for long periods also causes social isolation, separating children from their peers. The psychosocial consequences include loss of autonomy and reduced quality of life [6–8]. Supervised physical activity and exercise can counteract these adverse physical and social side effects of childhood cancer treatment across diagnoses, as shown in controlled trials [8–11]. However, the body of evidence shows that adherence rates to exercise interventions have substantial individual variability [8–11]. Motivation is a driver for adhering to and engaging in physical activity and exercise, and it might be a crucial variable for understanding how participating and engaging in exercise fluctuates throughout cancer treatment [12–14]. It is therefore relevant to explore the barriers and facilitators of motivation in children and adolescents during cancer treatment, as this influences their ability to potentially mitigate treatment-related side effects.

Purpose

This study aims to improve our understanding of what influences the motivation of children and adolescents diagnosed with cancer (ages 6–17) to engage in an exercise intervention during the first six months of cancer treatment. In this study, motivation will be operationalized by the following three areas: amotivation, controlled regulation, and autonomous self-regulation.

METHODS

Approach

This study used a qualitative design based on in-depth semi-structured interviews [15]. Data was analyzed using a deductive thematic analysis based on the principles of self-determination theory [16–18]. The reporting of the study follows the Standards for Reporting Qualitative Research in Medical Education (SRQR)[19].

Context

The participants in this study were all enrolled and allocated to the intervention group in the Integrative Neuromuscular Training in Adolescents and Children Treated for Cancer (INTERACT) randomized controlled trial. [20]. The INTERACT trial investigates the effects of a six-month integrative neuromuscular training intervention in children and adolescents diagnosed with cancer (age 6–17 years) from three of four university hospitals in Denmark (Aarhus, Odense, and Copenhagen University Hospital – Rigshospitalet) compared with an active usual care group.

Intervention components

In addition to usual care, the intervention group received a six-month strength-based exercise intervention: integrative neuromuscular training. The exercise intervention started within two weeks of treatment initiation and was designed as games and play-based exercise or performed as a structured strength-and-conditioning program, depending on the participant's age, gross motor skill level, and daily variations in side effects (e.g. nausea, fatigue, dizziness, pain). In contrast to more traditional forms of physical activity (e.g. walking, cycling), integrative neuromuscular training specifically targets neuromuscular deficits by stimulating neural plasticity, enhancing motor unit recruitment, firing frequency, and synchronization of motor unit activation [21–26]. This integrative neuromuscular training program is designed to improve physical fitness in children ages 6–17 during cancer treatment.

The intervention used an autonomy-supported approach; although exercise professionals designed and supervised the exercise sessions, the individual participant's decisions, perspectives, and interests were acknowledged and included. Consequently, the participant was encouraged to suggest exercises or activities in each session.

The children would receive supervised training when hospitalized or visiting the outpatient clinic. When at home, the participants were encouraged to do home-based exercises based on an individual program, or they could choose to do any type of physical activity (any bodily movement that would increase their heart rate), depending on the child's physical state. Elaborative descriptions of the components of the intervention are described elsewhere [20].

Sampling strategy

A purposeful criterion-based sampling strategy was used [27,28]. Participants and parents were interviewed between February 2022 and March 2023. Eligible for this study were children (participants) who were enrolled in the INTERACT intervention arm for at least three months (and their respective parents or guardians) from all three centers, and who were no more than two months post-intervention termination.

We strived to select children and adolescents with different diagnoses, ages, sexes, and adherence rates to the exercise intervention.

Data collection methods and instruments

An overall framework for the interview guides used in this study was specifically developed to collect insights from the participants and their parents concerning their experience with the intervention based on the principles of self-determination theory: 1) autonomy (e.g. "Can you give an example of an activity that you did in the exercise session that you decided?" and "Did you do some of the components of the intervention on your own?"); 2) relatedness (e.g. "What makes the

interventions components fun/dull?"); and 3) competence (e.g. "Do you feel any change in your physical condition due to the intervention?").

Three semi-structured interview guides were developed: one for children (ages 6–10), one for adolescents (11–18), and one for parents (Supplementary file 1). We divided the participants into two groups to accommodate potential differences in developed language and knowledge. For example, the interview guide for younger children would accommodate how young participants would not understand terms like exercise and physical activity (would be translated to "movement that makes you sweat") or would have prompting questions to help them distinguish side effects. Parents' questions were framed as proxies, and they were also asked to recollect how they viewed their own role during exercise and physical activity at the hospital and at home.

Participants and parents were interviewed separately, but the parents were present if requested by the child.

Both interviewers (NNP and PSA) had extensive experience with communicating with children diagnosed with cancer and their parents in the context of physical activity. None of the interviewers and participants had met previously. As one of the two interviewers (PSA) conducted the intervention in one center, interviewer NNP conducted these interviews. Interviews were scheduled with the parents and took place in a quiet, undisturbed environment (the patient's room or a hospital conference room), and they were audio-recorded. Online, videoconference-based interviews were used and recorded if an interview at the hospital was impossible.

Ethical considerations

The present study complies with the Helsinki II Declaration, and the handling of data has been approved by the Danish Data Protection Agency (jr. nr.: P-2021-14). Furthermore, the INTERACT study has been approved by the Danish National Committee on Health Research Ethics (Approval Number: H-20040897).

For the interviews, the participants all provided informed consent to participate and, independent of age, were asked if they would like their parents to be present during the interview.

Data processing

In this study, the participants' motivation, including facilitators and barriers to participation in physical exercise and physical activity during cancer treatment, is based on the principles of self-determination theory (SDT) and how they can be applied in the healthcare context [12,14,18]. SDT illuminates the dynamic interplay between intrinsic and extrinsic motivational forces (16–19): two distinct forms of motivation that drive human behavior. Intrinsic motivation arises within the individual, stemming from internal desires, interests, and personal satisfaction. The driving force behind intrinsic motivation is often the inherent pleasure, curiosity, or sense of accomplishment one experiences while engaging in the task itself. Conversely, extrinsic motivation originates from external factors and relies on external incentives, money, praise, social status, or even punishment, to encourage behavior.

The theory identifies three inherent intrinsic psychological needs: autonomy ("the feeling of being the origin of one's own behavior"), competence ("feeling effective"), and relatedness ("feeling understood and cared for by others") as a counterpart to extrinsic motivation, which shapes this interplay [29].

As a continuum, SDT spans from pure autonomy-driven or -supported motivation to strictly externally controlled behavior deprived of any autonomy, leading to amotivation. This continuum, and how intrinsic (autonomy, relatedness, and competence) and extrinsic motivational factors are regulated into behavior, are addressed in this study as amotivation, controlled regulation, and autonomous self-regulation, as these domains broadly cover the whole continuum [18,29]. This applied analytic approach favors internalization (i.e. how a regulated behavior can potentially develop a framework for sustained autonomous behavior).

