frontiers | Research Topics

Exercise and childhood cancer

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Published in
Frontiers in Pediatrics
Frontiers in Oncology

ISSN 1664-8714
ISBN 978-2-83251-022-3
DOI 10.3389/978-2-83251-022-3

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Exercise and Childhood Cancer

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Citation
Mizrahi, D., Götte, M., Wurz, A., eds. (2022). *Exercise and childhood cancer*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-83251-022-3

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frontiers | Frontiers in Pediatrics

TYPE Editorial
PUBLISHED 28 November 2022
DOI 10.3389/fped.2022.1097836

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Oncology, a section of the journal Frontiers in Pediatrics

RECEIVED 14 November 2022
ACCEPTED 15 November 2022
PUBLISHED 28 November 2022

CITATION
Mizrahi D, Wurz A and Götte M (2022) Editorial: Exercise and childhood cancer.
Front. Pediatr. 10:1097836.
doi: 10.3389/fped.2022.1097836

Editorial: Exercise and childhood cancer

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KEYWORDS

exercise, physical activity, childhood cancer, pediatric oncology, cancer

Editorial on the Research Topic
Exercise and childhood cancer

Globally, >175,000 children (i.e., individuals aged ≤18–21years) are diagnosed with cancer each year (1). For some of the most common cancers (e.g., acute lymphoblastic leukemia, non-Hodgkin lymphoma), medical advances have led to improved survival rates, with up to 85% expected to survive the disease for at least 5-years (1).[1] Despite improving prognoses, most children affected by cancer experience, or are at elevated risk, for numerous negative effects during and after treatment, with some effects observed decades later (i.e., late effects) (2). Health behaviors, including physical activity (any movement requiring energy expenditure) and exercise (structured or planned physical activity), may help this cohort manage the effects of their disease during and beyond treatment (3). In fact, based on a burgeoning evidence base, guidelines have recently been published suggesting that all children affected by cancer "move more" (4, 5).

This Research Topic, *Exercise and Childhood Cancer*, includes 11 articles that collectively advance the field of "pediatric exercise oncology" (6), an area of study exploring physical activity, including exercise, for children affected by cancer. The articles included summarize the current literature, provide further evidence supporting the role of physical activity and exercise for children affected by cancer, and offer insights into forthcoming trials and novel approaches in the field.

[1]Prognosis varies across cancer types and is lower in middle- and low-income countries.

The past: summarizing prior research

Prior published literature reviews have deemed physical activity, including exercise, as safe and potentially beneficial for children affected by cancer, regardless of stage along the cancer trajectory (4–6). However, few efforts have been made to summarize the evidence for children diagnosed with solid and brain tumors, who have historically experienced poorer outcomes (1). Further, few efforts have been made to explore physical activity among those experiencing long-term and late-effects (e.g., cardiotoxicity), which is problematic since this subgroup may need movement more. Thus, we are pleased to share two articles in this Research Topic that address these gaps. Kohler and colleagues conducted a systematic scoping review of 17 studies. The authors concluded that physical activity and exercise interventions were safe, feasible, and seemingly beneficial for children who had completed treatment for brain and other solid tumors. Caru and Curnier provide an in-depth summary of challenges and the potential therapeutic role of integrating physical activity into cancer care to address cancer-related cardiotoxicity in this population.

The present: advancing the field

The field of pediatric exercise oncology, though still relatively recent, is at an exciting stage with an increasing number of studies published each year. Within this Research Topic, we share two original articles covering innovative interventions, study designs, and approaches to collect data. We also share three articles that explore novel relationships between physical activity (including exercise) and topical outcomes.

In their study with 10 children (6–14 years) who had completed treatment for acute lymphoblastic leukemia, Marchese and colleagues found a 6-week targeted exercise program (supervised and home-based progressive beaded jumping rope) improved gross motor performance and augmented observed neuromuscular impairments, which could offer a low-cost intervention for at-home and in-school. The authors assessed neuromuscular outcomes with tools that have rarely, if ever, been utilized in this population (e.g., electromyography, motion capture, force plates). In their randomized controlled trial (RCT), Gaser and colleagues assigned 41 children and adolescents (4–18 years), who were receiving treatment for leukemia or non-Hodgkin lymphoma, to an individualized resistance intervention or standard exercise (sports games, aerobic or coordination exercises) for an average of 7.4 months. This is among the first superiority RCT in the field, with findings suggesting both groups experienced improvements in activities of daily living, though the resistance intervention was more beneficial for explosive strength.

The observational studies included herein provide early evidence that physical activity, including exercise, may provide important short and long-term health benefits. Specifically, Bratteteig and colleagues examined the association between device-measured physical activity intensities and cardiovascular disease risk among 157 children (9–18 years) who had completed treatment ≥1 year prior. Vigorous physical activity was associated with clinically meaningful improved cardiovascular disease risk profiles, suggesting monitoring and promoting vigorous physical activity may be important for long-term cardiovascular health. Among 185 adults previously diagnosed with cancer as a child, Goodenough and colleagues found that $p16^{INKa}$ (a biomarker of cellular senescence) and inflammation, were associated with lower exercise capacity. These findings offer possible targets to remediate some of the adverse physiologic outcomes observed in this population. In their study of 1,166 adults who had been diagnosed with acute lymphoblastic leukemia as a child, Wogksch and colleagues found that being obese was associated with a higher energy cost when walking, worse adaptive physical function, and lower health-related quality of life than controls. These findings suggest weight loss interventions may be important as a means of supporting the growing population of adults who were diagnosed with cancer as a child.

The future: work in preparation and progress

In this Research Topic, we are able to look ahead to planned and ongoing work, which will undoubtedly advance the field of pediatric exercise oncology. Indeed, the included articles address recently identified research and innovation needs (4). Specifically, Schmidt-Andersen and colleagues are conducting the INTERACT trial, a multi-site study that will recruit 127 newly diagnosed children (6–17 years) and randomize them into 6-months of supervised (and home-based) integrative neuromuscular exercise or an unsupervised active usual care group (resistance, aerobic and stretching exercises). The primary outcome explored will be muscular strength, with findings aiming to support adapted interventions for hospital and home settings. The same research group led by Pouplier and colleagues will randomize 84 newly diagnosed pre-school aged children (1–5 years) to a combined intervention with in-hospital, structured active play and home-based active play, or usual care, and explore effects on gross motor function and social and personal skills. Findings will contribute vital evidence, not only for this subgroup within the childhood cancer population who are understudied, but for the efficacy of play-based interventions. Of note, this trial will utilize the

FIGURE 1
Participant from a pediatric exercise oncology research study.

RePlay Model, a conceptual model for structured active play for pre-schoolers created by the same study team and published herein (i.e., Pouplier et al.). Finally, in their paper Grimshaw and colleagues developed a behavior change intervention entitled: CanMOVE for school-aged children undergoing treatment (5–16 years), which incorporates 15 strategies designed to promote and increase physical activity.

Collectively, the studies published in this Research Topic address gaps in knowledge and highlight innovations in research seeking to promote physical activity, including exercise, among children affected by cancer. While much remains to be discovered, these findings bring us one step closer to ensuring all children affected by cancer have the opportunity to improve their health by moving more (**Figure 1**).

Author contributions

All authors contributed to the manuscript text and editing, and provided critical feedback and shaped the direction of the manuscript.

Acknowledgments

The authors of this Editorial would like to thank all the researchers who submitted manuscripts, the peer reviewers for their time and efforts, the Frontiers team for making this Research Topic a success and an advocacy piece for this important topic, and all the participants for contributing their time to the science.

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.

Publisher's note

References

1. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin.* (2014) 64(2):83–103. doi: 10.3322/caac.21219

2. Morales JS, Valenzuela PL, Rincón-Castanedo C, Santos-Lozano A, Fiuza-Luces C, Lucia A. Is health status impaired in childhood cancer survivors? A systematic review and meta-analysis. *Crit Rev Oncol Hematol.* (2019) 142:94–118. doi: 10.1016/j.critrevonc.2019.07.008

3. Bernal JDK, Recchia F, Yu DJ, Fong DY, Wong SHS, Chung P-K, et al. Physical activity and exercise for cancer-related cognitive impairment among individuals affected by childhood cancer: a systematic review and meta-analysis. *Lancet Child Adolesc Health.* (2022). doi: 10.1016/S2352-4642(22)00286-3. [Epub ahead of print]

4. Wurz A, McLaughlin E, Lategan C, Chamorro Viña C, Grimshaw SL, Hamari L, et al. The international Pediatric Oncology Exercise Guidelines (iPOEG). *Transl Behav Med.* (2021) 11(10):1915–22. https://doi.org/10.1093/tbm/ibab028

5. Götte M, Gauß G, Dirksen U, Driever PH, Basu O, Baumann FT, et al. Multidisciplinary Network ActiveOncoKids guidelines for providing movement and exercise in pediatric oncology: consensus-based recommendations. *Pediatr Blood Cancer.* (2022) 69(11):e29953. doi: 10.1002/pbc.29953

6. Wurz A, McLaughlin E, Chamorro Viña C, Grimshaw SL, Hamari L, Götte M, et al. Advancing the field of pediatric exercise oncology: research and innovation needs. *Curr Oncol.* (2021) 28(1):619–29. doi: 10.3390/curroncol28010061

frontiers in Pediatrics

CLINICAL TRIAL
published: 14 March 2022
doi: 10.3389/fped.2022.833850

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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OPEN ACCESS

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Specialty section:
This article was submitted to Pediatric Oncology, a section of the journal Frontiers in Pediatrics

Received: 12 December 2021
Accepted: 14 February 2022
Published: 14 March 2022

Citation:
Schmidt-Andersen P, Fridh MK, Müller KG, Anna Pouplier, Hjalgrim LL, Faigenbaum AD, Schmiegelow K, Hasle H, Lykkedegn S, Zhang H, Christensen J and Larsen HB (2022) Integrative Neuromuscular Training in Adolescents and Children Treated for Cancer (INTERACT): Study Protocol for a Multicenter, Two-Arm Parallel-Group Randomized Controlled Superiority Trial. Front. Pediatr. 10:833850. doi: 10.3389/fped.2022.833850

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

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

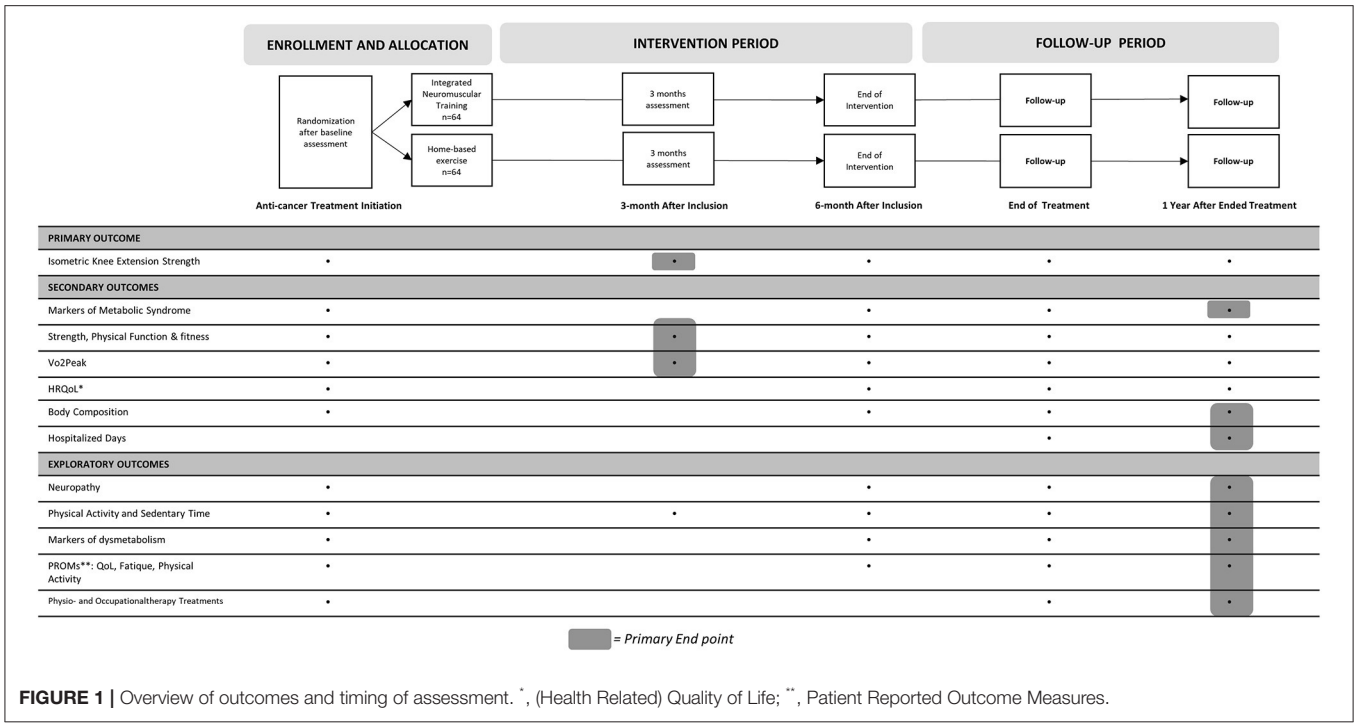

FIGURE 1 | Overview of outcomes and timing of assessment. *, (Health Related) Quality of Life; **, Patient Reported Outcome Measures.

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.

FUNDING

The INTERACT study has been peer-reviewed and funded by the Danish Childhood Cancer Foundation (Grant numbers: 2019-5954 and 2020-6769), the Research Fund of Copenhagen University Hospital (Grant number: E-22597-01), Capital Region of Denmark's Research Foundation for Health Research 2020 (Grant number: A-6868), Helsefonden (Grant number: 20-B-0409), Danish Cancer Research Fund (Grant number: FID2157728), the Research Fund of the Association of Danish Physiotherapists (Grant number: R23-A640-B408),

and Fabrikant Einar Willumsen's Memorial Scholarship (Grant number: N/A). This work is part of Childhood Oncology Network Targeting Research, Organization & Life expectancy (CONTROL). None of the funders will have any role in the design of this study, in the collection of data, the analysis, the interpretation of data, or the dissemination of data.

ACKNOWLEDGMENTS

A special thanks to the staff at the Department of Pediatrics and Adolescent Medicine and the Department of Occupational- and Physiotherapy at Copenhagen University Hospital, Rigshospitalet; the Department of Pediatrics and Adolescent Medicine and Department of Physiotherapy and Occupational Therapy at Aarhus University Hospital; the Department of Pediatric Hematology and Oncology at H.C. Andersen Children's Hospital, Odense University Hospital for making this study possible. Sincere gratitude is also extended to medical writer Jon Jay Neufeld for providing language editing on the final manuscript.