Data analysis

Participant and parent interviews were transcribed ad verbatim, separately, and PSA and NNP thematically analyzed the transcripts using a deductive approach, as described by Braun and Clarke [16].

The analysis consisted of five steps: (1) an overall framework for potential codes was written while listening through the recorded interviews; (2) coding the transcripts into meaning units, which would be categorized within the overall self-determination domains: autonomy, relatedness, competence, and extrinsic motivation; (3) transforming the meaning units into condensed meaning units; (4) further categorizing the units within the three self-determination behavior regulation domains (amotivation, controlled regulation, autonomous self-regulation) and comparing the themes with the transcribed data to ensure accurate representation; and (5) the meaning units and categorization was iteratively discussed within the author group, and the themes were refined according to the discussion. See Figure 1 for a visual representation of the analysis, including identified themes and subthemes.

Techniques to enhance trustworthiness

In this study, trustworthiness is based on concepts of credibility, dependability, and transferability [30]. Measures taken to improve credibility and transferability are described in the sampling strategy, data collection methods, and analysis.

We continuously interviewed and analyzed data to assess the potential saturation of data if no new themes would emerge. We were aware of how we may have affected dependability by interviewing and analyzing data simultaneously, as the interviewers may have narrowed their focus. We did not alter the interview guide, however, and the deductive approach allows us to maintain the scope of the study.

FINDINGS

The data comprised 24 interviews with 12 participants paired with their parents. Ten interviews were conducted as online video consultations, and two interviews were conducted via telephone. We included nine boys and three girls with a median age of 11 (range 6–17). Six participants were diagnosed with acute lymphoblastic leukemia, six with different types of solid tumors, one of whom had a solid tumor in the central nervous system (see Table 1 for a description of the participants). Three participants—one girl (age 8) and two adolescents (16-year-old boy, 17-year-old girl)—who had very low adherence rates to the supervised exercise sessions were approached but declined to participate or did not respond.

Several factors facilitating the initiative and, ultimately, autonomous exercise or barriers leading to amotivation were identified. Based on the analysis, these are described within the three SDT behavioural domains: amotivation, controlled regulation, and autonomous self-regulation. See Figure 1 for an overview of the analysis, themes, and subthemes. An overview of identified facilitators and barriers for motivation in each theme can be found in Table 2.

Theme: Amotivation

Treatment-related side effects

Feeling ill and fatigued due to treatment was described as a dominant factor for amotivation. Participants explained that they would categorically decline exercise and physical activity during the most intensive cancer treatment periods or in the last periods of a treatment block. They described how the most strenuous parts of treatment would deprive them of their energy and motivation, keeping them bedridden due to fatigue or because they needed to conserve their energy.

> *When you're here, it's because you're undergoing treatment or going through a particularly tough time. During that month when I had pneumonia, my energy was very low. And then they came in and asked, "What do you say to a little exercise? Just getting up, out of bed, standing up, sitting down, stepping once, up and down?" And I*

said, "No, I can't do it anymore!" All my energy is being used to fight cancer. So right now, I really need all my energy.

(Participant, 16 years)

During such periods, because of the magnitude of side effects (e.g. fatigue, nausea, dizziness), the participants declined to participate in exercise and physical activity, leaving the exercise professional and parents with limited options to facilitate the intervention.

If I've been feeling really awful, then I haven't been able to do anything […] *I mean, it was like I couldn't do anything at all.*

(Participant 17 years)

Even though parents described how they would see improvement in physical competencies, they could not distinguish if this improvement was due to exercise or simply treatment-related side effects (or toxicities) subsiding.

Physically, I think it's difficult to find something measurable—because [girl] *has been very ill during certain periods. So, you could say there may have been a period where we thought it was working. And when we have been here many times, she has received a lot of training. And she thought she could do a lot. And then suddenly, she had a setback, and we're back to square one. It's hard to say whether it's the training itself that makes it better or if it's the side effects of the medication that are wearing off.*

(Father to participant, 9 years)

Experiencing these fluctuating periods of either feeling ill and being sedentary versus active and closer to usual self was a source of frustration and amotivation for parents and participants alike.

External regulation of behavior

If the participants had prolonged periods with sedentary behavior, parents or exercise professionals would turn to a more externally regulated approach (e.g. pressure or negative reinforcement).

Children would describe how they would do the "prescribed" exercises at home simply because they were pressured to do so or ultimately sanctioned by their parents.

> Child: *I hate it* [doing exercise]. *I don't like it. It's my mother's idea.*
>
> Mother: *Every time, right? Well, it's really serious. I say, "If you don't come now, I'll unplug the internet." That's when he goes, "Okay, okay." And then we go.*
>
> Interviewer: *But you still do it?*
>
> Child: *Yes.* […] *Because there are consequences if I don't.*
>
> (Mother and participant, 10 years)

Although this approach facilitated exercise on a short-term basis, the activity was perceived as irrelevant with a lack of value that would lead to amotivation for the participants. Exercise was therefore seen as a necessary but tiresome, daunting, and even agonizing activity. Ultimately, this would compromise the intensity and duration of exercise, limiting the potential physical benefits of exercise as children would describe how these benefits on physical competencies were unachievable when parent used this impersonal approach.

> *It's mostly just my dad who kind of pushes me because I don't really enjoy exercising* […] *He just scolds me* […] *And, well, it's not like it makes me want to exercise more. It's just like that. Well, I do want to get stronger, but maybe that's not the best motivation.*
>
> (Participant, 17 years)

Children would respond by further declining physical activity and exercise unless they experienced more intrinsically motivated drivers (e.g. feeling a perceived improvement of physical competencies).

Theme: Controlled regulation

Internalization through external regulation

Parents described extrinsic motivation through external regulation as a necessary tool to facilitate physical activity and exercise; otherwise, the children would be inactive. This could eventually

introject and internalize insight into being able to improve their physical competence and facilitate intrinsically motivated behavior.

> *At home, we've said: "You have to do this before you continue watching your screen." He has been a bit grumpy about it, but he has done it. And then he himself actually said at one point: "It was good that you told me to do it because I can feel that I'm getting stronger."*
>
> (Mother to participant, 8 years)

Even though the children described the side effects as being a dominant factor for amotivation, they also experienced exercise as being able to counter the treatment-related deficiencies, as they felt that they were getting physically stronger and could endure longer activities by doing exercise. The thought of improving physical competencies would make the transition from going back and forth between the hospital and home environment easier.

> *I can actually participate in a lot more. Today, we're even going up* [the stairs] *to the 13th floor. I've come a long way. I've improved a lot. And there's a lot more I can do.*
>
> (Participant, 14 years)

If this internalization happened (i.e. by introjecting a perceived benefit on physical competencies), exercise was described as a positive aspect during hospitalization and as an intrinsic motivational driver for going to the hospital.

> […] *as a caregiver, you need to have different things that can motivate* [the participant to go to the hospital]*: There is pampering. There are things you can buy. And this exercise has been one of the things that we could use as motivation.*
>
> (Father to participant, 14 years)

Further, parents explained that being a part of an exercise intervention facilitated physical activity as a part of hospitalization. At home, it would create routines for physical activity and exercise,

which benefitted the whole family. By presenting the children with a framework, either by aligning expectations or scheduling physical activity, the children were kept in an active everyday life, which the parents described as benefiting the course of treatment.

> *I think it makes so much sense. I easily believe that you can fall into a mindset where, when your child gets ill, there are many hospitalizations. And, well, that's what we experienced. Almost from one day to the next, he was lying in a hospital bed most of the time. Trying to get him up and moving early on, I believe, has been crucial for his progress, and he had a really good treatment trajectory because he was out of that bed early on and active. He almost didn't have a chance to just lie there, because then* [the exercise professional] *would come, and they would do all sorts of things, play and exercise, and whatever they were up to.*
>
> (Mother to participant, 6 years)

Controlled regulation was therefore a necessary tool to ultimately introject and internalize the importance of physical activity and exercise and to facilitate motivation.

Guidance

The parents and children all described how outside help and guidance from exercise professionals was necessary to promote and facilitate exercise. Parents felt that their own resources were limited, as they were adjusting their everyday lives to the different demands and concerns relating to caring for a child with a cancer diagnosis. As parents, they had certain responsibilities (e.g. showing up to appointments, adhering to fasting regimes, administering medication) usually facilitated through extrinsically regulated behavior. Accordingly, they described how, in their current role as a parent to a child with cancer, they could not facilitate exercise; at least not in the same way as an exercise professional without such controlled obligations. As one parent described:

> *It's really fantastic* [the training]. *It's great to have someone with enthusiasm and motivation that we as parents don't possess. And having someone external who*

connects well with [girl] *and enjoys working with her is very positive* […] *because it gets her going—maybe more than what we would do. We're all caught up in our duties and "must-do" tasks. So it's really cool to have someone come from the outside with an "excitement task"* […] *Dad is very into being active and thought it was a great idea. I also think it's a really great idea, because we don't currently have that same enthusiasm and motivation. So it's nice to have some external help.*

(Mother to participant, 7 years)

Some parents experienced that their presence during exercise was a barrier for their child, as the child would be reluctant and show less initiative. However, parents also described how observing or even taking part in the exercise sessions provided inspiration which could be adapted to the home environment.

The reason I've stepped back [leaving the room when exercise was occurring] *is that I have a sense that he follows* [the exercise professional's] *instructions more when I'm not around. There's something about me observing.* [Exercise professional] *might be able to get him to do certain things more easily when I'm not there.*

(Mother to participant, 8 years)

The parents also possessed insight into their child's unique body language and behaviour, being able to read signals and signs, which would ensure the child's well-being during exercise but also provide guidance and push their boundaries. For example, one parent described how it was important that they were present, as the child would be reluctant to say "Stop," because he would not disappoint the exercise professional.

Actually, he struggles with saying "No" sometimes. We've practiced it a lot—the ability to say "No." That he doesn't disappoint others, you know? When he really

wants to do something, I also tell him that if he's feeling nauseous, he should say "No." And it's not like he isn't active at home.

(Mother to participant, 12 years)

A positive relationship with the exercise professional facilitated motivation for physical activity and exercise. If activities were considered fun for the child, it facilitated motivation, as the exercise sessions were perceived as a break or diversion from some of the strenuous parts of treatment. Guidance from an exercise professional made children and parents aware of the children's physical abilities, which would further facilitate exercise and physical activity at home and help to set boundaries.

I think it makes a difference that I see [girl] *being able to do certain things with* [exercise professional] *that she may not always be able to do with me. It also gives me more courage as a mother to push a little and say, "Oh, you can squat down." Because in the beginning, when* [girl] *was really unwell and kept pulling on me and falling many times, I became incredibly worried. Every time we were out, I held onto her all the time. But when you see that she can crawl around on the floor and do all sorts of things with* [exercise professional]*, you also realize that if I relax a bit, she might relax more, too. I think it has definitely made a difference, especially at home.*

(Mother to participant, 9 years)

In that sense, guidance and a good relationship with the exercise professional facilitated motivation. This relationship would also be essential to adjusting the intensity or challenge of exercise.

Appropriate challenge and intensity

The parents and participants described how adjustments of intensity to accommodate variations in side effects and motivation were facilitating, as it meant that the child felt acknowledged in terms of expressing their current state and physical symptoms. This approach in exercise sessions fostered positive experiences.

I think that [exercise professional] *has been quite good at doing something that* [boy] *found fun and varied, and a bit more playful than just boring training. And* [exercise professional] *has also, as far as I have experienced, been good at meeting* [boy] *where he was each day... I mean, where he was on the motivation scale, and also accepting that, "OK—today you're not up for much."*

(Mother to participant, 8 years)

If the exercise professionals were attentive to the current state of the individual participant, offering appropriate exercise according to side effects, this could eventually spark interest and curiosity, which would facilitate exercise and physical activity in situations where children would otherwise decline physical activity and exercise.

In the beginning, both [exercise professional] *and I together assessed that* [boy] *was too tired and unenthusiastic and had too much of a negative attitude towards the training. And I think it has been so great that acknowledging that was an option. But gradually, it's as if* [boy] *has become more and more curious and interested in it because he started feeling better and better. So I believe it has definitely made a difference in the course of the treatment.*

(Mother to participant, 6 years)

Naturally, adhering to exercise became easier as symptoms and treatment-related side effects were reduced and vice versa: if symptoms progressed, children would become less motivated to do exercise. One mother explained how she felt her son was less motivated to participate in exercise sessions during hospitalization, as his symptoms would only progress throughout treatment,

In the beginning, every time [exercise professional] *said, "Now squeeze a little, now jump, now throw that ball," it was more fun at the start, but he also had more energy.*

Towards the very end [of treatment], *he became so weak and affected by the treatment that he didn't find it as enjoyable anymore. But overall, I think it has been good.*

(Mother to participant, 10 years)

Conversely, the children also described how the feeling of being able to complete a training session despite feeling ill made them feel as though they were actively combating the negative effects of treatment, and the thought of further improving their physical competence was motivating. Therefore, they acknowledged that a little push was necessary.