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

REFERENCES

1. Schrøder H, Rechnitzer C, Wehner PS, Rosthøj S, Møller JK, Lausen B, et al. Danish childhood cancer registry. *Clin Epidemiol.* (2016) 8)461–4. doi: 10.2147/CLEP.S99508
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin.* (2017) 67:7–30. doi: 10.3322/caac.21387
3. Carozzi VA, Canta A, Chiorazzi A. Chemotherapy-induced peripheral neuropathy: what do we know about mechanisms? *Neurosci Lett [Internet].* (2015) 596:90–107. Available online at: doi: 10.1016/j.neulet.2014.10.014
4. Gilliam LAA, St. Clair DK. Chemotherapy-induced weakness and fatigue in skeletal muscle: the role of oxidative stress. *Antioxid Redox Signal [Internet].* (2011) 15:2543–63. doi: 10.1089/ars.2011.3965
5. Gotte M, Kesting S, Winter C, Rosenbaum D, Boos J. Comparison of self-reported physical activity in children and adolescents before and during cancer treatment. *Pediatr Blood Cancer.* (2014) 61:1023–8. doi: 10.1002/pbc.24898
6. Tan SY, Poh BK, Chong HX, Ismail MN, Rahman J, Zarina AL, et al. Physical activity of pediatric patients with acute leukemia undergoing induction or consolidation chemotherapy. *Leuk Res [Internet].* (2013) 37:14–20. doi: 10.1016/j.leukres.2012.09.005
7. Fuemmeler BF, Pendzich MK, Clark K, Lovelady C, Rosoff P, Blatt J, et al. Diet, physical activity, and body composition changes during the first year of treatment for childhood acute leukemia and lymphoma. *J Pediatr Hematol Oncol.* (2013) 35:437–43. doi: 10.1097/MPH.0b013e318279cd3e
8. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med [Internet].* (2006) 355:1572–82. doi: 10.1056/NEJMsa060185
9. Tanir MK, Kuguoglu S. Impact of exercise on lower activity levels in children with acute lymphoblastic leukemia: a randomized controlled trial from Turkey. *Rehabil Nurs.* (2012) 38:48–59. doi: 10.1136/archdischild-2012-302724.0416
10. Ness KK, Kaste SC, Zhu L, Pui CH, Jeha S, Nathan PC, et al. Skeletal, neuromuscular, and fitness impairments among children with newly diagnosed acute lymphoblastic leukemia. *Leuk Lymphoma.* (2015) 56:1004–11. doi: 10.3109/10428194.2014.944519
11. Marchese VG, Chiarello LA, Lange BJ. Effects of physical therapy intervention for children with acute lymphoblastic leukemia. Pediatr Blood Cancer [Internet]. (2004) 42:127–33. doi: 10.1002/pbc.10481
12. Braam KI, van Dijk-Lokkart EM, Kaspers GJL, Takken T, Huisman J, Bierings MB, et al. Cardiorespiratory fitness and physical activity in children with cancer. *Support Care Cancer.* (2016) 24:2259–68. doi: 10.1007/s00520-015-2993-1
13. Thorsteinsson T, Larsen HB, Schmiegelow K, Thing LF, Krustrup P, Pedersen MT, et al. Cardiorespiratory fitness and physical function in children with cancer from diagnosis throughout treatment. *BMJ Open Sport Exerc Med.* (2017) 3:1–10. doi: 10.1136/bmjsem-2016-000179
14. Lam KKW, Li WHC, Chiu SY, Chan GCF. The impact of cancer and its treatment on physical activity levels and quality of life among young Hong Kong Chinese cancer patients. *Eur J Oncol Nurs [Internet].* (2016) 21:83–9. doi: 10.1016/j.ejon.2016.01.007
15. Nielsen MKF, Larsen HB, Schmiegelow K, Christensen JF. Muscle dysfunction in childhood cancer: biological mechanisms and implications for long-term survivorship. *EMJ Oncol.* (2016) 4:78–85.
16. Ness KK, Hudson MM, Pui CH, Green DM, Krull KR, Huang TT, et al. Neuromuscular impairments in adult survivors of childhood acute lymphoblastic leukemia: associations with physical performance and chemotherapy doses. *Cancer.* (2012) 118:828–38. doi: 10.1002/cncr.26337
17. Wolfe RR. The underappreciated role of muscle in health and disease. *Am J Clin Nutr.* (2006) 84:475–82. doi: 10.1093/ajcn/84.3.475
18. Nielsen MKF, Christensen JF, Frandsen TL, Thorsteinsson T, Andersen LB, Christensen KB, 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.* (2020) 18:1–12. doi: 10.1186/s12916-020-01634-6
19. Winter C, Muller C, Brandes M, Brinkmann A, Hoffmann C, Hardes J, et al. Level of activity in children undergoing cancer treatment corinna. *Pediatr Blood Cancer.* (2009) 53:438–43. doi: 10.1002/pbc.22055
20. Ness KK, Mertens AC, Hudson MM, Wall MM, Leisenring WM, Oeffinger KC, et al. Limitations on physical performance and daily activities among long-term survivors of childhood cancer. Ann Intern Med. (2005)143:639–47. doi: 10.7326/0003-4819-143-9-200511010-00007
21. Lucía A, Earnest C, Pérez M. Cancer-related fatigue : can exercise physiology assist oncologists? *Lancet Oncol.* (2003) 2045:616–25. doi: 10.1016/S1470-2045(03)01221-X
22. Rayar M, Webber CE, Nayiager T, Sala A, Barr RD, Chb MB. Sarcopenia in children with acute lymphoblastic leukemia. *J Pediatr Hematol Oncol.* (2013) 35:98–102. doi: 10.1097/MPH.0b013e318279eea2
23. Nielsen MM, Mathiesen S, Suominen A, Sørensen K, Ifversen M, Mølgaard C, et al. Altered body composition in male long-term survivors of paediatric allogeneic haematopoietic stem cell transplantation: impact of conditioning regimen, chronic graft-vs.-host disease and hypogonadism. *Bone Marrow Transplant.* (2021) 56:457–60. doi: 10.1038/s41409-020-01038-3
24. Friedman DN, Tonorezos ES, Cohen P, Sloan M, Cancer K, Sloan M, et al. Diabetes and metabolic syndrome in survivors of childhood cancer. *Horm Res Paediatr.* (2020) 91:118–27. doi: 10.1159/000495698
25. Grimshaw SL, Taylor NF, Shields N. The feasibility of physical activity interventions during the intense treatment phase for children and adolescents with cancer: a systematic review. *Pediatr Blood Cancer.* (2016) 63:1586–96. doi: 10.1002/pbc.26010
26. Baumann FT, Bloch W, Beulertz J. Clinical exercise interventions in pediatric oncology: a systematic review. *Pediatr Res.* (2013) 74:366–74. doi: 10.1038/pr.2013.123

27. Braam KI, van der Torre P, Takken T, Veening MA, van Dulmen-den Broeder E, Kaspers GJL. Physical exercise training interventions for children and young adults during and after treatment for childhood cancer. *Cochrane Database Syst Rev*. (2016) 3:17. doi: 10.1002/14651858.CD008796.pub3
28. Zucchetti G, Bertorello N, Rossi F, Fagioli F, Vina CC. Exercise program for children and adolescents with leukemia and lymphoma during treatment : a comprehensive review. *Pediatr Blood Cancer*. (2018) 65:1–6. doi: 10.1002/pbc.26924
29. Thorsteinsson T, Schmiegelow K, Friis L, Lars T, Andersen B, Sofie A, et al. Classmates motivate childhood cancer patients to participate in physical activity during treatment : a qualitative study. *Eur J Cancer Care*. (2019) 28:1–10. doi: 10.1111/ecc.13121
30. Ruiz JR, Fleck SJ, Vingren JL, Ramírez M, Madero L, Fragala MS, et al. Preliminary findings of a 4-month intrahospital exercise training intervention on IGFs and IGFBPs in children with leukemia. *J Strength Cond.* (2010) 5:1292–7. doi: 10.1519/JSC.0b013e3181b22ac5
31. Speyer E, Herbinet A, Vuillemin A, Briancon S, Chastagner P. Effect of adapted physical activity sessions in the hospital on health-related quality of life for childrenwith cancer: a cross-over randomized trial. *Pediatr Blood Cancer*. (2010) 55:1160–6. doi: 10.1002/pbc.22698
32. Chamorro-Vina C, Ruiz JR, Santana-Sosa E, González Vicent M, Madero L, Pérez M, et al. Exercise during hematopoietic stem cell transplant hospitalization in children. *Med Sci Sports Exerc*. (2010) 42:1045–53. doi: 10.1249/MSS.0b013e3181c4dac1
33. Yeh CH, Man Wai JP, Lin US, Chiang YC, A. pilot study to examine the feasibility and effects of a home-based aerobic program on reducing fatigue in children with acute lymphoblastic leukemia. *Cancer Nurs*. (2011) 34:3–12. doi: 10.1097/NCC.0b013e3181e4553c
34. Rosenhagen A, Bernhörster M, Vogt L, Weiss B, Senn A, Arndt S, et al. Implementation of structured physical activity in the pediatric stem cell transplantation. *Klin Padiatr*. (2011) 223:147–51. doi: 10.1055/s-0031-1271782
35. Gohar SF, Comito M, Price J, Marchese V. Feasibility and parent satisfaction of a physical therapy intervention program for childrenwith acute lymphoblastic leukemia in the first 6 months of medical treatment. *Pediatr Blood Cancer*. (2011) 56:799–804. doi: 10.1002/pbc.22713
36. Geyer R, Lyons A, Amazeen L, Alishio L, Cooks L. Feasibility study: the effect of therapeutic yoga on quality of life in children hospitalized with cancer. *Pediatr Phys Ther*. (2011) 23:375–9. doi: 10.1097/PEP.0b013e318235628c
37. Cortés-Reyes E. Escobar-zabala P, Gonzalez-Garcia L. The effect of game-based exercise on infant acute lymphocytic leukaemia patients. *Fac Med*. (2013) 61:349–55.
38. Winter CC, Müller C, Hardes J, Gosheger G, Boos J, Rosenbaum D. The effect of individualized exercise interventions during treatment in pediatric patients with a malignant bone tumor. *Support Care Cancer*. (2013) 21:1629–36. doi: 10.1007/s00520-012-1707-1
39. Müller C, Winter C, Boos J, Gosheger G, Hardes J, Vieth V, et al. Effects of an exercise intervention on bone mass in pediatric bone tumor patients. *Int J Sports Med*. (2014) 35:696–703. doi: 10.1055/s-0033-1358475
40. Diorio C, Schechter T, Lee M, O'Sullivan C, Hesser T, Tomlinson D, et al. A pilot study to evaluate the feasibility of individualized yoga for inpatient children receiving intensive chemotherapy. *BMC Complement Altern Med*. (2015) 15:4–9. doi: 10.1186/s12906-015-0529-3
41. van Dijk-Lokkart EM, Braam KI, van Dulmen-den Broeder E, Kaspers GJL, Takken T, Grootenhuis MA, et al. Effects of a combined physical and psychosocial intervention program for childhood cancer patients on quality of life and psychosocial functioning: results of the QLIM randomized clinical trial. *Psychooncology*. (2016) 822:815–22. doi: 10.1002/pon.4016
42. Götte M, Kesting SV, Gerss J, Rosenbaum D, Boos J. Feasibility and effects of a home-based intervention using activity trackers on achievement of individual goals, quality of life, and motor performance in patients with paediatric cancer. *BMJ Open Sport Exerc Med*. (2018) 4:1–8. doi: 10.1136/bmjsem-2017-000322
43. Nielsen MKF, Christensen JF, Frandsen TL, Thorsteinsson T, Andersen LB, Christensen KB, et al. Testing physical function in children undergoing intense cancer treatment—a RESPECT feasibility study. *Pediatr Blood Cancer*. (2018) 65:1–9. doi: 10.1002/pbc.27100
44. Fiuza-Luces C, Padilla JR, Soares-Miranda L, Santana-Sosa E, Quiroga J V, Santos-Lozano A, et al. Exercise intervention in pediatric patients with solid tumors: the physical activity in pediatric cancer trial. *Med Sci Sports Exerc*. (2017) 49:223–30. doi: 10.1249/MSS.0000000000001094
45. De Macedo TMF, Oliveira KMC, Melo JBDC, De Medeiros MG, De Medeiros Filho WC, Ferreira GMH, et al. Inspiratory muscle training in patients with acute leukemia: preliminary results. *Rev Paul Pediatr*. (2010) 28:352–8. doi: 10.1590/S0103-05822010000400011
46. Shore S, Shepard R. Immune responses to exercise in children treated for cancer. *J Sport Med Phys Fit*. (1999) 39:240–3.
47. San Juan A, Fleck S. Chamorro-Vina, Mate-Munoz JL, Moral S, Garcia-Castro J, et al. Early-phase adaptations to intrahospital training in strength and functional mobility of children with leukemia. *J Strength Cond Res*. (2007) 21:173–7. doi: 10.1519/00124278-200702000-00031
48. San Juan AF, Fleck SJ, Chamorro-Viña C, Maté-Muñoz JL, Moral S, Pérez M, et al. Effects of an intrahospital exercise program intervention for children with leukemia. *Med Sci Sports Exerc*. (2007) 39:13–21. doi: 10.1249/01.mss.0000240326.54147.fc
49. Hinds PS, Hockenberry M, Rai SN, Zhang L, Razzouk BI, Cremer L, et al. Clinical field testing of an enhanced-activity intervention in hospitalized children with cancer. *J Pain Symptom Manage*. (2007) 33:686–97. doi: 10.1016/j.jpainsymman.2006.09.025
50. Keats M, Culos-Reed S, A. Community-based physical activity program for adolescents with cancer (Project TREK) program feasibility and preliminary findings. *J Pediatr Hematol Oncol*. (2008) 30:272–80. doi: 10.1097/MPH.0b013e318162c476
51. Moyer-mileur LJ, Ransdell L, Bruggers CS. Fitness of children with standard-risk acute lymphoblastic leukemia during maintenance therapy- response to a home-based exercise and nutrition program. *J Pediatr Hematol Oncol*. (2009) 31:259–66. doi: 10.1097/MPH.0b013e3181978fd4
52. Hartman A. te Winkel M, van Beek R, de Muinck Keizer-Schrama S, Kemper H, Hop W, et al. 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) 53:64–71. doi: 10.1002/pbc.21942
53. Naclerio F, Faigenbaum A. Integrative neuromuscular training for youth. *Kronos, Pediatr Phys Act*. (2011) 1:49–56.
54. Aagaard P. Training-induced changes in neural function. *Exerc Sport Sci Rev*. (2003) 31:61–7. doi: 10.1097/00003677-200304000-00002
55. Faigenbaum AD, Macdonald JP. Dynapenia : it's not just for grown-ups anymore. *Acta Paediatr*. (2017) 106:696–7. doi: 10.1111/apa.13797
56. Alonso-Aubin DA, Picón-Martínez M, Rebullido TR, Faigenbaum AD, Cortell-Tormo JM, Chulvi-Medrano I. Integrative neuromuscular training enhances physical fitness in 6- to 14-year-old rugby players. *J Strength Cond Res*. (2021) 35:2263–71. doi: 10.1519/JSC.0000000000003995
57. Faigenbaum AD, Farrell A, Fabiano M, Radler T, Naclerio F, Myer GD. Effects of integrative neuromuscular training on fitness performance in children. *Pediatr Exerc Sci*. (2011) 23:573–84. doi: 10.1123/pes.23.4.573
58. Duncan MJ, Eyre ELJ, Oxford SW. The effects of 10-week integrated neuromuscular training on fundamental movement skills and physical self-efficacy in 6–7-year-old children. *J Strength Cond Res*. (2018) 32:3348–56. doi: 10.1519/JSC.0000000000001859
59. Menezes GB, Alexandre DRO, Mortatti AL. Effects of integrative neuromuscular training on motor performance in prepubertal soccer players. *J Strength Cond Res*. (2020). doi: 10.1519/JSC.0000000000003666. [Epub ahead of print].
60. Panagoulis C, Chatzinikolaou A, Avloniti A, Leontsini D, Deli CK, Draganidis D, et al. In-season integrative neuromuscular strength training improves performance of early-adolescent soccer athletes. *J Strength Cond Res*. (2018) 34:516–26. doi: 10.1519/JSC.0000000000002938
61. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, KrleŽa-Jerić K, et al. Spirit 2013 statement: defining standard protocol items for clinical trials. *Chinese J Evidence-Based Med*. (2013) 13:1501–7. doi: 10.7326/0003-4819-158-3-201302050-00583
62. Thorsteinsson T, Helms AS, Adamsen L, Andersen LB, Andersen K V, Christensen KB, et al. Study protocol: rehabilitation including social and physical activity and education in children and teenagers with cancer (RESPECT). *BMC Cancer*. (2013) 13:1–7. doi: 10.1186/1471-2407-13-544