Well, there are times when, to be honest, I don't really feel like it. But of course I've thought to myself, "Oh no, it sounds tough." But then I've gone ahead and done it. And afterwards I've been really satisfied with myself for actually doing it.

(Participant 14 years)

To facilitate motivation and engagement in exercise, the exercise professionals therefore needed to tailor their approach to suit the child's age and physical capabilities. This would foster a meaningful intervention for parents and participants, emphasizing the child's autonomy.

Theme: Autonomous self-regulation

Opportunity for initiative

The hospital was described as a controlled and regulated environment, with many "must-do activities" with little or no co-determination regarding treatment and treatment-related procedures or examinations. Having an intervention using an autonomy-supported approach was therefore important to facilitate initiative and motivation.

He [the exercise professional] *would say: "Today, you can try doing this activity or game, or something like that. It's also okay if it doesn't happen." You shouldn't feel like you must do it because it can ruin your motivation. There are already enough "must-do-activities" in this process, I'd say.*

(Father to participant, 9 years)

This meant that having a say regarding the level of participation, having the opportunity for co-creation during the exercise sessions (i.e. being offered different options for exercise, activities or games), and even being in charge of the exercise sessions was described as motivating. As one child explained:

> Child: *Yesterday, I simply made a whole program. Just to get "revenge" of* [exercise professional] *after he trained with me* [laughs]. *So, I made a program for the two of us to do together. He actually said it was really tough, so I'm really happy about that.*
>
> Interviewer: *Awesome, good that you can push him a bit* [laughing].
>
> Child: *Yeah, I did! Well, he also often lets me decide what we do, you know.*
>
> Interviewer: *Yeah, so he might ask, "What do you feel like doing?"*
>
> Child: *Yes, he does that every time. Like, how do I feel, what do I want to do. It's also a good thing.*
>
> (Participant, 14 years)

Therefore, being attentive to the child's current situation, making them speak their mind, and providing them with a choice and options is necessary for facilitating self-determined exercise.

The child's voice

Parents and participants described that having a voice and being heard, i.e. being able to say "No" to exercise if they were feeling too ill or extensively tired, was an important facilitator. This "contract" was an important framework for sustaining exercise during the six months of intervention.

> Mother: *Actually, we often say "yes"* [to exercise while hospitalized].
>
> Child: *As far as I can recall, we've only said "No" once. I was furious.*
>
> Mother: *It was a bad day.*
>
> Child: *It was a really bad day.*
>
> (Mother and participant, 7 years)

Children reported that they eventually would learn which periods were ideal for partaking in exercise and physical activity and felt it was motivating if they, together with the exercise professional, could regulate the exercise sessions according to their current needs and status. This would improve self-reliance and would facilitate exercise even though they felt tired or motivate them to be active on their own.

> Interviewer: *Do you sometimes end up doing some of the exercises, even when you're tired?*
>
> Child: *I say, "I can do a little bit."*
>
> (Participant, 6 years)
>
> *Sometimes we say "No." For example, if I'm really tired, you know* [...] *When I've just had chemotherapy, my numbers are down, and I can't handle anything. But when my numbers are up, I can easily do it.*
>
> (Participant, 14 years)

Supported-self-regulated exercise

Whether doing activity at home or at the hospital, children described doing exercise and physical activity with someone, whether it is a peer, sibling, exercise professional or parent; was a facilitator for exercise and physical activity during treatment. If peers showed interest in the prescribed activities, it was generally described as a facilitator, as they would emphasize relatedness, social closeness, and belonging. Further, participants would use them as a physiological proxy: as a normal reference, illuminating disabilities and seclusion, which can be regarded as a barrier. However, this would also show which physical competencies the child needed to regain through exercise and would be a facilitator for self-determined exercise. Waning peer and sibling interest would influence the participant's motivation.

Your older brother even said, "Oh man, we're going to become really strong doing this!" But over time, their [siblings] *interest in it has waned, and that might mean it's not as fun for him anymore.* […] *So, I think he found it more fun in the beginning, but he's still participating and still wants to do it."*

(Mother to participant, 6 years)

Being at home, with limited contact with exercise professionals or peers, would lead to sedentary behavior, and parents noticed that as boredom would set in, showing the necessity for varied stimuli through social interactions or supervised exercise and physical activity.

It's definitely the hardest when it's just me and [girl] *there. I mean, when her siblings are at school and* [mom] *is at work, it's tough to facilitate physical activities. It's nice when her siblings come home from school, and we can be together. And if they want to go for a walk, or sit and play on the floor, or play tickle games, or anything else—she wants to join in. But when it's just me and her, we get bored.*

(Father to participant, 7 years)

DISCUSSION

This study explored how the motivation of children with cancer to be physically active in an exercise intervention during the first six months of cancer treatment is affected and how the motivation for physical exercise and activity can be both facilitated and negatively affected by treatment, parents, peers, and exercise professionals.

Externally regulated behavior, primarily through parents, nurses, doctors, and exercise professionals, is inherently present from the beginning of hospitalization [31,32]. Therefore, impersonal, compulsory, externally controlled behavior is expected and naturally occurring in pediatric health care [31,32]. This study demonstrates how these opposing poles of autonomous self-regulated behavior versus externally controlled regulation do not constitute a binary

explanation as either facilitating or inhibiting motivation for exercise and physical activity, but should be regarded instead as a spectrum, where more externally regulated approaches can be necessary relative to the situation and level of motivation of the participants [14].

As our results illustrate, downright externally regulated behavior may lead to amotivation, but it can also introject positive experiences with exercise; i.e. children can eventually experience the benefits and joy of exercise if basic intrinsic needs such as autonomy, relatedness, and competence are facilitated. In self-determination theory, this is known as internalization: "the active transformation of controlled regulation to a more autonomous form of self-regulation"[12]. Therefore, externally regulated behavior should not be considered a universal negative influence, causing amotivation, but more likely a necessary tool for introducing exercise and physical activity within the early stages of cancer treatment. According to SDT, external and introjected regulations are mainly unrelated to long-term adherence, and therefore, approaches to make participants identify and integrate this behavior must be further supported [14].

An autonomy-supported approach, being attentive to the child's current situation and addressing exercise and physical activity, accordingly, can facilitate self-determined exercise. In line with the findings by Götte et al., being offered exercise is, in its entirety, facilitating [2]. This study further adds how taking part in the decisions-making process of regulating exercise (i.e. being able to decline, postpone, and plan exercise sessions) can further facilitate motivation.