63. Foss KDB, Thomas S, Khoury JC, Myer GD. Hewett TE. A school-based neuromuscular training program and sport-related injury incidence: a prospective randomized controlled. *Clinical Trial.* (2018) 53:20–8. doi: 10.4085/1062-6050-173-16
64. Kirkham AA, Bland KA, Zucker DS, Bovard J, Shenkier T, Mckenzie DC, et al. "Chemotherapy - periodized" exercise to accommodate for cyclical variation in fatigue. *Med Sci Sports Exerc*. (2019) 52:278–86. doi: 10.1249/MSS.0000000000002151
65. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. *Am Psychol.* (2000) 55:68. doi: 10.1037/0003-066X.55.1.68
66. World Health Organization. *International Classification of Functioning, Disability, and Health: Children & Youth Version: ICF-CY*. Geneva: World Health Organization (2007).
67. Zimmet P, Mm AKG, Kaufman F, Tajima N, Silink M, Arslanian S, et al. The metabolic syndrome in children and adolescents – an IDF consensus report. *Pediatr Diabetes.* (2007) 8:299–306. doi: 10.1111/j.1399-5448.2007.00271.x
68. World Health Organization. *Waist circumference and waist-hip ratio: report of a WHO expert consultation, Geneva, 8–11 December 2008*. Geneva: World Health Organization (2011).
69. Bohannon RW. Dynamometer measurements of hand-grip strength predict multiple outcomes. *Percept Mot Skills.* (2001) 93:323–8. doi: 10.2466/pms.2001.93.2.323
70. Geiger R, Strasak A, Treml B, Gasser K, Kleinsasser A, Fischer V, et al. 6-min walk test in children and adolescents. *J Pediatr.* (2007) 150:395–9. doi: 10.1016/j.jpeds.2006.12.052
71. Bohannon RW. Measurement of muscle performance with sit-to-stand test. *Percept Mot Ski Ski.* (1995) 80:163–6. doi: 10.2466/pms.1995.80.1.163
72. Gurses HN, Zeren M, Denizoglu Kulli H, Durgut E. The relationship of sit-to-stand tests with 6-min walk test in healthy young adults. *Medicine.* (2018) 97:1–5. doi: 10.1097/MD.0000000000009489
73. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc.* (1991) 39:142–8. doi: 10.1111/j.1532-5415.1991.tb01616.x
74. Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The pedsQL^{TM} in pediatric cancer: reliability and validity of the pediatric quality of life inventory^{tm} generic core scales, multidimensional fatigue scale, and cancer module. *Cancer.* (2002) 94:2090–106. doi: 10.1002/cncr.10428
75. Gilchrist LS, Tanner L. The pediatric-modified total neuropathy score: a reliable and valid measure of chemotherapy-induced peripheral neuropathy in children with non-CNS cancers. *Support Care Cancer.* (2013) 21:847–56. doi: 10.1007/s00520-012-1591-8
76. Cohen H, Blatchly CA, Gombash LL, A. study of the clinical test of sensory interaction and balance. *Phys Ther.* (1993) 73:346–51. doi: 10.1093/ptj/73.6.346
77. Marchese VG, Chiarello LA, Lange BJ. Strength and functional mobility in children with acute lymphoblastic leukemia. *Med Pediatr Oncol.* (2003) 40:230–2. doi: 10.1002/mpo.10266
78. Borg G. *Borg's Perceived Exertion and Pain Scales*. Champaign, IL: Human Kinetics (1998).

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.

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CLINICAL TRIAL
published: 09 May 2022
doi: 10.3389/fped.2022.834512

Rehabilitation Including Structured Active Play for Preschoolers With Cancer (RePlay)—Study Protocol for a Randomized Controlled Trial

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Edited by:
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Specialty section:
This article was submitted to Pediatric Oncology, a section of the journal Frontiers in Pediatrics

Received: *13 December 2021*
Accepted: *31 March 2022*
Published: *09 May 2022*

Citation:
Pouplier A, Winther H, Christensen J, Schmidt-Andersen P, Zhang H, Frandsen TL, Schmiegelow K, Fridh MK and Larsen HB (2022) Rehabilitation Including Structured Active Play for Preschoolers With Cancer (RePlay)—Study Protocol for a Randomized Controlled Trial. Front. Pediatr. 10:834512. doi: 10.3389/fped.2022.834512

Background: Children diagnosed with cancer experience muscle weakness and impaired physical function caused by treatment and related immobility. The situation forces them into a negative cycle of diminished participation in physical and leisure activities and isolation from peers; inhibiting the natural development of social and gross motor skills. This manuscript presents a protocol for a study that explores the effects of using structured active play to maintain preschoolers' age specific gross motor function and social and personal skills while undertaking intensive cancer treatment.

Methods: The study is a two-arm, superiority randomized controlled trial with an intervention and a control group designed to evaluate the effects of a structured active play intervention on gross motor function. Gross motor subtests of the Peabody Developmental Motor Scales, Second Edition (PDMS-2) are used for measurement; with the primary end-point at 6 months post-treatment initiation. Eighty-four preschool children (aged 1–5 years), newly diagnosed with cancer at the Copenhagen University Hospital are randomly assigned to either an intervention or control group, using a 1:1 allocation. The intervention group receives a combined in-hospital and home-based program that includes structured active play activities, while the control group receives standard care, including physiotherapy. During hospital admission, the intervention group undertakes 45-min structured active play group sessions three times weekly, conducted by exercise professionals. Parents receive training and supervision to facilitate daily individual sessions outside of group sessions. Secondary study outcomes target the children's overall function level in everyday life, general physical performance, and health-related quality of life. As well, children's and parents' experiences within the intervention are explored and the children's social and personal development is observed.

Discussion: Limited evidence exists regarding the effectiveness of rehabilitation interventions, particularly those including active play, for preschoolers diagnosed

with cancer. This manuscript reporting on a study protocol will enhance clarity and transparency in reporting and offer insights for others with interest in this same topic. Once completed, findings from this study could extend knowledge about the conduct and measurement of effectiveness in rehabilitation initiatives. If study findings suggest that the intervention is effective, structured active play may become a standard part of rehabilitation.

Trial Registration: ClinicalTrials.gov: NCT04672681. Registered December 17, 2020. https://clinicaltrials.gov/ct2/show/NCT04672681.

Keywords: preschool children, rehabilitation, structured active play, physical activity, gross motor function, social skills, randomized, pediatric oncology

INTRODUCTION

Childhood cancer treatment causes multiple adverse events including myopathy, neuropathy, and loss of gross motor function (jumping, running, hopping, throwing and kicking, etc.). When experienced in parallel with treatment-related infections, inactivity and long-term bed rest this can lead to muscle weakness and decreased cardiorespiratory fitness (1–4). Such physical acute adverse events have been detected in cancer patients aged 4–18 years (1, 2, 4), and studies have shown that significantly impaired physical performance and gross motor function start in children immediately following cancer diagnosis (1, 5).

Findings suggest that younger children diagnosed with cancer (aged 6 months to 3 years) are significantly more affected by neuropathy and gross motor function impairment compared with school aged children (3). Further, interview and observational data suggest that younger children (under the age of 7) diagnosed with cancer still have a need to play, however, when visibly affected by the disease and treatment they tend to engage in sedentary play and have difficulty participating in physical activities with peers (6, 7). As such, there is an urgent need for interventions that counteract consequences of cancer treatment on gross motor function.

Previously published research indicates that physical activity and testing physical performance during cancer treatment are safe and feasible in children 6–18 years old (4, 8, 9). Moreover, physical activity positively correlates with cardiorespiratory fitness, physical function and health-related quality of life in children diagnosed with cancer (2, 4, 8, 10, 11). However, most of these studies focus on children with cancer, aged 4–18 years.

Physical activity is positively associated with bone and cardiorespiratory health, development of gross motor skills and cognition in healthy school-aged children (12–14). Developing fundamental motor function early in life ensures later development of finer motor skills (15, 16). Inadequate gross motor function in healthy preschoolers causes movement insecurity and can lead to sedentary behavior (17–20). Collectively, researchers have found significant gross motor function improvement in healthy preschoolers who followed a physical activity program compared with control groups who did not receive physical activity (16, 21–24). Yet, this has not been explored in preschoolers facing cancer treatment.

Gross motor function must be developed and reinforced through activity and interaction with others (15, 16, 20). Physical activity for preschoolers takes the form of play (25). Playing allows children to explore a world they can master, use their imagination and confronts their fears (26). Learning essential gross motor skills increases self-esteem (20) and is associated with language development, social cognition and interaction (27). Hence, gross motor function is fundamental to engaging in social and physical activities throughout the life span. Structured active play with others provides an initial arena for socialization and these peer interactions are vital to developing personal and social skills (20, 26, 28, 29). As such, structured active play is directly linked to the development of interdependent motor, social and personal skills (20, 26, 29, 30).

Taken together, cancer can impede preschoolers' fundamental gross motor function and delaying social and personal skills development. The RePlay study (Rehabilitation including structured active play for preschoolers with cancer) targets these risks in this population group. This protocol introduces the RePlay study and offer greater transparency about the study by reflecting the choices made and the expected challenges.

Study Aims and Hypotheses

The RePlay study investigates the effectiveness of a 6-month structured active play intervention on gross motor function development in children aged 1–5 years, who are diagnosed with cancer. We hypothesize that children in the intervention group will acquire improved gross motor function compared with the children receiving standard care, in the control group.

Secondary study aims include investigation of the effectiveness of the intervention on the children's: (1) functional level in everyday life; (2) general physical performance (2 and 6 min. walk test and handgrip strength); and (3) heath-related quality of life of the children and their parents.

The study also qualitatively explores the experiences of the children and their parents. Specifically, the children's confidence

Abbreviations: PDMS-2, Peabody Developmental Motor Scales, Second Edition; PEDI, Pediatric Evaluation of Disability Inventory; 6MWT, Six-minute walk test; 2MWT, Two-minute walk test; HRQoL, Health-related quality of life; ITT, Intention-to-treat; TTI, Treatment initiation; CONTROL, Childhood Oncology Network Targeting Research, Organization & Life expectancy.

in movement, joy of movement and social interactions will be probed in an effort to capture social and personal development.

We hypothesize that the intervention group will have improved gross motor function, general physical performance and health-related quality of life post-intervention compared with the standard care control group.

METHODS AND ANALYSES

This protocol is reported according to SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (31).

Study Design

The study is a two-arm, superiority randomized controlled trial (RCT) with an intervention and a control group. The 6-month structured active play intervention is initiated, in parallel, with the treatment start and ends with a follow-up session 1 year post-treatment. Qualitative and quantitative data are collected and will be reported independently. The study is registered at ClinicalTrials.gov: NCT04672681.

Setting

The study is carried out in the Department for Pediatrics and Adolescent Medicine at Copenhagen University Hospital, Denmark. All children participating in the study are screened in accordance with the study's eligibility criteria.

Eligibility Criteria

Children eligible to participate in the study must be: (1) newly diagnosed with cancer or cancer-like benign disorders; (2) between the ages of $\geq$1 to $<$6 years at the time of diagnosis; (3) undergoing chemotherapy and/or radiation therapy at the Department for Pediatrics and Adolescent Medicine at Copenhagen University Hospital; and (4) have parents able to understand and communicate in Danish. Children considered ineligible are those diagnosed with mental disorders that prevent them from following instructions in relation to the intervention and testing.

Recruitment

Recruitment started January 2021. Participants are recruited through referral from pediatricians in the Department for Pediatrics and Adolescent Medicine to the project nurse. Eligible participants will receive information about the study verbally, and their parents are given oral and written study information by a project nurse before providing written informed consent for their child to participate.

Randomization

Following baseline data collection, participants are randomly placed in either the intervention or control group by means of centrally administered computer-generated (R-studio) random numbers and using a secure concealed allocation procedure. The randomization procedure is stratified by age at inclusion [respectively, $<$36 and $\geq$36 months old) and diagnostic group (hematologic malignancy, tumors located in the central nervous system (CNS tumor), and extracranial solid tumors]. The project nurse who includes the children is blinded to the randomization strategy and randomization is performed by a statistician who is not a member of the research group and who is blinded to baseline results. Due to the nature of the intervention, neither the children nor parents are blinded to their group allocation. If baseline assessment cannot be performed within two weeks of treatment initiation, randomization is carried out first, after which the children commence in either the intervention or control group without a baseline assessment.

Structured Active Play Intervention (RePlay)

Children and their parents who are allocated to the intervention group participate in a combined in-hospital and home-based program that comprises 45 min of daily structured active play activities targeting gross motor function. In-hospital structured active play is conducted in group sessions at the hospital's pediatric physiotherapy clinic three times weekly, when the children are either admitted or visit the out-patient clinic. Outside of these group sessions, parents (or a parental figure) facilitate individual sessions for their child either in the hospital or at home. The intervention content is inspired by the Mighty Moves intervention (21). Further, the intervention was developed in collaboration with a parent panel comprising six families, each with a child aged 1–5 years and diagnosed with cancer. Different aspects of the study design were pilot tested on healthy children and children with cancer. More specifically, pilot testing of the primary outcome was done using four healthy children and two children with cancer. Additionally, two children with cancer undertook two months of the structured active play intervention prior to the inclusion process for the randomized trial. **Table 1** shows the weekly schedule for the Study's intervention group.

Intervention Concept

The concept of "Structured Active Play" used in this study refers specifically to instructor- or parent-led sessions of goal-oriented, age sensitive, fun movement activities that teach preschoolers gross motor skills while enhancing their social and personal skills (20, 25, 26).

Group Structured Active Play Sessions

Group sessions are characterized by socialization amongst children and their parents. However, the primary aim of the sessions is to enhance the children's gross motor skills as well as social and personal skills through structured active play (20, 26, 32). Each session is guided by three core principles: (1) ritual practices; (2) reinforcement of movement through repetition; and (3) development through appropriate challenge (15, 20, 33). As such, all sessions have the same start and ending ritual to establish recognizability and security for the children. Many of the activities are repeated from session to session to reinforce gross motor function development and all sessions aim to challenge the children's movement skill level. The exercise professional subjectively assesses, on a daily basis, each child's progress and sets the appropriate challenge level that can either be up- or down-scaled accordingly.

TABLE 1 | Example of a weekly schedule of structured active play for preschoolers with cancer, during treatment.

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Individual structured active play session*	Individual structured active play session* or Group structured active play session**	Individual structured active play session*	Individual structured active play session* or Group structured active play session**	Individual structured active play session* or Group structured active play session**	Individual structured active play session*	Individual structured active play session*

**The individual sessions are conducted by the parents either at home or in the hospital room. **The group sessions are conducted by an exercise professional or a trained pediatric physiotherapist.*

The group sessions are supervised by an exercise professional or a trained pediatric physiotherapist and take place in the pediatric occupational and physiotherapeutic clinic of the hospital. Respecting age-specific development, participants are divided into two groups: children <36 months old and those ≥36 months old. Families (including siblings if present) participate when admitted to the Department for Pediatrics and Adolescent Medicine or during appointments in the out-patient clinic. To ensure participation, the parents receive a text message reminder on the morning of each group session as well as being reminded in person. A member of the project team communicates regularly with the family and the nurse assigned to the child regarding the child's treatment and care status to ensure his/her participation in group sessions. For safety's sake, a set of daily inclusion criteria are applied to ensure that each child participating in a group session on any given day can avoid risk of an adverse event (i.e., hemoglobin >5.0 mmol/l; platelets >10 billion/l at moderate to intense activities; no active diarrhea, coughing, or cold; temperature <38.5°C; no severe comorbidities that could hinder structured active play). The treating physician and nurse are consulted prior to each child participating in a session. Admitted families treated in isolation or otherwise prevented from participating in a group session are offered an individual session with the exercise professional or pediatric physiotherapist for 45 min. These substitute sessions comprise similar activities to those in group sessions.

Individual Structured Active Play Sessions

On days when there are no intervention group sessions or when the children are not hospitalized, the parents facilitate individual sessions in the ward or at home. Inspirational packs are provided to assist them in facilitating active play with their child while they continue to receive oral instruction and supervision from the project team throughout the intervention. Packs include an introductory page and cards with drawings and explanations of the different activities (see introductory page and sample activities—**Supplementary File 1**). Many of the activities are the same as in the group sessions. Parent participation in group sessions serves to teach and inspire them to do new and old activities. Activities are color coded according to the achieved gross motor skill level of the child (34, 35). Materials are developed for two age groups: children <36 months old and those ≥36 months old; with illustrative drawings that engage the child in selecting activities that he/she prefers. Activity descriptions encourage participation by siblings and other family members.