The exercise professional, as a health care authority, is an effective—albeit extrinsic—motivator, and an important bystander to the parents to facilitate more exercise and physical activity. As stated by the consensus-based recommendations from the ActiveOncoKids Network: building a basis of trust between exercise professionals and children by actively involving children based on voluntariness is a key component for keeping children physically active throughout the treatment trajectory [33]. Based on our finding, we would argue that voluntariness may not be an accurate

term when conducting physical activity and exercise intervention in children with cancer, as none of the included children described that they were performing systematic exercise and physical activity without at least some regulatory motivation from parent, peers, and/or exercise professionals. Instead of "voluntariness," we believe that "autonomy-based approach" is a more accurate term, as a regulatory approach is necessary to a varying degree throughout the cancer treatment. In line with the ActiveOncoKids and the International Pediatric Oncology Exercise Guidelines [33,34], such regulatory approaches can be: suggesting different intensities, exercises, or scheduling at different time for exercise if the initial offer of physical exercise is declined. Our results demonstrate that exercise professionals can extrinsically push through exercise. Although effective, this should be used with a focus on internalizing physical behavior without compromising the child's autonomy and the exercise professional's confidentiality with the participants and parents to facilitate motivation and the potential long-term self-determined physically active behavior. In a clinical setting, we would advise aligning expectations with parents as well as relevant clinical staff when using a more regulatory approach.

The result of this study describes how parents can facilitate motivation for exercise by participating in and promoting exercise—but also how they can hinder physical activity and exercise by subconsciously undermining the child's autonomy and limiting physical activity due to over-protective safety concerns. Nonetheless, parents or guardians constitute an important stakeholder. They have unique insight into their child's signals and behavior, which can ensure the child's safety and well-being during exercise and further promote exercise in a home setting. Grimshaw et al. [35]have described how parents regard themselves as an "underutilized resource." We suggest that parents are included in planning and systemizing physical activity throughout the treatment trajectory, and the potential barriers should be addressed (i.e. if they should be present during exercise sessions).

In line with previous studies, we found several intrinsic motivational factors (e.g. improving physical competencies, maintaining self-reliance, coping with treatment-related side effects) that facilitate initiative and, ultimately, autonomous exercise [2,35,36]. Similar to findings presented by Petersen et al., we found peers to be an essential mediator for exercise, mostly positively by participating and thereby promoting the social benefits of exercise, including engagement, as a distraction and combatting loneliness [36]. However, the individual preference of the child is crucial; the current well-being of the child affects their incentives to be physically active with peers, as these children prefer to do physical activity alone when treatment-related side effects are high [37]. In our findings, we found that peers could be used as a proxy for the competencies they were missing, which could be both facilitator and barrier. In situations where treatment-related side effects are highly present, it may therefore be more beneficial for the child to focus on small improvements in physical competence instead of how far they are from achieving normality. This highlights the need to include children in the planning of exercise sessions and whether peers should participate.

Strengths and limitations

In this study, we used a deductive approach using SDT, which can be regarded as both a strength and a limitation, as we may have omitted factors pertaining to psychological well-being that this theory does not account for, such as emotional regulation, self-acceptance, and resilience [12]. However, we chose SDT because of its high heuristic value, being widely applied to the study of motivation in children [28,38] and in a healthcare setting [12].

Using semi-structured interviews with open-ended questions can be challenging for children and adolescents. With some of the younger children, the interviewer was required to facilitate a narrower approach, as younger children would sometimes give short or one-word answers, and the interviewer could end up asking close-ended questions (e.g. “Do you think it was fun?”), which

risks introducing interviewer bias. If the child was uncomfortable with the interview situation, they could request that a parent be present. To make children feel more comfortable in the interview situation, facilitating longer vivid answers, we could have chosen interviewers who were known to the participants, such as the exercise intervention staff [38]. However, to minimize response bias (i.e. participants giving answers they think are "correct"), we chose an interviewer with limited knowledge of the participants[38].

We used a purposeful criterion-based sampling strategy based on achieving a variety of age, diagnosis, and adherence to exercise. We approached three children: one who dropped out of the intervention after three months and two who had very low adherence to supervised training during hospitalization, who refused to participate in the interviews or did not respond. However, children with low adherence to the intervention did participate in the interviews and provided several recurring perspectives on amotivation and barriers, including lack of interest in any type of physical activity and exercise during the treatment trajectory.

Contributions to the field

Although exercise interventions may be challenging to conduct in children during the first six months of cancer treatment, with fluctuating side effects and hospitalization, children can be motivated to participate. A clinical environment that reinforces physical exercise offers supervised exercise and uses an autonomy-supportive and age-appropriate approach that is key for facilitating motivation and reducing sedentary behavior. For children who are sedentary or reluctant to participate in exercise, a more external regulatory approach may be useful but should be used with the intent of introjecting and ultimately internalizing behavior through autonomy support. To do so, facilitating principles such as co-creation, diverting attention from treatment-related side effects through fun activities, and social interactions should be incorporated to make children with cancer identify and integrate exercise and active behavior into their everyday lives.

Supporting autonomy does not mean that exercise and physical activity during hospitalization should be regarded as purely voluntary, as regulatory approaches are needed and can facilitate motivation. Similarly, adjusting exercise to treatment-related side effects should not compromise the intensity of exercise, as this secures the long-term effectiveness of the exercise interventions. Clinical knowledge of treatment and treatment-related procedures and close cooperation with parents, nurses, and doctors are therefore necessary to conduct meaningful and effective exercise and physical activity interventions in the fluid nature of treatment-related side effects. Appropriate intensity and challenge do not necessitate exercise being regarded as exhausting or daunting, but rather as an important factor to maintain and increase motivation.

Conclusion

Treatment-related side effects are key barriers to participation in the exercise; strategies for motivating children to be physically active during treatment are therefore crucial to counteract the adverse physical and social side effects of childhood cancer treatment across diagnoses. Externally regulated motivation (i.e. through pressure and negative reinforcement) is a necessary tool, as it can facilitate exercise on a short-term basis when children are sedentary and hesitant to engage in physical activity and exercise. However, more internally regulated approaches, supporting the child's autonomy, and acknowledging concerns and the current physical state through appropriate and personalized exercise can all contribute to motivation and long-term engagement. Factors such as parents and peers can be engaged to facilitate motivation further. Being trained by a familiar exercise professional can establish secure boundaries and create a foundation for staying motivated throughout cancer treatment—even when side effects are considerable.

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Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions

This protocol article was primarily drafted by HBL, NNP and PSA, and JC. All authors (HBL, NNP, AP, JC, KGM, and PSA) have contributed substantially to the study design, including the interview guide, theoretical approach, and methods used. All authors have revised and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to Danish and EU personal data legislation but are available from the corresponding author on reasonable request.