Control Group

Children allocated to the control group receive standard care, including physiotherapy for deficits during hospitalization. Following hospital discharge, these patients may also undergo rehabilitation, based on a deficits plan. For ethical reasons, post-intervention, those randomly allocated to the control group are offered the same inspirational material and an option to participate in the same structured active play group sessions as the intervention group families. However, they do not receive instruction or supervision for any parent-led session.

Intervention Fidelity and Feasibility

Feasibility is assessed through acceptance, attrition, and adherence (36–38). Acceptance is defined as interest and willingness to participate in the study (i.e., the number of eligible children entering the study). Attrition is assessed by registering the number of children leaving prior to the study's completion. Adherence is measured by participation level in the intervention (i.e., monitoring of participant compliance) (36); and for which several strategies are used. Each child's participation in group sessions (including rationale for non-participation) as well as the type and duration of his/her activities are registered on standard forms. Parents are also provided a logbook for their child's individual sessions and in which they must record duration and type of activities undertaken or reasons for not doing activities.

Outcomes

Assessments for all included children are conducted at treatment initiation (T1, baseline), 3 months after treatment initiation (T2), and at 6 months after treatment initiation (T3, post-intervention, primary end-point). Long-term follow-up will occur at 12 months after treatment initiation (T4), and 1-year post-treatment (T5). An overview of the study design, including enrollment and assessments, is summarized in **Table 2**.

Participant Characteristics

Upon inclusion socio-demographic information from the children and parents is collected through a questionnaire, including: place of birth, place of residence, family structure, parent admitted with the child, support from friends/relatives, daycare/preschool attendance, physical and leisure activities of the child and parents, and educational level of the parents. Furthermore, the following data are extracted from the children's medical records: sex, age, diagnosis, date of diagnosis, date of treatment initiation, date of relapse, possible date of death, comorbidity, treatment (e.g., treatment protocol, medical

TABLE 2 | Schedule of enrollment, interventions, and assessments of participants in the RePlay study that explores gross motor function in children aged 1–5 years during intensive cancer treatment.

	STUDY PERIOD						
	Enrolment	Pre-allocation	Post-allocation				
			Intervention			Follow-up	
Timepoints	**TTI**	**T1 (Baseline)**	**T1[1]**	**T2**	**T3 (primary end-point)**	**T4**	**T5**
ENROLMENT							
Eligibility screen	X						
Oral and written information	X						
Informed consent		X					
INTERVENTION							
Structured active play			■	■	■		
Standard care			■	■	■	■	■
ASSESSMENTS							
Medical record info		■	■	■	■	■	■
PDMS-2		X		X	X	X	X
PEDI		X		X	X	X	X
Handgrip strength		X		X	X	X	X
6-min walk		X		X	X	X	X
Socio-demographics		X			X	X	X
PedsQL Generic Core Scale (parent proxy report)		X			X	X	X
PedsQL Cancer (parent proxy report)		X			X	X	X
PedsQL Multidimensional Fatigue Scale (parent proxy report)		X			X	X	X
RAND 36-item Health Survey		X			X	X	X
INTERVENTION ASSESSMENTS							
Adverse events			■	■	■		
Adherence to structured active play intervention			■	■	■		
Safety measures			■	■	■		
ADDITIONAL EMPIRICAL DATA							
Interview					X		
Observation			■	■	■		

TTI, Treatment initiation; T1 = +1–14 days after TTI (Baseline), T1[1] = +1–14 days after TTI, T2 = 3 months (±14 days) after TTI, T3 = 6 months (±14 days) after TTI (post-intervention, primary end-point), T4 = 12 months (±14 days) after TTI, and T5 = 1 year (±14 days) after ended treatment.

treatment) and medical care. In relation to daily inclusion safety criteria, data on hemoglobin level; platelets; leukocyte levels; temperature; infection symptoms and infections (organism, place, cause) are gathered from the treating physician and nurse.

Primary Outcome Measure

Gross Motor Function

Gross motor function is measured using Peabody Developmental Motor Scales, Second Edition (PDMS-2), that calculates fine and gross motor function in children aged 0–6 years (39). Only the gross motor function subtests of the PDMS-2 are used in this study and consist of a total of 143 items, each scored from 0 to 2. The items are divided into three domains [i.e., stationary (30 items), locomotion (89 items) and object manipulation (24 items)] (39). The assessment is done by a trained member of the project team. The test is conducted by starting with a given item in the domain, depending on the child's age (specified in months). The items are treated singularly until the child scores 2 in three consecutive items, after which the lower level can then be determined. It may be necessary to revert to earlier items to achieve three consecutive scores of 2. The remaining items are given the score of 2. The test then proceeds with further items until the child scores 0 in three consecutive items, determining the ceiling level. The remaining items are then given the score of 0. The raw score for each domain is the sum of all the items. The test has shown acceptable psychometric properties including Cronbach $\alpha = 0.89–0.97$, test-retest $r = 0.82–0.93$, and interscorer $r = 0.96–0.99$ (39, 40).

Secondary Outcome Measures

Level of Everyday Function

The children's function level is determined using the Pediatric Evaluation of Disability Inventory (PEDI). The assessment is a structured interview with parents of children aged 6 months

to 7 years old. PEDI is assessed by a trained member of the project team possessing comprehensive experience with the tool (41). The instrument measures capability and performance of selected functional activities on three scales: functional skills, caregiver assistance, and modifications (41, 42). In this study, the modification scale is not used. The functional skills scale is divided into three domains: self-care (73 items), mobility (59 items), and social function (65 items). Each item in the functional skill scale is scored with a 0 or 1. The caregiver assistance scale is divided into three domains: self-care (8 items), mobility (7 items) and social function (5 items). Each item in the caregiver assistance scale is scored 0 to 5 Aggregate scores are defined as the sum of each domain (42).

Handgrip Strength

Handgrip strength is measured using the handgrip strength test and the KLS Martin Vigorimeter (KLS Martin group, 78532 Tuttlingen, Germany) (43, 44). The instrument is a pneumatic dynamometer with three sizes of rubber bulbs. The smallest bulb is recommended for smaller children and is used for all participants in this study (43, 44). The bulb is placed with the air tube extending outward between the thumb and index finger and the fingers wrap around the bulb. The test is given twice per hand, with left and right hands alternated and a 30 s break between each trial. The children are verbally encouraged to squeeze the bulb as hard as they can. All scores (kPa) are registered and the highest score for each hand is used for the analysis.

Six-Minute Walk Test

The six-minute walk test (6MWT) is a general physical performance indicator (45). The test is done in a hallway with a 15-meter track that is clearly marked at each end. The child is asked to walk from one mark to the other as many times as he/she can within 6 min. The assessor verbally encourages the child to keep walking during the 6 min; if needed, parents can walk beside their child along the track and are reminded that it is the child who sets the pace. Given that the 6MWT with younger children whose concentration is limited can be difficult there will also be a recording of the distance walked after the initial 2 minutes (2MWT) in case they can't walk all 6 minutes. The 2MWT is validated in younger children (46, 47).

Health-Related Quality of Life (HRQoL)

HRQoL of the children and parents are measured through four standardized questionnaires. HRQoL of the children is measured through three parent proxy-report questionnaires designed to assess the parent's perceptions of their child's health-related quality of life. The PedsQL Generic Core Scale measures quality of life using 21 items in 4 domains; physical, emotional and social function; and school/preschool activity (48). PedsQL Cancer measures the effect of cancer on the child using 25 items in 8 domains: pain, nausea, procedure anxiety, treatment anxiety, worry, cognitive issues, physical appearance and communication (48). The PedsQL Multidimensional Fatigue Scale measures fatigue through 18 items in 3 domains: general fatigue, sleep/rest fatigue, and cognitive fatigue (48). The PedsQL questionnaires use a five-point Likert scale: 0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem.

Parental HRQoL is measured by means of a Short Form Survey Instrument (RAND 36-item Health Survey) (49). It consists of 36 items divided into 8 domains (Physical functioning, limitations due to physical health, limitations due to emotional health, energy/fatigue, emotional well-being, social functioning, pain, and general health). All items are scored on a 5-point Likert scale from 0 to 100, with 100 representing the highest level of functioning possible. Aggregate scores are compiled as a percentage of the total points possible, using the RAND scoring table. The scores from the items within each domain are averaged, for a final score per domain (49). A physical and a mental component summary score can be calculated but not a total score (49).

Additional Interview and Observations

Semi-structured Interview

Interviews take place with the intervention group children and parents within two weeks post intervention. The interview guide is semi-structured, with open-ended questions to help understand parents' and children's experiences and perspectives (50, 51). The interview guide is attached as **Supplementary File 2**. The interview guide seeks to explore the children's confidence in movement, joy of movement and social interactions. The interviewer asks the child questions such as: "What activities do you do at the hospital?"; "Can you tell me what you think is fun to play?"; "Can you tell me what you think is boring to play?"; or "Who do you play with?". The parents are asked questions within the same focus sphere, such as: "How is your child's gross motor function right now?"; "Have you seen any changes over the last 6 months?"; "How do you feel about having participated in the intervention?"; "How do you feel challenging your child to develop his/her gross motor functioning?", "How do you experience your child's belief in his/her own abilities?". Follow-up questions are posed to both children and parents for deeper understanding and clarification purposes. Darcy et al. (6, 52) inspired the interview modality for the participants aged 3–5 years. Each child-parent dyad is interviewed as a unit with a clear indication when the questions are directed to the parents or to the child. Playing and toys are used to break the ice and to facilitate responses from the children. When a child is hesitant to participate, the interviewer directs questions only to the parents while the child can join in at any desired moment (6). Only the parents are interviewed when the child is younger than 3 years old, however, those children are encouraged to join in if they desire.

Observation

Observations are made during the active play sessions to get an understanding of how structured active play impacts the development of the children's social and personal skills and focuses on confidence in movement, joy of movement and social interactions. Observations are made over the first 12 months of the intervention when conducted at the hospital. The intervention research team members are considered participant observers during the sessions as they

both actively participate while simultaneously observing the children (53). This active insider-observer perspective is selected to allow upfront observation of the children. Written notes are consequently made directly following each session and then reformulated into scenic descriptions, a narrative-inspired observation method (54, 55). Scenic descriptions create nuanced insight and understanding of what occurs during session activities. The researcher's voice can be present in the descriptions, however, he/she must remain true to what is experienced (54, 56, 57).

Sample Size

RCT

No studies have been identified in the literature that investigate the potential effectiveness of a structured active play intervention on gross motor function in preschool children diagnosed with cancer. Hence, the sample size for the current study is based on a study that investigated the effectiveness of a structured active play intervention on gross motor function in healthy preschool children (21). Based on the mean and standard deviation (SD) in the intervention group = 99.31 (9.07), and a mean (SD) in the control group = 93.24 (9.02), an Alpha = 0.05 and Power = 80%, it is estimated that 70 children are required for the study. However, to account for possible attrition, 20% more participants are included. Hence, the study includes 84 children in total (42 in each group).

Interviews

To ensure credibility and data adequacy, a minimum sample of 20 families will be interviewed at T3 (post-intervention, primary end-point) (51, 58, 59). Broad representation will be attempted by including all age groups, diagnostic groups and family structures (50, 60, 61). However, a convenience sampling strategy will be applied. Only the intervention group families are invited to be interviewed with the project team, within two weeks post-intervention.

Analysis

Statistical Considerations

The collected data will be analyzed based on intention-to-treat (ITT). The treatment effect difference will be estimated through constrained longitudinal data analysis that constrains the mean at baseline to be equal between the arms. Constrained linear mixed models will be applied in two scenarios. In the 1st scenario, predictors include follow-up time points categorized as T2 (3 months after treatment initiation) and T3 (6 months after initiation) to account for any non-linear effect and dummy variables representing the intervention group at T2 and T3 follow-ups, respectively. In the 2nd scenario, the time variable will be treated as a continuous variable and interaction between groups and the time variable will be included instead. Baseline characteristics such as age (as a continuous variable) and cancer type (hematologic malignancy, tumors located in the central nervous system (CNS tumor), and extracranial solid tumors) will be included additionally as covariates in both scenarios. Patient identity serves as a random intercept. Likelihood ratio tests based on maximal likelihood will be applied for model selection of the fixed effects to determine linear or non-linear associations. A significance level at 0.05 will be used.

Thematic Analysis

Interviews will be transcribed verbatim and the observation notes will be transformed into scenic descriptions. Thematic analysis will be conducted on all data (interview and scenic description transcripts) (62). The analysis will be inductive and focuses on the children's and parents' experiences with structured active play. The interview and scenic descriptions will be analyzed independently. Both sets of qualitative data will be analyzed following four flexible steps: (1) reading the material to obtain an overall understanding; (2) identifying meaningful units; (3) coding the units; and (4) summarizing the codes into key themes (62, 63). Two researchers will conduct the analysis independently and then together, and reflect and discuss results during the process to strengthen credibility and dependability of the data and, as such, the trustworthiness of the study (50, 60). Credibility will be enhanced through the use of relevant direct quotes from the data (60).

Data Management

All data are collected in paper form and then manually entered in a secure electronic database (REDCap) by a member of the project team. As this process can produce data management errors, the data will be cross-checked independently by two members of the project team to assure their quality.

DISCUSSION

This two-arm parallel, superiority randomized controlled trial (RCT), with an intervention group and a control group, can potentially examine the effects of a structured active play intervention on gross motor function in preschool children diagnosed with cancer. Additionally, it can explore the children's and parents' experiences with structured active play and how that impacts their child's gross motor, social, and personal development. This protocol reflects choices made when designing this study and considers the expected challenges, strengths and dilemmas of exploring the experience of preschool children undergoing intensive cancer treatment in parallel with an intervention and securing viable outcome measurements.

Testing children is generally difficult and testing preschool children (1 to 5 years old) diagnosed with cancer is expected to be even more challenging due to their burdened physical and mental state. Testing for objective data in this age group and the results of these tests will vary on any given day in correlation with the child's level of well-being (e.g., treatment-related side effects, including pain or nausea, etc.), mood (including mood changes related to dexamethasone treatment) and ability to understand instructions and to cooperate. However, as we are aware of this methodological challenge, various efforts have been made to optimize the opportunity of obtaining data, such as: (1) having an assessor who is an experienced

pediatric physiotherapist assigned to the patient group and when performing the gross motor function tests; (2) creating an environment in which the children feel a sense of familiarity and security; and (3) including parent proxy assessments. To create a trusting testing environment, parents are present during all tests as they often provide both familiarity and security for their child. We also prioritized having experienced physiotherapists familiar to the participant group as outcome assessors to increase the probability of successfully obtaining data. This outweighed having blinded outcome assessors. To further strengthen findings from this study a secondary outcome that measures gross motor function is selected (i.e., the PEDI). This is a subjective parent proxy means of reporting the child's level of everyday function.

With regards to the intervention design, the research team developed an intervention program targeting preschoolers' gross motor function through structured active play. Similar to above, conducting this type of activity intervention within the preschooler age group is challenging given developmental considerations and disease characteristics. The study intervention uses a structured active play approach. Play is fundamental for children, fun and provides an opportunity for them to create and explore a world they can master (26). When using play in physical activity it is possible to stimulate imagination and have fun using gross motor skills in a way that appeals to the child. Instead of asking a child to practice balance and build leg strength by merely jumping, a scenario can be created in which the child can imagine being a frog jumping through a forest. Designing a structured active play intervention, while allowing for individualization, also means compromising and forgoing a strict protocol. The trade-off is reduced reproducibility. When playing with children, it is necessary to be open to their imagination and be prepared to spontaneously change an activity in order to entice them. Not all children are motivated by the same thing and this raises the question of whether it is possible to describe exactly what the intervention comprises. This intervention uses three theoretical core principles, including: ritual practices, repetition and challenge; all aiming to establish recognizability, security and motivation for the children. These components also ensure that all the sessions are identically structured, with the same starting and ending rituals, repeated activities and challenges. Exact activities performed during each session are documented.

Gross motor function in preschoolers is developed through interaction with others (children, parents or other adults) and reinforced through activities. The intervention is therefore designed to allow intervention group children and parents to participate together in the in-hospital sessions, when possible. Moreover, the exercise professional conducting the sessions at the hospital as well as parents and siblings participate by either following, supporting the child or leading in an activity. Whether moving across the floor like an animal or balancing through an obstacle course, each party participates. Active participation by parents during the sessions can also reinforce the parents' ability to carry out the same activities with their child at home. Participation with others in activities is not only essential in supporting the child's physical development but also his/her social and personal skills. Group activities necessitate patience, ability to take turns and to cooperate with others.

Finally, a strength of this study is that it will collect long-term data. Being physically active is correlated with optimal gross motor function development and the latter is associated with social-, cognitive-, language- and personal- development in healthy preschool children (12–14, 27). The longitudinal relationship between gross motor function and health shows that reduced motor function competence during childhood is associated with higher body fat, lower cardiorespiratory fitness and lower physical fitness later in life (64, 65). Studies of children diagnosed with cancer, aged 1–18 years show that gross motor function impairments are still present two years after diagnosis and up to seven years post-treatment (5, 66). Research in physical activity and preschoolers diagnosed with cancer is important to better understand how physical activity can play a role in counteracting impairments of gross motor function and increase the possibility of sustaining normal everyday activities during and after treatment.

This protocol describes a study that will contribute by providing data on differences in gross motor function between preschoolers diagnosed with cancer who participate in an early initiated structured active play intervention and children diagnosed with cancer who are receiving standard care. Findings from this study, once completed, will also provide insights into the intervention group children's and parents' experiences with structured active play. If the trial proves the intervention to be effective, structured active play may become a standard rehabilitation component and findings from the study may be transferable to children with other chronic diseases and those experiencing long-term hospitalization.

ETHICS AND DISSEMINATION

The study complies with the ethical research principles described in the Declaration of Helsinki II. The study has been peer-reviewed and approved by the National Committee on Health Ethics Research through the Regional Research Ethics Committee in the Capital Region of Denmark (jr.nr.: H-20023949), and data handling is approved by the Danish Data Protection Agency (jr. nr.: P-2020-290). Written informed consent is obtained from parents prior to inclusion in the study and parents are informed that participation is voluntary and that their child or themselves can drop out of the study at any time.

Safety and Adverse Events

Previous studies have shown physical activity is found safe for children with cancer, regardless of diagnosis (2, 4, 5, 11, 67). Nevertheless, all adverse events defined as unintended negative consequences that are experienced during the structured active play sessions are documented, despite the possibility of a causal relationship between the intervention and usual care (68).

Dissemination Policy

Future results will be presented in peer-reviewed scientific journals and at international conferences. Authorship eligibility will follow the Vancouver Recommendations for authorships.

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 National Committee on Health Ethics Research through the Regional Research Ethics Committee in the Capital Region of Denmark (jr.nr.: H-20023949). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

The intervention content was developed by AP. The outcome measures were selected and evaluated by AP, MF, HL, PS-A, JC, and HW. The statistical analysis plan was prepared by HZ. KS and TF provided childhood cancer specific expertise. HL and MF led the project. AP wrote the initial draft of the manuscript. All authors contributed the final version, actively and substantially contributed to the design of the intervention study, and read and approved the final manuscript.

FUNDING

This work is a part of Childhood Oncology Network Targeting Research, Organization & Life expectancy (CONTROL), supported by Danish Cancer Society (R-257-A14720) and the Danish Childhood Cancer Foundation (2019-5934). Furthermore, this study was specifically supported by individual grants from the Danish Cancer Society (R-284-A16272-20-S15 and R296-A16956) and the Danish Childhood Cancer Foundation (2019-5947; 2020-6756; 2021-7400). Funding sources played no role in the design or conduct of the study, collection of data, analysis, interpretation of results, preparation, review, approval of the manuscript or decision to submit the manuscript for publication.

ACKNOWLEDGMENTS

The authors thank the staff of the Department for Pediatrics and Adolescent Medicine and of the Department of Occupational and Physiotherapy at Copenhagen University Hospital, Rigshospitalet for their commitment to the study. Sincere gratitude is also extended to the steering committee members for their expertise and support.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.834512/full#supplementary-material

REFERENCES

1. Ness KK, Kaste SC, Zhu L, Pui CH, Jeha S, Nathan PC, et al. Skeletal, neuromuscular and fitness impairments among children with newly diagnosed acute lymphoblastic leukemia. *Leuk Lymph.* (2015) 56:1004–11. doi: 10.3109/10428194.2014.944519
2. Thorsteinsson T, Larsen HB, Schmiegelow K, Thing LF, Krustrup P, Pedersen MT, et al. Cardiorespiratory fitness and physical function in children with cancer from diagnosis throughout treatment. *BMJ Open Sport Exerc Med.* (2017) 3:e000179. doi: 10.1136/bmjsem-2016-000179
3. Vainionpää L. Clinical neurological findings of children with acute lymphoblastic leukaemia at diagnosis and during treatment. *Eur J Pediatr.* (1993) 152:115–9. doi: 10.1007/BF02072486
4. Nielsen MKF, Christensen JF, Frandsen TL, Thorsteinsson T, Andersen LB, Christensen KB, 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.* (2020) 18:1–12. doi: 10.1186/s12916-020-01634-6
5. Hartman A, Winkel ML, van Beek RD, de Muinck Keizer-Schrama SMPF, Kemper HCG, van den Heuvel-Eibrink MM, et al. 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) 53:64–71. doi: 10.1002/pbc.21942
6. Darcy L, Enskär K, Björk M. Young children's experiences of living an everyday life with cancer – a three year interview study. *Eur J Oncol Nurs.* (2019) 39:1–9. doi: 10.1016/j.ejon.2018.12.007
7. Björk M, Nordström B, Hallström I. Needs of young children with cancer during their initial hospitalization: an observational study. *J Pediatr Oncol Nurs.* (2006) 23:210–9. doi: 10.1177/1043454206289737
8. Nielsen MKF, Christensen JF, Frandsen TL, Thorsteinsson T, Andersen LB, Christensen KB, et al. Testing physical function in children undergoing intense cancer treatment—a RESPECT feasibility study. *Pediatr Blood Cancer.* (2018) 65:1–9. doi: 10.1002/pbc.27100
9. Thorsteinsson T, Schmiegelow K, Thing LF, Andersen LB, Helms AS, Ingersgaard MV, et al. Classmates motivate childhood cancer patients to participate in physical activity during treatment: a qualitative study. *Eur J Cancer Care.* (2019) 28:1–10. doi: 10.1111/ecc.13121
10. Braam K, Van der Torre P, Takken T, Veening MA, Van Dulmen-den Broeder E, Kaspers GJL. Physical exercise training interventions for children and young adults during and after treatment for childhood cancer (Review) SUMMARY OF FINDINGS FOR THE MAIN COMPARISON. *Cochrane Database Syst Rev.* (2016) 3:CD008796. doi: 10.1002/14651858.CD008796.pub3
11. Fiuza-Luces C, Padilla JR, Soares-Miranda L, Santana-Sosa E, Quiroga J V., Santos-Lozano A, et al. Exercise intervention in pediatric patients with solid tumors: the physical activity in pediatric cancer trial. *Med Sci Sports Exerc.* (2017) 49:223–30. doi: 10.1249/MSS.0000000000001094
12. WOLD HEALTH ORGANIZATION. *Guidelines on Physical Activity, Sedentary Behaviour and Sleep*. World Health Organization (2019). p. 4. Available online at: https://apps.who.int/iris/bitstream/handle/10665/325147/WHO-NMH-PND-2019.4-eng.pdf?sequence=1&isAllowed=y%0Ahttp://www.who.int/iris/handle/10665/311664%0Ahttps://apps.who.int/iris/handle/10665/325147

13. Timmons BW, Leblanc AG, Carson V, Gorber SC, Dillman C, Janssen I, et al. Systematic review of physical activity and health in the early years (aged 0-4 years). *Appl Physiol Nutr Metab.* (2012) 37:773–92. doi: 10.1139/h2012-070
14. Barnett LM, Salmon J, Hesketh KD. More active pre-school children have better motor competence at school starting age: an observational cohort study. *BMC Public Health.* (2016) 16:1–8. doi: 10.1186/s12889-016-3742-1
15. Clark JE. On the problem of motor skill development. *J Phys Educ Recreat Danc.* (2007) 78:39–44. doi: 10.1080/07303084.2007.10598023
16. Logan SW, Robinson LE, Wilson AE, Lucas WA. Getting the fundamentals of movement: a meta-analysis of the effectiveness of motor skill interventions in children. *Child Care Health Dev.* (2012) 38:305–15. doi: 10.1111/j.1365-2214.2011.01307.x
17. Williams HG, Pfeiffer KA, O'Neill JR, Dowda M, McIver KL, Brown WH, et al. Motor skill performance and physical activity in preschool children. *Obesity.* (2008) 16:1421–6. doi: 10.1038/oby.2008.214
18. Wrotniak BH, Epstein LH, Dorn JM, Jones KE, Kondilis VA. The relationship between motor proficiency and physical activity in children. *Pediatrics.* (2006) 118:e1758–65. doi: 10.1542/peds.2006-0742
19. Piek JP, Baynam GB, Barrett NC. The relationship between fine and gross motor ability, self-perceptions and self-worth in children and adolescents. *Hum Mov Sci.* (2006) 25:65–75. doi: 10.1016/j.humov.2005.10.011
20. Garcia C, Garcia L, Floyd J, Lawson J. Improving public health through early childhood movement programs. *J Phys Educ Recreat Danc.* (2002) 73:27–31. doi: 10.1080/07303084.2002.10605876
21. Bellows LL, Davies PL, Anderson J, Kennedy C. Effectiveness of a physical activity intervention for head start preschoolers: a randomized intervention study. *Am J Occup Ther.* (2013) 67:28–36. doi: 10.5014/ajot.2013.005777
22. Zeng N, Ayyub M, Sun H, Wen X, Xiang P, Gao Z. Effects of physical activity on motor skills and cognitive development in E.: GCU library resources - all subjects. *Biomed Res Int.* (2017) 2017:1–13. doi: 10.1155/2017/2760716
23. Veldman SLC, Jones RA, Okely AD. Efficacy of gross motor skill interventions in young children: an updated systematic review. *BMJ Open Sport Exerc Med.* (2016) 2:e000067. doi: 10.1136/bmjsem-2015-000067
24. Reilly JJ, Kelly LA, Montgomery C, Willamson A, Fisher A, McColl JH, et al. Physical activity to prevent obesity in young children: cluster randomised controlled trial. *Bmj.* (2006) 333:1171. doi: 10.1136/bmj.38979.623773.55
25. Pellegrini AD, Smith PK. Physical activity play: the nature and function of a neglected aspect of play. *Child Dev.* (1998) 69:577–98. doi: 10.1111/j.1467-8624.1998.tb06226.x
26. Ginsburg KR, Shifrin DL, Broughton DD, Dreyer BP, Milteer RM, Mulligan DA, et al. The importance of play in promoting healthy child development and maintaining strong parent-child bonds. *Pediatrics.* (2007) 119:182–91. doi: 10.1542/peds.2006-2697
27. Leonard HC, Hill EL. Review: the impact of motor development on typical and atypical social cognition and language: a systematic review. *Child Adolesc Ment Health.* (2014) 19:163–70. doi: 10.1111/camh.12055
28. Hart S (editor). *Inclusion, Play and Empathy: Neuroaffective Development in Children's Groups*. 1st ed. London; Philadelphia, PA: Jessica Kingsley Publisher (2017).
29. Bjorklund DF, Brown RD. Physical play and cognitive development: integrating activity, cognition, and education. *Child Dev.* (1998) 69:604–6. doi: 10.1111/j.1467-8624.1998.tb06229.x
30. Hart S. Inclusion, play and empathy: neuroaffective development in children's groups. 1 ed. In: Hart S, editor. Jessica Kingsley Publisher (2017). Available online at: http://bcu.summon.serialssolutions.com/2.0.0/link/0/eLvHCXMwbV07T8MwED5Bu3SDAiJtqTIx0cqN4zzGpGpgQ0KF1UpiW0JqqwrRIfz63jkPoOpo2Tq_73Tn-z4DcG_OZic6wfdDLbjmqtSLwjA81blhMTNFwXnJjAXMrYK3Z3-difdfhiFy57fVZ5cShJuMexULHkb-o8WxVlhucTQ_Ws2LsmXar6sv0R1jlOr3ukjac0akeAJ
31. Chan A, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleza-Jeric K. SPIRIT 2013 Statement: defining standard protocol items for clinical trials | The EQUATOR Network. *Ann Intern Med.* (2016) 158:200–7. doi: 10.7326/0003-4819-158-3-201302050-00583
32. Henderson K, Glancy M, Little S. Putting the fun into physical activity. *J Phys Educ Recreat Danc.* (1999) 70:43–5. doi: 10.1080/07303084.1999.10605706
33. Spagnola M, Fiese BH. Family routines and rituals. *Encycl Hum Relations.* (2013) 20:284–99. doi: 10.1097/01.IYC.0000290352.32170.5a
34. University of Minnesota. *Developmental Skills for Ages 2 to 3 Years*. Fairview Heal Serv. (2010). p. 3–6. Available online at: https://www.fairview.org/fv/groups/internet/documents/web_content/developmen_201009262104505.pdf
35. University of Minnesota. *Developmental Skills for Ages 4 to 5 Years*. Fairview Heal Serv. (2010). Available online at: https://www.fairview.org/fv/groups/internet/documents/web_content/developmen_2010092621054611.pdf
36. Schmidt-Andersen P, Møller T, Mogensen PR, Schmiegelow K, Larsen HB, Nielsen MKF. Feasibility and validity of the actiheart activity monitor in children who were hospitalized with cancer coadmitted with classmates: a RESPECT study. *Pediatr Phys Ther.* (2020) 32:226–33. doi: 10.1097/PEP.0000000000000712
37. Wilson RW, Jacobsen PB, Fields KK. Pilot study of a home-based aerobic exercise program for sedentary cancer survivors treated with hematopoietic stem cell transplantation. *Bone Marrow Transplant.* (2005) 35:721–7. doi: 10.1038/sj.bmt.1704815
38. Bowen DJ, Kreuter M, Spring B, Linnan L, Weiner D, Bakken S, et al. How we design feasibility studies. *Am J Prev Med.* (2009) 36:452–7. doi: 10.1016/j.amepre.2009.02.002
39. Folio MR, Fewell RR. *Peabody Developmental Motor Scales - Second Edition - Examiner's Manual*. 2nd ed. Austin, TX: PRO-ED (2000). Available online at: https://onlinelibrary.wiley.com/doi/10.1002/9780470373699.speced1552
40. Wang HH, Liao HF, Hsieh CL. Reliability, sensitivity to change, and responsiveness of the Peabody Developmental Motor Scales-Second Edition for children with cerebral palsy. *Phys Ther.* (2006) 86:1351–9. doi: 10.2522/ptj.20050259
41. Stahlhut M, Christensen J, Aadahl M. Applicability and intrarespondent reliability of the pediatric evaluation of disability inventory in a random danish sample. *Pediatr Phys Ther.* (2010) 22:161–9. doi: 10.1097/PEP.0b013e3181dbf965
42. Berg M, Jahnsen R, Frøslie KF, Hussain A, Berg M, Frøslie KF, et al. Reliability of the pediatric evaluation of disability inventory (PEDI). *Phys Occup Ther Pediatr.* (2004) 24:61–77. doi: 10.1300/J006v24n03_05
43. Neumann S, Kwisda S, Krettek C, Gaulke R. Comparison of the grip strength using the martin-vigorimeter and the JAMAR-dynamometer: establishment of normal values. *In Vivo.* (2017) 31:917–24. doi: 10.21873/invivo.11147
44. Robertson A, Deitz J. A Description of gripstrength in preschool children. *Am J Occup Ther.* (1987) 42:647–52. doi: 10.5014/ajot.42.10.647
45. Enright PL. The six-minute walk test. *Respir Care.* (2003) 48:783–5.
46. Bohannon RW, Wang YC, Bubela D, Gershon RC. Normative two-minute walk test distances for boys and girls 3 to 17 years of age. *Phys Occup Ther Pediatr.* (2018) 38:39–45. doi: 10.1080/01942638.2016.1261981
47. Bohannon RW, Bubela D, Magasi S, McCreath H, Wang YC, Reuben D, et al. Comparison of walking performance over the first 2 minutes and the full 6 minutes of the Six-Minute Walk Test. *BMC Res Notes.* (2014) 7:1–6. doi: 10.1186/1756-0500-7-269
48. Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The PedsQL^{TM} in pediatric cancer: reliability and validity of the pediatric quality of life inventory^{TM} generic core scales, multidimensional fatigue scale, and cancer module. *Cancer.* (2002) 94:2090–106. doi: 10.1002/cncr.10428
49. Patel AA, Donegan D, Albert T. The 36-Ltem short form. *J Am Acad Orthop Surg.* (2007) 15:126–34. doi: 10.5435/00124635-200702000-00007
50. Lincoln YS, Guba EG. But is it rigorous? Trustworthiness and authenticity in naturalistic evaluation. *New Dir Progr Eval.* (1986) 1986:73–84. doi: 10.1002/ev.1427
51. Smith B, Sparkes AC. Interview - qualitative interviewing in the sport and exercise sciences. In: Smith B, Sparkes AC, editors. *Routledge Handbook of Qualitative Research in Sport and Exercise*. 1st ed. London; New York, NY: Routledge (2017). p. 103–23.
52. Darcy L, Björk M, Enskär K, Knutsson S. The process of striving for an ordinary, everyday life, in young children living with cancer, at six months and one year post diagnosis. *Eur J Oncol Nurs.* (2014) 18:605–12. doi: 10.1016/j.ejon.2014.06.006
53. Ciesielska M, Broström KW, Ölhander M. Observation Methods. In: Ciesielska M, Jemielniak D, editors. *Qualitative Methodologies in Organization Studies*. Cham: Palgrave Macmillan (2018). p. 33–52.