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FIGURE AND TABLE LEGENDS:

Table title: TABLE 1 Descriptions of participants and their parents
[Table legend: Table 1: * two sets of parents were interviewed together
A = High: participated in ≥80 % of expected supervised exercise sessions (24 sessions)
B = Intermediate: participated in 50-79 % of expected supervised exercise sessions
C = Low: participated in <50 % of expected supervised exercise sessions
**parent and child were present during the interview]

Table title: TABLE 2 Overview of identified facilitators and barriers for perceived motivation for exercise
[Table legend: Overview of identified facilitators, barriers, and explanatory factors within each theme. PA= Physical Activity]

Figure title: FIGURE 1 visual illustration of the deductive analysis, including identified themes and subthemes
[Figure Legend: visual illustration of the deductive qualitative analysis. When subthemes had been defined within the four SDT domains: autonomy, relatedness, competence, and extrinsic motivation, these subthemes were fitted into the three SDT behavioral model domains: amotivation, controlled regulation, and autonomous self-regulation.]

Implications for Rehabilitation

- Although exercise interventions may be challenging to conduct in children during the first six months of cancer treatment, with fluctuating side effects and hospitalization, children can be motivated to participate.
- An autonomy-supportive and age-appropriate approach is critical to facilitate motivation and reduce sedentary behavior in children undergoing cancer treatment.
- Supporting autonomy does not mean that exercise and physical activity during hospitalization should be regarded as purely voluntary, as regulatory approaches are needed and can facilitate motivation, in particular in sedentary or reluctant children
- Clinical knowledge of treatment and close cooperation with parents, nurses, and doctors are necessary to conduct meaningful and effective exercise and physical activity interventions in the fluid nature of treatment-related side effects.

Informants characteristics	Children (n =12)	Parents or guardians (n=12)
Sex (male/female)	9/3	4/10*
Age (median, [range])	11 [6-17]	-
Combined**/separate interviews	5/7	5/7
Centers		
Copenhagen University Hospital	7	
Aarhus University Hospital	3	
Odense University Hospital	2	
Diagnosis		
Hematologic cancers	6	
Extracranial solid tumors	5	
CNS tumors	1	
Adherence to Exercise		
High[A]	3	
Intermediate[B]	6	
Low[C]	3	

Table 1: * two sets of parents were interviewed together

A = High: participated in ≥80 % of expected supervised exercise sessions (24 sessions)

B = Intermediate: participated in 50-79 % of expected supervised exercise sessions

C = Low: participated in <50 % of expected supervised exercise sessions

**parent and child were present during the interview

SDT Domains	Quote, excerpts	Condensed Meaning Unit
Autonomy	"Oh, yes. Well, I could definitely [do exercises on my own initiative]. It's not so much that I play basketball because sometimes I find it a bit annoying with the CVK I have."	I can do PA on my own
	" So, we've said, 'come on over and play football.' He usually wants to, and the four times he said no, he came cycling over right after we started anyway. And sometimes he say that he needs to stop a bit earlier that usual. But still, he can come over and give it a try."	Initiative
	"I actually think it's been good to train while I've been hospitalized. I mean, it's been nice to be able to think about something else for a while."	PA helps me focus on other things than being sick
	"He (the exercise professional) was very good at introducing himself, saying, 'This is what I do, this is what we're working towards.' Then he gave me some time. He wasn't like, 'You have to join in! We need to hurry! We don't have time for this.' He was very good at just taking it easy and calmly."	Time and trust make me feel in control/secure
	"If he didn't have the energy or the desire one day, it's possible that we tried to push a little, but if he said, 'I don't want to,' we have also respected that, and we haven't forced him to do it."	Saying NO!
	"When he's really low in numbers, it doesn't make any sense at all (to train), because he's been lacking both blood and all sorts of other things, so he doesn't have the energy for it. And then it's just fine that a couple of days pass before he can take up exercise again."	I CANT
	"I feel that this trail has helped us keeping him active. And even though we may not have been able to do much with him because he has been really tired, we have at least reminded each other that (boy) needs to out. That has often meant taking a walk or going up and down the stairs. We have used it to keep him on track and ourselves a bit disciplined in making sure it gets done."	Mediating role of Parents
Relatedness	The reason I've stepped back (leaving the room when exercise was occurring) is that I have a sense that he follows (exercise professional's) instructions more when I'm not around. There's something about me observing. (The exercise professional) might be able to get him to do certain things more easily when I'm not there.	PA as Social activities
	"Sometimes as an adult, you can have an idea that, 'I have to attend (training) three times a week,' these are the kind of frameworks one sets for oneself. It's difficult for him to comprehend. He's still at the stage where it's all play for him. When he goes out to play basketball, he's not training; he's out there playing. And he's skilled with a ball."	I don't do exercise - I do fun and games
	"I also think that (exercise professional) is good at assessing (when enough is enough) [...] And it's nice that he knows her so well that she doesn't need to use many words to say, 'I can't handle it anymore' or 'I can't do it now.' Because that can also be difficult."	PT-patient relationship
Competence	"I can actually participate in a lot more. Today we're even going up to the 13th floor [stairs]. I've come a long way. I've improved a lot and their it much more I can do"	Benefits of exercise
	"Because of cancer, I can no longer participate in, football and karate (...). My muscles shrink completely, so I am very weak, which makes it difficult to exercise"	Negative effects of treatment
	"It's easier to get back into the training rhythm, and there's not as long of a way to go to be physically strong as if you hadn't done anything, you know."	Appropriate challenge
	"Well, we tried when the weather was a little better. We borrowed one of those heavy balls (medicine balls) and brought it home, where we tried to fill some bottles with water and went out in the garden and did some bowling and that sort of thing. […] So it was, ok, but, I think he thinks it's a bit boring when it's just been mum or dad saying: "now we're going to do this!" He does more what (the exercise professional) says."	Guidance
	"Yes, I don't think training should be easy. I mean, we do a lot of the exercises I used to do when I played basketball, and I've gotten better at them, and maybe I have a bit more control over the technique."	Appropriate challenge
Extrinsic Motivation	"Well, yes, I've done what he (the exercise professional) has said. He said I should do my best to stay active, do it 2-3 times a week, so I've definitely done that, including squats and such. I don't think I would have come up with it myself or wanted to do it. So, I've done it because I thought it's good and because (the exercise professional) recommended it."	I do some of the "prescribed" exercises
	"[...] and then he's said, 'Why are you forcing me to do it?' And we've tried to explain, 'Well, we actually do it because you need to get stronger.' 'I know it's tough when you have no strength.' 'But you'll have even less strength if you don't do it.' And then he could actually see the point in it.	Paternalism - facilitator
	Mother: "You do know it's healthy for you, right?" Child: "No, it's really unhealthy for me. I really enjoy relaxing."	Paternalism – barrier