54. Winther H. Pratitioner research. In: Thing LF, Ottesen L, editors. *Methods in Sport and Physioterapy Research*. 2 ed. Copenhagen: Munksgaard. (2015). p. 172–89.
55. Winther H. Let's move: embodiment, leadership, and dance in education. In: Tin MB, Telseth F, Tangen JO, Giulianotti R, editors. *The Nordic Model and Physical Culture. Routledge Reasearch in Sport, Culture and Society*. 1 ed. Oxon; New York, NY: Routhledge (2020). p. 51–67.
56. Sparkes AC. Researching the senses in sport and exercise. In: Smith B, Sparkes A, editors. *Routledge Handbook of Qualitative Research in Sport and Exercise*. New York, NY: Routledge (2017). p. 343–54.
57. Thorpe H, Olive R. Conducting observations in sport and exercise settings. In: Smith B, Sparkes AC, editors. *Routledge Handbook of Qualitative Research in Sport and Exercise*. 1st ed. London; New York, NY: Routledge (2017). p. 124–38.
58. Morse JM. Data were saturated. *Qual Health Res.* (2015) 25:587–8. doi: 10.1177/1049732315576699
59. Vasileiou K, Barnett J, Thorpe S, Young T. Characterising and justifying sample size sufficiency in interview-based studies: systematic analysis of qualitative health research over a 15-year period. *BMC Med Res Methodol.* (2018) 18:1–18. doi: 10.1186/s12874-018-0594-7
60. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today.* (2004) 24:105–12. doi: 10.1016/j.nedt.2003.10.001
61. Patton M. Purposeful sampling. In: *Qualitative Evaluation and Research Methods*. Beverly Hills, CA: Sage (1990). p. 169–86.
62. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol.* (2006) 3:77–101. doi: 10.1191/1478088706qp063oa
63. Malterud K. Systematic text condensation: a strategy for qualitative analysis. *Scand J Public Health.* (2012) 40:795–805. doi: 10.1177/1403494812465030
64. Lima RA, Bugge A, Ersbøll AK, Stodden DF, Andersen LB. The longitudinal relationship between motor competence and measures of fatness and fitness from childhood into adolescence. *J Pediatr.* (2019) 95:482–8. doi: 10.1016/j.jped.2018.02.010
65. Utesch T, Bardid F, Büsch D, Strauss B. The relationship between motor competence and physical fitness from early childhood to early adulthood: a meta-analysis. *Sport Med.* (2019) 49:541–51. doi: 10.1007/s40279-019-01068-y
66. Hartman A, Van Bos C Den, Stijnen T, Pieters R. Decrease in motor performance in children with cancer is independent of the cumulative dose of vincristine. *Cancer.* (2006) 106:1395–401. doi: 10.1002/cncr.21706
67. Morales JS, Santana-Sosa E, Santos-Lozano A, Baño-Rodrigo A, Valenzuela PL, Rincón-Castanedo C, et al. Inhospital exercise benefits in childhood cancer: a prospective cohort study. *Scand J Med Sci Sport.* (2020) 30:126–34. doi: 10.1111/sms.13545
68. FDA. *What is a Serious Adverse Event?*. FDA (2016). Available online at: https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event~

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frontiers | Frontiers in Pediatrics

ORIGINAL RESEARCH
published: 11 May 2022
doi: 10.3389/fped.2022.891650

The Efficacy of Targeted Exercise on Gross Motor and Neuromuscular Performance in Survivors of Childhood Leukemia: A Pilot Study

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Objectives: This quasi-experimental study examined the efficacy of targeted exercise training on gross motor performance and neuromuscular impairments in survivors of childhood acute lymphoblastic leukemia (ALL CCS).

Materials and Methods: Ten ALL CCS (median age: 10 years; range: 6–14 years) performed a 6-week training program three times per week (five in-person sessions), including a warm-up, total body stretching, progressive jump rope training, and a cool down. Gross motor performance (test of gross motor proficiency) and lower extremity rate of muscle activation (electromyography), joint torques (motion capture and force plate), and jump height (motion capture) were measured during a countermovement jump at baseline and post-training.

Results: Post-training, ALL CCS demonstrated improvements in body coordination, strength and agilty, bilateral coordination, running speed and agility, and strength gross motor performance (mean change: 1.6–8.1; $p < 0.05$), the rate of muscle activation of the tibialis anterior and vastus lateralis muscles (mean change: 0.58–0.75; $p < 0.05$), hip and ankle joint torques (mean change: 0.07; $p < 0.05$), and jump height (mean change: 0.05; $p < 0.05$).

Conclusion: This study demonstrated that targeted exercise training can improve gross motor performance and neuromuscular impairments in ALL CCS post-medical treatment.

Keywords: pediatrics, cancer, children, oncology, physical therapy, rehabilitation, survivorship, intervention

OPEN ACCESS

Edited by:
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The University of Sydney, Australia

Reviewed by:
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National Child Cancer Network, New Zealand
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Specialty section:
This article was submitted to Pediatric Oncology, a section of the journal Frontiers in Pediatrics

Received: *08 March 2022*
Accepted: *21 April 2022*
Published: *11 May 2022*

Citation:
Marchese V, Rock K, York T, Ruble K and Gray VL (2022) The Efficacy of Targeted Exercise on Gross Motor and Neuromuscular Performance in Survivors of Childhood Leukemia: A Pilot Study. Front. Pediatr. 10:891650. doi: 10.3389/fped.2022.891650

INTRODUCTION

With advances in medical treatment, 5-year survival rates for children with acute lymphoblastic leukemia (ALL) exceed 90% (1). However, short- and long-term effects of chemotherapy agents such as vincristine and methotrexate can cause neuromuscular impairments that affect muscle performance (2, 3). The medical treatment of ALL can lead to neuromuscular impairments including decreased neuromuscular activation, delayed muscle contraction initiation timing, reduced amplitude of the muscle activity, and decreased muscle force-generating capacity (4, 5). These treatments can also result in activity limitiations in gross motor performance including

decreased balance, impaired coordination, and reduced movement speed and agility (3, 6–9). Body structure and function impairments and activity limitiations in survivors of childhood ALL (ALL CCS) extend well beyond the completion of medical treatment (5, 10, 11).

ALL CCS experience gross motor performance delays during a critical period of motor development. While ALL CCS' peers are developing muscle strength, balance control, and gross motor skills, many ALL CCS decline in these skills during medical treatment (7, 8). As a result, ALL CCS have difficulty keeping up with their peers in achieving physical activity recommendations and maintaining an active lifestyle (12, 13). Ultimately, ALL CCS are at an increased risk for developing obesity, metabolic syndrome, and early frailty at an earlier than expected age (14, 15). Thus, training programs that can reverse neuromuscular impairments and impaired gross motor performance are important for ALL CCS during childhood and adolescence, a sensitive period of motor development.

Over the past 20 years, there have been a limited number of exercise intervention programs designed for children with cancer and, more specifically, for ALL CCS (16). Most published programs have focused on general strengthening and aerobic activities because the programs have been designed for children with various types of cancer (16). To date, programs for survivors of childhood cancers have largely focused on adventure-based training, prospective surveillance models, health education programs, group physical activity programs, and computer game-based exercise programs (8, 17–19). These engaging programs have demonstrated feasibility and improvements in gross motor performance and physical activity with high satisfaction levels (8, 17–19). The encouraging results from these previous studies have offered the support for future studies to begin developing targeted training programs for the unique needs of specific types of childhood cancer survivors. Research supports training programs that incorporate functional tasks that target the neuromuscular system, such as jumping rope, improve muscle strength and gross motor performance including balance and speed and agility in children without health conditions (20, 21).

The purpose of this study was to examine the efficacy of a targeted neuromuscular training program that utilized jumping rope. We hypothesized that after the training program, ALL CCS would demonstrate improved gross motor performance, improved neuromuscular performance during a countermovement jump, measured by the rate of muscle activation and joint torques of the lower extremity, and jump height.

MATERIALS AND METHODS

This was a pilot quasi-experimental intervention study design.

Participants

Study participants were recruited through flyers and in-person communication from the University of Maryland Medical Center Pediatric Oncology Clinic and the Johns Hopkins Medical, The Sidney Kimmel Comprehensive Cancer Center, Long-Term Survivors Program for participation in this study at the Department of Physical Therapy and Rehabilitation Science in the School of Medicine at the University of Maryland, Baltimore. Participants were included if the participants: (1) were children 6–17 years old; (2) completed medical treatment for ALL within the past 5 years (1–60 months); and (3) had the ability to communicate in English. Participants were excluded if the participants: (1) had a diagnosis of a neurological disorder such as cerebral palsy or Down syndrome; or (2) were currently receiving physical therapy services. This study was approved by the University of Maryland, Baltimore, Institutional Review Board. All participants provided informed assent and caregivers provided informed consent.

The Bruininks-Oseretsky Test of Motor Proficiency, 2nd edition (BOT-2) subtests were used to assess bilateral coordination, balance, running speed and agility, and strength at baseline and post-training (22). There were two standard composite tests calculated from these subtests, the body coordination composite test, which included the bilateral coordination and balance subtests, and the strength and agility composite test, which included the strength and running speed and agility subtests. Items were administered and scored according to standardized procedures (22). The BOT-2 has established interrater reliability and test-retest reliability for each subtest and each age group (22). The established mean for each subtest scale score is 15 with a standard deviation (SD) of 5, and the mean for each composite standard score is 50 with a standard deviation of 10 (22). Below average (BA) performance and well-below average (WBA) performance on the BOT-2 is defined as 1 SD and 2 SD below the mean, respectively, for subtest scale scores and composite standard scores (22).

The participants performed five trials of a countermovement jump before training (baseline) and after completing training (post-training). At the start of each trial, the participants stood on two adjacent force platforms (AMTI, Inc., Newton, MA, USA) in an upright position. The participant's arms were positioned at the side, and both hands were slightly anterior to the hips. The outline of the participant's feet was traced on a paper taped to the force platforms to ensure a similar start position for the trials at baseline and post-training. After a demonstration trial, participants were instructed to "jump as high as you can." The jump was performed with a downward movement into a squat position followed by a push-off from force platforms into a jump.

Electromyography (EMG) activity was recorded using dual electrodes with a 2-cm interelectrode distance using surface EMG with a TeleMyo^{TM} DTS 24-channel wireless EMG system (Noraxon, USA Inc. Scottsdale, AZ, USA). Sensors placed bilaterally over the muscle belly of the lateral gastrocnemius, tibialis anterior, and vastus lateralis, muscles were according to SENIAM recommendations (23). EMG signals were collected with MyoResearch XP software (Noraxon, USA Inc., Scottsdale, AZ, USA) at a sampling rate of 1,500 Hz and later exported to MATLAB for analysis. After subtracting the mean DC bias, the EMG signals were rectified and high pass filtered at 20 Hz. The onset of the muscle activity was identified when the EMG amplitude was greater than two standard deviations above the baseline activity, which was calculated 500 milliseconds preceding movement onset. The rate of muscle activation was calculated as the EMG amplitude, from the onset to peak, and

then was divided by the time duration from onset to peak muscle activity. Values were normalized by dividing by the peak EMG amplitude of each muscle during the task. The values for the right and left limbs were averaged.

The lower extremity joint torques and jump height were measured from reflective markers placed on the bilateral acromion, lateral epicondyles, ulnar styloid processes, greater trochanters, lateral condyles, lateral malleoli, 2nd metatarsal heads, interaural axes, and on the top of the head. Kinematic data were recorded with a ten-camera motion capture system (VICON, Los Angeles, CA, USA) at 150 Hz. Ground reaction forces were measured using dual force plates at 600 Hz and resampled to 120 Hz. The joint torque for the hips, knees, and ankles was estimated by inverse dynamics as described by Zatsiorsky (24). Peak joint torque of the hips, knees, and ankles were identified as the maximum value during the jump acceleration phase from the lowest point of the body center of mass (COM) to toe-off from the force plates. Joint torques were normalized to the height and weight of the participant. Ground reaction forces and kinematic data were filtered using a 10 Hz low-pass 4^{th} order Butterworth zero-lag filter (MATLAB filtfilt) (MathWorks, Natick, MA, USA). Data were bandpass filtered between 16–500 Hz. The jump height, measured in the sagittal plane, was calculated from the body COM and estimated using the method described by Winter (25). Jump height was calculated as the difference between peak COM height during the jump and COM height at the start of the jump and then normalized by the height of the participant.

Intervention

Over a 6-week interval, each participant performed 18 training sessions, including five one-on-one sessions with a physical therapist twice the first week and once the second, third, and fifth weeks (**Table 1**). The first intervention occurred during the same day as the baseline assessment and the final intervention session occurred within a week of the post-training assessment. The participants were also instructed to perform the training program at home a total of three times per week (including the in-person visits) for the duration of the study (**Table 1**). The study participants were provided with an exercise diary to track the home exercise program that was reviewed at each in-person session. Each in-person session included: (1) discussion of home exercise program completion and progress; (2) discussion of session goals and short-term goals; (3) warm-up; (4) total body stretching; (5) exercise program; and (6) cool-down. The physical therapist provided verbal cues and feedback for proper body position, but only provided hands-on contact to maintain safety, not to physically assist with performing the movement. During each in-person session, the jumping rope program total duration, set duration, rest time, revolution count, and the complexity of jumping task was modified based on the participant's individualized progress and logged.

The warm-up included walking for 5 min, fast enough to achieve an 11 on the 6–20 rate of perceived exertion scale (RPE). Stretching was then performed for trunk flexors, trunk extensors, trunk lateral flexors, hip flexors, hip extensors, hip internal and external rotators, knee flexors and extensors, ankle plantarflexors, and ankle dorsiflexors. Each stretch was performed one time and held for 15 s. The participants then performed the jumping rope intervention using a beaded jump rope (∼$10 USD; BuyJumpRopes.net. Wenatchee, WA, USA). The participants were instructed on the proper use and mechanics of jumping the rope. The participants started with a 5-s bout of jumping with a 10-s rest break for 10 sets. The program progression goal was to achieve 15 s of jumping with a 30-s rest break for 15–20 sets. The session goal was to increase the number of times the rope revolved during the 15-s jumping period. The jump roping techniques used included: pre-traditional jumping (jumping over a stationary rope), traditional jumping, scissor jumping, side stradding, straddle cross, heel-toe, criss-cross, toe-touch, 360, can can, and long-rope jumping.

Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Inc., Chicago, IL, USA). Due to the sample size and non-normality of data, two-sided Wilcoxon signed-rank tests were used to compare the differences between the baseline and post-training for the BOT-2 subscale scaled scores and composite standard scores, rate of activation of the muscles (lateral gastrocnemius, tibialis anterior, vastus lateralis), the joint torques (hip, knee, and ankle), and the jump height. For all statistical analyses, the level of significance was set at an alpha value of 0.05. Effect size (r) was calculated using the formula: $r = \frac{Z}{\sqrt{N}}$ (26). Effect sizes were considered "small" if $r \geq 0.10$, "medium" if $r \geq 0.30$, and "large" if $r \geq 0.60$ (27).

RESULTS

The 10 participants (5 males; 5 females) had a median age of 10 years (range: 6–14 years), and a median time from completion of treatment 3.79 years (range 1.75–4.42 years). Of the 10 participants successfully referred to and enrolled in this study, 100% completed every scheduled session, including the baseline and post-training assessments and the five training sessions. **Table 2** summarizes the elements of the jumping rope intervention progression that were increased or decreased during each of the in-person training sessions. Due to the COVID-19 pandemic, one child (participant 7) completed two of the five in-person training sessions using a live synchronous telehealth video conferencing format vs. coming to the research training facility.

TABLE 1 | Timeline of the intervention sessions.

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
In-person PT	√ √	√	√	− − -	√	− − -
Home-program	√	√ √	√ √	√ √ √	√ √	√ √ √

TABLE 2 | In-person jumping rope training progression.

Participant	Session 1	Session 2	Session 3	Session 4	Session 5
1	–	↑TD	↑SD, ↑C	↑SD	↑C
2	–	↑SD, ↑C	↑SD, ↑C	↑SD, ↑C	↑SD
3	–	↑SD, ↑C, ↑RC	↑SD, ↑C, ↑RC	↑SD, ↓RT	↑SD, ↑RC
4	–	↑SD, ↓C, ↑RC	↑SD, ↑C, ↑RC	↑SD, ↑C, ↑RC	↑RC
5	–	↑RC	↑RC	↓RC	↑RC
6	–	↑SD, ↑C, ↑RC	↑RC	↑SD, ↑C, ↑RC	↑RC
7	–	↑SD, ↑C, ↑RC	↑SD, ↑C, ↓RT, ↑RC	↑RC	↑SD, ↑C, ↑RC
8	–	↑TD, ↑SD	↑RC	↑C, ↑RC	↑SD, ↑C, ↑RC
9	–	↑TD, ↑SD, ↑RC	↑SD, ↑RC	↑SD, ↑C, ↑RC	↑RC
10	–	↓C, ↑RC	↑RC	↑SD, ↑RC	↑C

TD, total duration; SD, set duration; C, complexity; RT, rest time; RC, revolution count; ↑, increase; ↓, decrease.

In addition, part of this participant's post-training assessment was completed virtually, but the laboratory-based measures of the countermovement jump and BOT-2 testing items requiring the balance beam and distance running were not performed. Therefore, complete data sets from nine participants were analyzed for the rate of muscle activation, jump height, joint torques, BOT-2 balance and running speed and agility subtests scale scores, and BOT-2 body coordination and speed and agility composite standard scores.

At the baseline assessment, seven ALL CCS presented with below average or well-below average BOT-2 composite scores of the body coordination and five of ALL CCS presented with impaired strength and agility standard composite scores (**Table 3**). ALL CCS demonstrated below average or well-below average BOT-2 standard composite scores of body coordination ($n = 3$), balance ($n = 6$), running speed and agility ($n = 3$), and strength ($n = 6$) at the baseline assessment (**Table 3**). The participants' individual BOT-2 scaled and standard composite scores at baseline and post-training assessments are reported in **Table 3**. After training, ALL CSS improved body coordination (mean change = 8.09; $p < 0.001$; $r = 0.60$; "large"), strength and agility (mean change = 3.06; $p = 0.039$; $r = 0.53$; "medium"), bilateral coordination (mean change = 3.60; $p = 0.001$; $r = 0.63$, "large"), running speed and agility (mean change = 1.60; $p = 0.015$; $r = 0.52$; "medium"), and strength (mean change = 3.06; $p = 0.037$; $r = 0.51$; "medium") (**Table 3**). Overall, ALL CCS improved BOT-2 balance scaled scores; however, statistical significance was not achieved (mean change = 3.06; $p = 0.146$; $r = 0.35$; "medium").

During the countermovement jump, there was a significant increase in the rate of activation of the tibialis anterior (mean change = 0.75; $p = 0.008$; $r = 0.63$; "large") and vastus lateralis muscles (mean change = 0.58; $p = 0.038$; $r = 0.49$; "medium") post-training compared to baseline (**Figure 1**). The rate of activation of the lateral gastrocnemius was not statistically significantly different after training (mean change = 0.47; $p = 0.140$; $r = 0.35$; "medium"). The joint torque of the hip (mean change = 0.07; $p = 0.038$; $r = 0.49$; "medium") and ankle (mean change = 0.07; $p = 0.008$; $r = 0.49$; "medium") significantly increased after training, along with the jump height (mean change = 0.05; $p = 0.008$; $r = 0.89$; "large") (**Figure 2**). The knee joint torque did not significantly increase after training (mean change = 0.07; $p = 0.069$; $r = 0.45$; "medium").

DISCUSSION

This targeted neuromuscular training program was feasible and improved gross motor and neuromuscular performance in ALL CCS post-training. In this study, these ALL CCS presented with baseline below average or well-below average BOT-2 standard composite scores of the body coordination (70%) and strength and agility (50%). Post-training the proportion of participants who performed below or well-below average decreased to 30% for body coordination and 40% for strength and agility, thus narrowing the gap in gross motor performance between these ALL CCS and a large normative sample of children without health conditions (22). Tanner & Hooke (8) reported similar findings with gross motor deficits in a cohort of ALL CCS and reported 47% and 73% of ALL CCS presented with body coordination and strength and agility composite scores within a healthy normative range, respectively (8). After this 6-week training, the participants in our study demonstrated significant improvements in gross motor performance, rate of tibialis anterior and vastus lateralis muscle activation, hip and ankle joint torque, and jump height. Previous randomized controlled trials have explored the effects of home exercise programs, including a standardized (28) and a progressive (29) flexibility, aerobic, and resistance training in ALL CCS post-treatment. These studies demonstrated improvements in gross motor performance and physical impairments including increased lower-extremity strength (28), decreased time to perform the Timed Up and Go (TUG) test (28, 29), decreased time to perform the Timed Up and Down Stairs (TUDS) test (28, 29), and increased distance on the 9-min run-walk test (28). However, Takken et al. (29, 30) found that after a community-based training program, no significant improvements were detected in hip, knee, ankle, or handgrip strength or performance on the TUG and TUDS. All of these interventions ranged from 12 weeks (28, 30) to 16 weeks (29). Our 6-week training, including five one-on-one sessions, shows that a shorter bout of targeted neuromuscular training using jumping rope can yield significant improvements in gross motor

TABLE 3 | Bruininks-Oserestrky test of motor proficiency, 2nd edition scores.

	Scaled score								Standard score			
	Bilateral coordination		Balance		Running speed and agility		Strength		Body coordination		Strength and agility	
	Baseline	Post-training	Baseline	Post-training	Baseline	Post-training	Baseline	Post-training	Baseline	Post-training	Baseline	Post-training
1	**7**	**10**	**7**	11	**9**	10	**6**	**8**	**30**	**37**	**34**	**37**
2	13	18	13	15	11	13	12	14	45	52	43	46
3	11	16	11	11	13	21	**5**	12	**38**	45	**35**	52
4	13	19	19	13	15	16	15	18	50	50	48	55
5	**7**	13	**4**	**7**	**6**	**7**	**4**	**8**	**30**	**39**	**31**	36
6	11	20	12	13	14	19	13	12	41	53	47	50
7	16	20	**8**	n/a	16	n/a	14	17	**40**	n/a	52	n/a
8	13	20	**7**	**9**	11	13	**7**	**7**	**38**	47	**36**	**39**
9	15	19	**6**	12	11	**10**	**9**	**7**	**37**	51	41	**38**
10	**2**	**9**	**8**	13	**8**	**8**	**3**	**5**	**29**	**39**	**28**	**30**
Mean	10.80	16.40*	**9.50**	11.56	11.40	13.00*	**8.80**	10.80*	**37.80**	45.89*	**39.50**	42.56*
SD	4.07	4.03	4.13	2.27	3.01	4.57	4.19	4.26	6.45	5.84	7.53	8.00
BA	20%	20%	50%	20%	30%	20%	30%	50%	40%	30%	40%	30%
WBA	10%	0%	10%	0%	0%	0%	30%	0%	30%	0%	10%	10%

Bold *indicates score below average (BA);* ***bold and underlined*** *indicates score well-below average (WBA). n/a indicates not applicable.*
**Indicates $P < 0.05$ for Wilcoxon signed-rank test between baseline and post-training.*

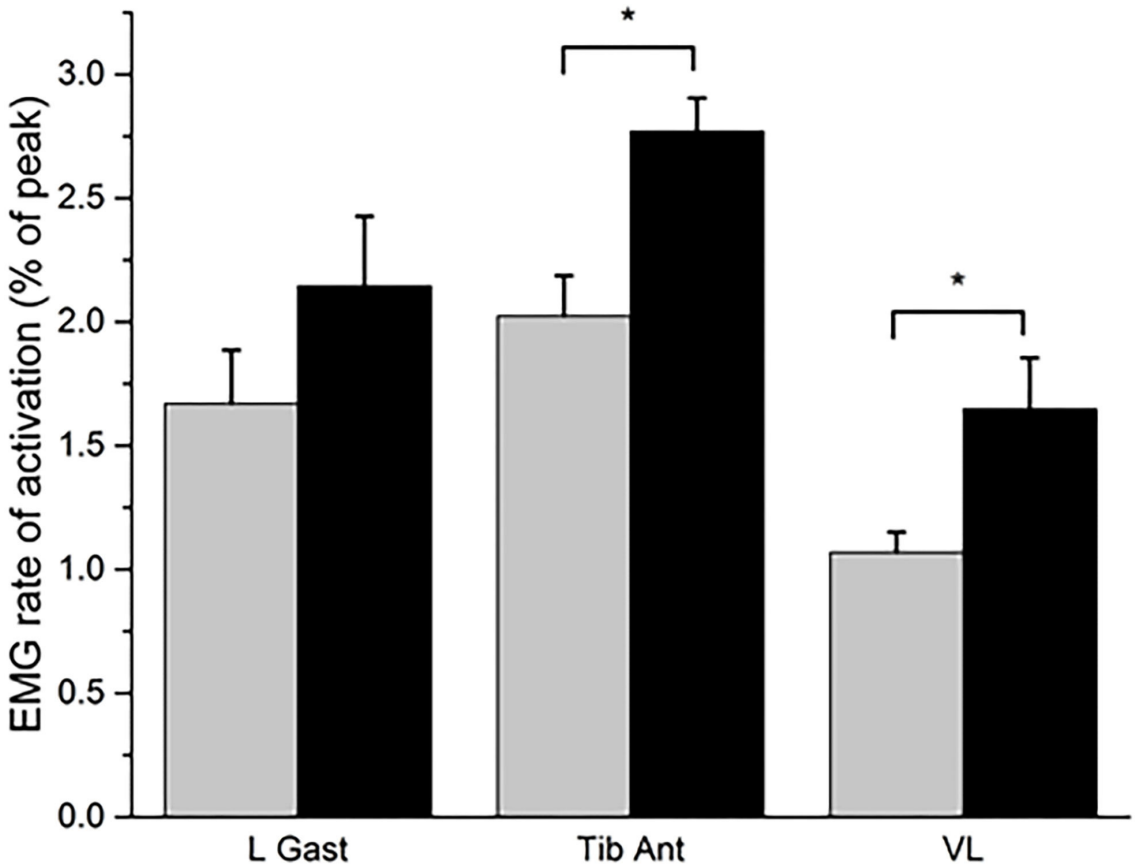

FIGURE 1 | The rate of activation of the lateral gastrocnemius (L Gast), tibialis Anterior (Tib Ant), and vastus lateralis (VL) muscles at baseline (gray bar) and post-training (black bar). Expressed as the mean and standard error. *$P < 0.05$ for the Wilcoxon signed-rank test.

performance, neuromuscular activation, knee and ankle torque during a functional task, and jump height post-training in ALL CCS after completion of medical treatment.

We used specific targeted measurements to assess neuromuscular activation, lower extremity joint torque, and jump height during a countermovement jump in ALL CCS post-treatment including EMG and a motion capture system. These methods provide valuable information regarding the underlying neuromuscular mechanisms and whole-body movement that contribute to countermovement jump performance. Similarly, Wright, Twose, and Gorter also utilized EMG and motion capture to assess gait characteristics in ALL CCS (4) also utilized EMG and motion capture to assess gait characteristics in ALL CCS. In addition to impaired temporal-spatial, kinematic, and kinetic characteristics of gait in ALL CCS, the authors found gastrocnemius and tibialis anterior muscles excessive co-activation and atypical timing of EMG activation during the gait cycle (4). The use of EMG and motion capture in our study allowed for increased sensitivity to changes experienced by participants in response to the training. Although laboratory-based measurements of lower extremity joint torques during a jump and jump height in this study are challenging to use clinically, previous studies have demonstrated concurrent validity and reliability of 3D motion analysis with clinically-available measurements of height using an iPhone app in adults (31) and software paired with a traditional commercial camera in children (32). Therefore, measurements of jump height may be performed in clinical settings with minimal equipment.

Despite many benefits of this study, including the sensitivity of measurements and clinically-relevant outcome measures, this quasi-experimental intervention study lacked a control group; therefore, it is challenging to isolate the effects of spontaneous gross motor and neuromuscular improvements. Overall, ALL CCS improved gross motor and neuromuscular performance with medium to large effect sizes, however the small sample size may have led to type II error related to the efficacy of the intervention on balance, rate of activation of the lateral gastrocnemius, and knee joint torque. Due to the small sample size of ALL CCS from a single metropolitan area, caution should be practiced when generalizing these results. A randomized control trial should be explored to elucidate the effects of this training program further. Future studies should be performed to further explore if longer duration of training can provide additional benefit to improvements in gross motor and neuromuscular performance.