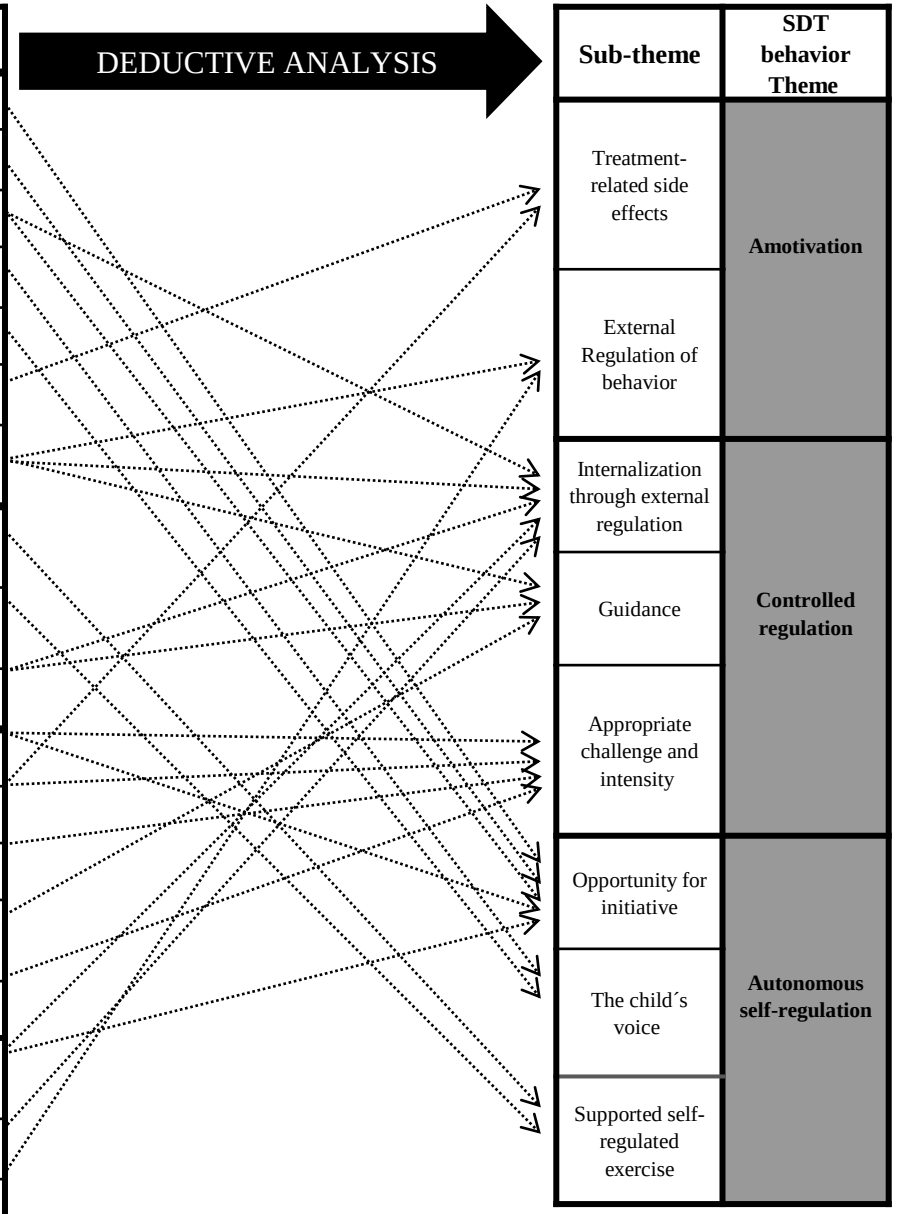

Figure title: Figure 1: visual illustration of the deductive analysis, including identified themes and subthemes
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Facilitator	(Mediating factor)	Barrier	Described in theme
Feeling of being able to counteract cancer deficiencies	**Treatment**	Side-effects etc. Feeling of physical set back after each treatment	Amotivation Controlled regulation
Autonomy support - Cocreation of exercise - Being able to say no To feel heard/acknowledge concerns Creating a foundation of activity that can be introjected and internalized	**Controlled regulation**	External controlled regulation Using negative reinforcement or sanctions	Amotivation Controlled regulation Autonomous self-regulation
Safety, reading the child's signals can facilitate exercise and PA at home	**Parents**	Can (unconsciously) undermine the child's autonomy Primarily relying on parents to conduct exercise and PA	Controlled regulation
Feeling connected, valued, and supported by others	**Exercise professional**	Using authority to hardline Exercise	Controlled regulation
Being a goal of "what I should be able do"	**Peers**	being a proxy of "what I can't do"	Autonomous self-regulation
Exercise is a positive aspect of cancer treatment — a break from routines and procedures			Controlled regulation
Feeling secure			Controlled regulation
Clear boundaries and guidelines			Controlled regulation
Appropriate challenge			Controlled regulation
Appropriate and fun activities initiated by exercise professionals			Autonomous self-regulation

Table 2: Overview of identified facilitators, barriers, and explanatory factors within each theme. PA= Physical Activity

Supplementary file 1: inteview guides

INTERACT Interview Guide for Children 6-10 Years

Introduction:

I will introduce myself (name), my role, and the purpose of the interview (to understand how it has been to train during treatment at the hospital and at home, as well as facilitators and barriers to physical activity).

I will inform that this conversation will be recorded, listened to at a later time, transcribed, and used as part of the INTERACT research project. There is confidentiality, and all information will be fully anonymized. I will explain the topics we will cover and conclude by asking if thers is have any questions.

About the Informant:

Q1: Can you tell me a little about yourself?

- How old are you, what grade are you in, and which city do you live in?

Q2: What do you do in your free time?

- Do you engage in activities that make you break a sweat, like playing soccer?
- What do you like about the activities you do in your free time?

Intervention:

Q3: What do you do with (exercise professional) when you're admitted to the hospital?

- Can you remember the last time you did something with (exercise professional)?
- What did you do? How did you feel about it? Was it fun, boring, or something else?
- What made it fun or boring?

Q4: Is there something you didn't find fun to do?

- Why or why not?
- What kinds of training, games, or activities have you decided to do with (exercise professional)?

Q5: When you think back to the times you've trained, played, or exercised with (exercise professional), is there something (exercise professional) could have done differently to get you out of bed and join in?

Q6: Are there any things you do with (exercise professional) that are challenging to participate in?

- If no, why not?
- If yes, what makes it difficult?

General Physical Activity and Exercise:

Q7: Is there anything that makes it difficult to exercise and play when you're in the hospital?

- What could it be?

Q8: Is there anything that makes it easier or more enjoyable for you to exercise when you're in the hospital?

- What could it be?

Q9: What activities do you do at home that make you break a sweat?

- Do you do any of the activities you do with (exercise professional) when you're at home?
- If yes or no, why is that?
- What do you do at home that you get to decide?

Side Effects:

Q10: Has it become easier or more fun to use your body for playing?

- Is there something you can do now that you couldn't do before?

Q11: Do you sometimes say no to training if you're feeling unwell?

- Why? (ask about side effects: nausea, fatigue, dizziness, pain)
- Do you think (exercise professional) was good at providing exercises when you were unwell?
- Is there something you think you're good at or have improved at after training with (exercise professional)?
    - What could it be?
    - What's the significance for you that you've gotten better at it?

Conclusion:

That's all I had to ask you. Is there anything else you'd like to talk about? Anything you think is important for (exercise professional) to know that you'd like me to pass on to them? Thank you for participating; we greatly appreciate it.

INTERACT Interview Guide for Young Adults (11-18 Years)

Introduction:

I will introduce myself (name), my role, and the purpose of the interview (to understand how it has been to train during treatment at the hospital and at home, as well as facilitators and barriers to physical activity). I will inform you that this conversation will be recorded, listened to at a later time, transcribed, and used as part of the INTERACT research project. There is confidentiality, and all information will be fully anonymized. I will explain the topics we will cover and conclude by asking if you have any questions.

About the Informant:

Q1: Can you tell me a little about yourself?

- How old are you, what grade are you in, and which city do you live in?

Q2: What do you do in your free time?

- Do you engage in activities that make you break a sweat, like playing soccer?
- What do you like about the activities you do in your free time?

Intervention:

Q3: Can you tell me about what you've done with (exercise professional) when you've trained during your hospital stay?

- What do you think about it? Was it fun, boring, or something else?
- What made it fun or boring?

Q4: Is there anything you didn't like doing?

- How come?
- What kinds of training, games, or activities have you chosen to do with (exercise professional) (when you're at home)?

Q5: When you think back to the times you've trained with (exercise professional), is there something (exercise professional) could have done differently to motivate you to get out of bed and train with them?

Q6: Are there any things you do with (exercise professional) that are difficult to participate in?

- If no, why not?
- If yes, what makes it difficult?

Training, Play, and Exercise:

Q7: Is there a difference between before and after you got sick in terms of what you can participate in? (Remember to refer to your answers from Q2.)

- How does it manifest?
- What do you think about it?

Q8: How has it been to train during your illness?

- Is there anything that makes it difficult to train and move when you're in the hospital?
- What could it be?
- Is there anything that makes it easier or more enjoyable for you to exercise when you're in the hospital?
- What could it be?
- What does it mean to you that it becomes easier/more fun to move?

Q9: Do you do something at home that makes you break a sweat when you're not in the hospital?

- If no, what was important for you to do while at home?
- If yes, what can you do when you're at home?

Q10: Can you think of doing some of the things that (exercise professional) did with you in the hospital when you're at home?

- Are you good at motivating yourself to do xx, or are your parents/siblings/friends good at motivating you?

Side Effects:

Q11: Have you experienced any side effects from your treatment?

- What side effects have you experienced? Like nausea, fatigue, dizziness, pain, or fatigue?
- What do you do when you're nauseous/tired or in pain?

Q12: Do you sometimes refuse to train with (exercise professional) when you're not feeling well?

- Why?
- Do you think (exercise professional) was good at providing exercises for you when you weren't feeling well?
- Is there something you feel you're good at or have gotten better at after training with (exercise professional)?
    - What could it be?

Conclusion:

That's all I had to ask you. Is there anything else you'd like to talk about? Anything you think is important for (exercise professional) to know that you'd like me to pass on to them? Thank you for participating; we greatly appreciate it.

INTERACT Interview Guide for Parents

Introduction:

I will introduce myself (name), my role, and the purpose of the interview (to understand how it has been to train during treatment at the hospital and at home, as well as facilitators and barriers to physical activity). I will describe the potential conflict of interest, emphasizing that although I believe that training is effective, the goal is to understand why it works or doesn't work. I will emphasize the importance of honest responses.

I will inform you that this conversation will be recorded, listened to at a later time, transcribed, and used as part of the INTERACT research project. There is confidentiality, and all information will be fully anonymized. I will explain the topics we will cover and conclude by asking if you have any questions.

About the Informant:

Q1: Can you tell me a little about yourself?

- How old are you, who is part of your family, and what do you work with?

Q2: What activities does your child engage in during their free time now?

Q3: Do you engage in activities that make you break a sweat?

Q4: Do you engage in family activities together?

- Is there a difference in what you do on regular days, weekends, vacations, or seasons?

Intervention:

Q5: Can you briefly describe your understanding of the INTERACT/training project that your child is participating in?

- Why did you choose to participate in INTERACT?
- Was it you as parents or xx who decided to participate in INTERACT?

Q6: How do you feel about the training with (exercise professional)?

- Do you think that xx benefits from the training?
- What do you think xx feels about the training?
- Does it make sense for xx to participate?
- How is it to motivate xx to train/be physically active when you're at home? (Friends/siblings/training equipment like a pedometer)
- Is there anything that makes it challenging to motivate xx to train, move, or play?
    - (Interest/energy/side effects/medication (DXA)/logistics (appointments, IV stands))
- Is it easier to train when you as parents are present or not present?
- Can you provide examples of when it might be challenging to motivate xx in the hospital?
- What about at home?

Q7: When you're at home, is it xx who suggests activities to do?

- What could those activities be?

Q8: Is there something you feel you've been missing regarding your participation in INTERACT?

- If yes, what could (exercise professional) have done differently?

Training, Play, and Exercise:

Q9: Is there a difference between before and after xx got sick when it comes to participating in sports/physical activity/training?

- If yes, how does it show?
- How was xx's physical condition before the illness in comparison to xx's physical condition now?
- Can you notice a difference in xx's physical abilities now compared to the beginning of the cancer treatment?

Q10: What does your daily life look like regarding physical activity when you're at home?

- Do you do some of the exercises that (exercise professional) does with xx?

Side Effects:

Q11: Have you noticed that xx has experienced any side effects from the treatment (pain, nausea, dizziness, fatigue, mood swings)?

- What side effects have you noticed as the most significant?

Q12: Do you feel that physical activity (during the treatment) has helped reduce side effects?

- Do you believe that side effects have an impact on xx's motivation to train with (exercise professional) in the hospital or at home?
- Why?

Conclusion:

That's all I had to ask you. Is there anything else you'd like to talk about? Anything you think is important for (exercise professional) to know that you'd like me to pass on to them? Thank you for participating; we greatly appreciate it.

Note: In the questions, "exercise professional" refers to the person responsible for the child's exercise regimen. Where "xx" refers to the name of the child or young adult involved.