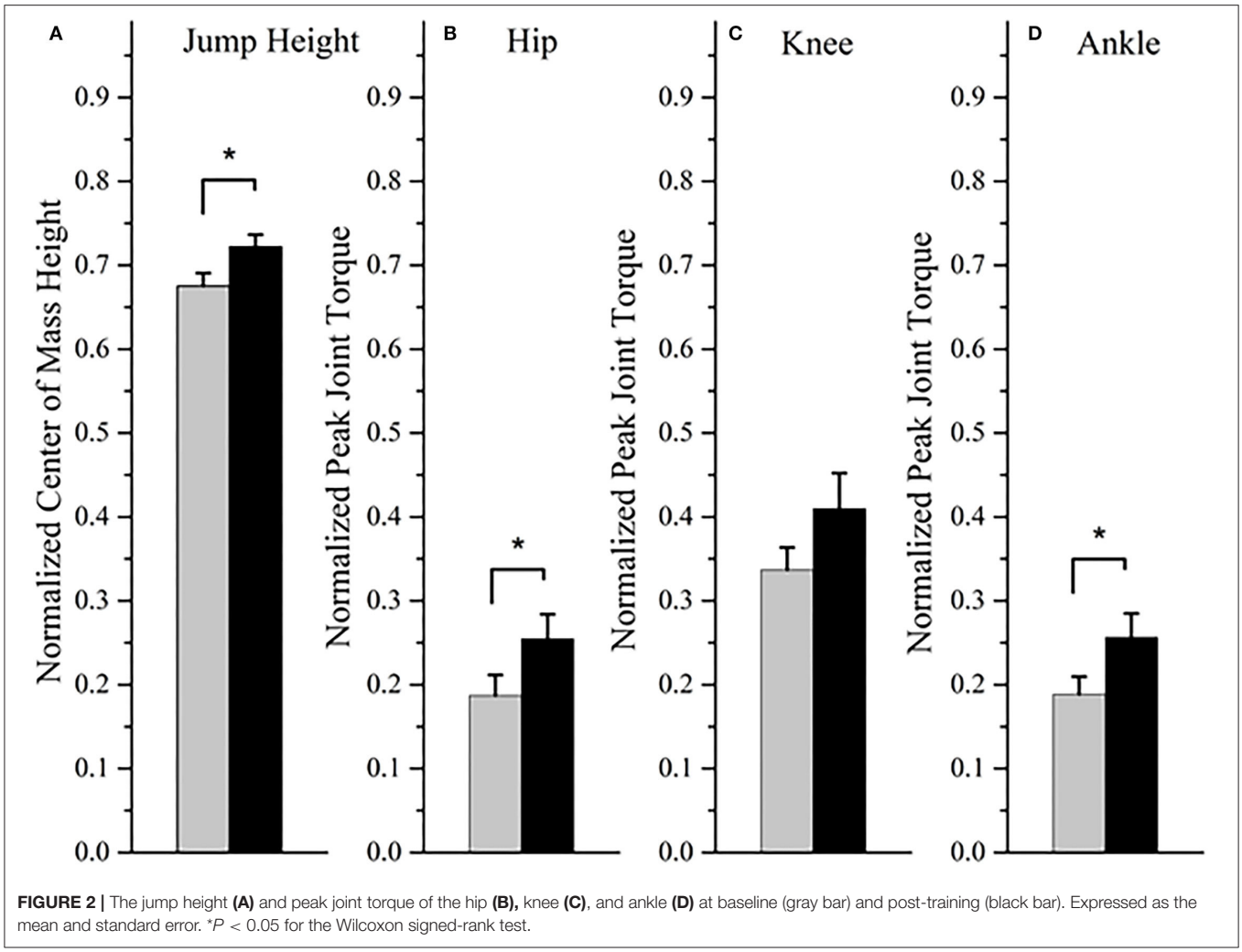

FIGURE 2 | The jump height **(A)** and peak joint torque of the hip **(B),** knee **(C)**, and ankle **(D)** at baseline (gray bar) and post-training (black bar). Expressed as the mean and standard error. *$P < 0.05$ for the Wilcoxon signed-rank test.

In conclusion, this feasible targeted neuromuscular training using jumping rope can improve gross motor and neuromuscular performance in ALL CCS post-medical treatment. The only equipment needed to perform this training was a beaded jump rope, which is a low-cost and long-lasting standard pediatric item in clinics, homes, and schools. Therefore, this training program has the potential to be easily implemented into current practices. The neuromuscular performance and motion capture methods used in this study are commonly used in research settings to identify movement system impairments. Still, this type of equipment is expensive and not readily available in most pediatric clinics, however, provides additional support of the efficiacy of this training program. However, in addition to gross motor performance testing, a vertical jump height during a counter movement jump can be measured and used as an indicator of rehabilitation progress in clinical settings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Maryland, Baltimore Institutional Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

VM, TY, KRu, and VG contributed to the conception and design of the research. VM and VG performed the data acquisition and processing. VM, KRo, and VG analyzed and interpreted the data and drafted the manuscript. All authors contributed to the revision, critical appraisal, and approval of the manuscript submitted for publication.

FUNDING

This study was supported in full by the American Physical Therapy Association Academy of Pediatric Physical Therapy Research Grant awarded to VM.

REFERENCES

1. Jemal A, Ward EM, Johnson CJ, Cronin KA, Ma J, Ryerson AB, et al. Annual report to the nation on the status of cancer, 1975–2014, featuring survival. *JNCI J Natl Cancer Inst.* (2017) 109:djx030. doi: 10.1093/jnci/djx030
2. Harila-Saari AH, Huuskonen UE, Tolonen U, Vainionpää LK, Lanning BM. Motor nervous pathway function is impaired after treatment of childhood acute lymphoblastic leukemia: a study with motor evoked potentials. *Med Pediatr Oncol.* (2001) 36:345–51. doi: 10.1002/mpo.1084
3. Varedi M, Lu L, Howell CR, Partin RE, Hudson MM, Pui CH, et al. Peripheral neuropathy, sensory processing, and balance in survivors of acute lymphoblastic leukemia. *J Clin Oncol.* (2018) 36:2315–22. doi: 10.1200/JCO.2017.76.7871
4. Wright MJ, Twose DM, Gorter JW. Gait characteristics of children and youth with chemotherapy induced peripheral neuropathy following treatment for acute lymphoblastic leukemia. *Gait Posture.* (2017) 58:139–45. doi: 10.1016/j.gaitpost.2017.05.004
5. Marchese V, Rock K, York T, Creath R, Gray V. Neuromuscular mechanisms that contribute to gross motor performance in survivors of childhood acute lymphoblastic leukemia. *J Pediatr Rehabil Med.* (2021) 14:415–23. doi: 10.3233/PRM-200784
6. Götte M, Kesting S V, Winter CC, Rosenbaum D, Boos J. Motor performance in children and adolescents with cancer at the end of acute treatment phase. *Eur J Pediatr.* (2015) 174:791–9. doi: 10.1007/s00431-014-2460-x
7. Gilchrist LS, Tanner LR. Short-term recovery of balance control: association with chemotherapy-induced peripheral neuropathy in pediatric oncology. *Pediatr Phys Ther.* (2018) 30:119–24. doi: 10.1097/PEP.0000000000000484
8. Tanner LR, Hooke MC. Improving body function and minimizing activity limitations in pediatric leukemia survivors: the lasting impact of the stoplight program. *Pediatr Blood Cancer.* (2019) 66:e27596. doi: 10.1002/pbc.27596
9. Leone M, Viret P, Bui HT, Laverdière C, Kalinova É, Comtois A-S. Assessment of gross motor skills and phenotype profile in children 9-11 years of age in survivors of acute lymphoblastic leukemia. *Pediatr Blood Cancer.* (2014) 61:46–52. doi: 10.1002/pbc.24731
10. Ness KK, Hudson MM, Pui CH, Green DM, Krull KR, Huang TT, et al. Neuromuscular impairments in adult survivors of childhood acute lymphoblastic leukemia: associations with physical performance and chemotherapy doses. *Cancer.* (2012) 118:828–38. doi: 10.1002/cncr.26337
11. Wright MJ, Galea V, Barr RD. Proficiency of balance in children and youth who have had acute lymphoblastic leukemia. *Phys Ther.* (2005) 85:782–90. doi: 10.1093/ptj/85.8.782
12. Wright MJ, Galea V, Barr RD. Self-perceptions of physical activity in survivors of acute lymphoblastic leukemia in childhood. *Pediatr Exerc Sci.* (2003) 15:191–201. doi: 10.1123/pes.15.2.191
13. Rueegg CS. von der Weid NX, Rebholz CE, Michel G, Zwahlen M, Grotzer M, et al. Daily physical activities and sports in adult survivors of childhood cancer and healthy controls: a population-based questionnaire survey. *PLoS ONE.* (2012) 7:e34930. doi: 10.1371/journal.pone.0034930
14. Gurney JG, Ness KK, Sibley SD, O'Leary M, Dengel DR, Lee JM, et al. Metabolic syndrome and growth hormone deficiency in adult survivors of childhood acute lymphoblastic leukemia. *Cancer.* (2006) 107:1303–12. doi: 10.1002/cncr.22120
15. Wilson CL, Chemaitilly W, Jones KE, Kaste SC, Srivastava DK, Ojha RP, et al. Modifiable factors associated with aging phenotypes among adult survivors of childhood acute lymphoblastic leukemia. *J Clin Oncol.* (2016) 34:2509–15. doi: 10.1200/JCO.2015.64.9525
16. Söntgerath R, Däggelmann J, Kesting S V., Rueegg CS, Wittke T-C, Reich S, et al. Physical and functional performance assessment in pediatric oncology: a systematic review. *Pediatr Res.* (2021). doi: 10.1038/s41390-021-01523-5. [Epub ahead of print].
17. Ruble K, Scarvalone S, Gallicchio L, Davis C, Wells D. Group physical activity intervention for childhood cancer survivors: a pilot study. *J Phys Act Health.* (2016) 13:352–9. doi: 10.1123/jpah.2015-0050
18. Li HCW, Chung OKJ, Ho KY, Chiu SY, Lopez V. Effectiveness of an integrated adventure-based training and health education program in promoting regular physical activity among childhood cancer survivors. *Psychooncology.* (2013) 22:2601–10. doi: 10.1002/pon.3326
19. Rabin C, Dunsiger S, Ness KK, Marcus BH. Internet-based physical activity intervention targeting young adult cancer survivors. *J Adolesc Young Adult Oncol.* (2011) 1:188–94. doi: 10.1089/jayao.2011.0040
20. Eler N, Acar H. The effects of the rope jump training program in physical education lessons on strength, speed and VO 2 max in children. *Univers J Educ Res.* (2018) 6:340–5. doi: 10.13189/ujer.2018.060217
21. Partavi S. Effects of 7 weeks of rope-jump training on cardiovascular endurance, speed, and agility in middle school student boys. *Sport Sci.* (2013) 6:40–3.
22. Bruininks R, Bruininks B. *Bruininks-Oseretsky Test of Motor Proficiency. 2nd ed Pearson Assessment.* Minneapolis, MN: NCS Pearson (2005).
23. Hermens HJ, Freriks B, Merletti R, Stegeman D, Blok J, Rau G, et al. European recommendations for surface electromyography. *Roessingh Res Dev.* (1999) 8:13–54.
24. Zatsiorsky VM, Gregory RW, Latash ML. Force and torque production in static multifinger prehension: biomechanics and control. *II Control Biol Cybern.* (2002) 87:40–9. doi: 10.1007/s00422-002-0320-7
25. Winter DA. Foot trajectory in human gait: a precise and multifactorial motor control task. *Phys Ther.* (1992) 72:45–53. doi: 10.1093/ptj/72.1.45
26. Pallant J. *SPSS Survival Manual: A Step by Step Guide to Data Analysis Using IBM SPSS*. 7th ed. Abingdon-on-Thames: Routledge. (2020). doi: 10.4324/9781003117407
27. Pautz N, Olivier B, Steyn F. The use of nonparametric effect sizes in single study musculoskeletal physiotherapy research: a practical primer. *Phys Ther Sport.* (2018) 33:117–24. doi: 10.1016/j.ptsp.2018.07.009
28. Tanir MK, Kuguoglu S. Impact of exercise on lower activity levels in children with acute lymphoblastic leukemia: a randomized controlled trial from Turkey. *Rehabil Nurs.* (2013) 38:48–59. doi: 10.1002/rnj.58
29. Manchola-González JD, Bagur-Calafat C, Girabent-Farrés M, Serra-Grima JR, Pérez RÁ, Garnacho-Castaño MV, et al. Effects of a home-exercise programme in childhood survivors of acute lymphoblastic leukaemia on physical fitness and physical functioning: results of a randomised clinical trial. *Support Care Cancer.* (2020) 28:3171–8. doi: 10.1007/s00520-019-05131-2
30. Takken T, van der Torre P, Zwerink M, Hulzebos EH, Bierings M, Helders PJM, et al. Development, feasibility and efficacy of a community-based exercise training program in pediatric cancer survivors. *Psychooncology.* (2009) 18:440–8. doi: 10.1002/pon.1484
31. Balsalobre-Fernández C, Glaister M, Lockey RA. The validity and reliability of an iPhone app for measuring vertical jump performance. *J Sports Sci.* (2015) 33:1574–9. doi: 10.1080/02640414.2014.996184
32. Harsted S, Holsgaard-Larsen A, Hestbæk L, Boyle E, Lauridsen HH. Concurrent validity of lower extremity kinematics and jump characteristics captured in pre-school children by a markerless 3D motion capture system. *Chiropr Man Ther.* (2019) 27:1–16. doi: 10.1186/s12998-019-0261-z

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.

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 25 August 2022
DOI 10.3389/fped.2022.977365

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Oncology, a section of the journal Frontiers in Pediatrics

RECEIVED 24 June 2022
ACCEPTED 03 August 2022
PUBLISHED 25 August 2022

CITATION
Bratteteig M, Anderssen SA, Rueegg CS, Ruud E, Torsvik IK, Kriemler S and Grydeland M (2022) Device-measured physical activity and cardiovascular disease risk in adolescent childhood cancer survivors. A physical activity in childhood cancer survivors (PACCS) study.
Front. Pediatr. 10:977365.
doi: 10.3389/fped.2022.977365

Device-measured physical activity and cardiovascular disease risk in adolescent childhood cancer survivors. A physical activity in childhood cancer survivors (PACCS) study

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Objectives: We aimed to compare cardiovascular disease (CVD) risk factors in childhood cancer survivors (CCS) with age- and sex-stratified reference material and examine the association between physical activity (PA) intensities and CVD risk factors in CCS.

Materials and methods: Within the cross-sectional, multicenter *Physical Activity in Childhood Cancer Survivors* (PACCS) study, we collected data on CVD risk factors [VO_{2-peak} ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$), body mass index (BMI, kg/m^2), systolic blood pressure (SBP, mmHg), and total-cholesterol/HDL-cholesterol (Total/HDL)] among CCS aged 9–18 years. CVD risk factors were compared to references with immediate *t*-tests. We transformed CVD risk factors into *z*-scores based on international references and generated an individual CVD risk score: [inverse ZVO_{2-peak} + Z_{BMI} + Z_{SBP} + $Z_{Total/HDL}$)/4]. Multivariable mixed linear regression models were used to analyze the associations between device-measured PA intensities and CVD risk factors.

Results: We included 157 CCS aged on average 13.4 years at inclusion and 8.2 years from diagnosis. Male CCS had lower VO_{2-peak} compared to references (45.4 vs. 49.4 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$, $P = 0.001$), higher diastolic BP (67 vs. 63 mmHg, $P < 0.001$), lower HDL (1.35 vs. 1.44 mmol/L, $P = 0.012$), as well as a tendency to higher CVD risk score (*z*-score=0.14 vs. 0.00, $P = .075$). Female

CCS' CVD risk factors were comparable to references. Vigorous-intensity PA (VPA) was associated with CVD risk factors. A 10-min increase in VPA was associated with higher VO_{2-peak} (β = 4.9, 95% CI, 2.1–7.7), lower Total/HDL (β = −0.3, 95% CI, −0.6 to −0.1) and a lower CVD risk score (β = −0.4, 95% CI, −0.6 to −0.2).

Conclusion: Male adolescent CCS had less favorable values of CVD risk factors compared to references. VPA in adolescent CCS is associated with clinically meaningful favorable values of CVD risk factors.

KEYWORDS

cardiovascular disease risk, cardiometabolic risk, physical activity, accelerometry, childhood cancer survivors

Introduction

Due to major improvements in childhood cancer management, 5-year survival rates have increased to > 80% for children and adolescents diagnosed after the millennium (1–3). However, survival comes at a cost; due to intensive treatment during development and growth, childhood cancer survivors (CCS) are at particularly high risk of developing disease and treatment-related late effects that can interfere with physical and mental health, social functioning, and quality of life (4–6). Cardiovascular disease (CVD) risk factors, such as low cardiorespiratory fitness (CRF), adiposity, and abnormal glucose and lipid metabolism are important late effects among CCS associated with premature mortality in adulthood (7). Notably, CCS may face a sevenfold increased risk of cardiac mortality 30 years after diagnosis compared to age- and sex-matched references (8).

In children and adolescents with no history of cancer, physical activity (PA) is favorably associated with single and clustering of CVD risk factors (9–11). The same beneficial effects of PA on CVD risk is seen among adult CCS, and is therefore proposed as a strategy for secondary prevention and treatment (12–14). However, the relationship between PA and CVD risk in young CCS has not yet been thoroughly investigated, and existing studies are limited by small sample sizes and/or subjective measurement methods (15–21). Subjective measurement methods, such as questionnaires, are prone to measurement errors due to biases such as recognition-, memory- and social desirability (22), and have shown to be unreliable in pediatric populations (23). Existing studies suggest that there is an association between PA and body composition in adolescent CCS also. However, associations with other CVD risk factors remain uncertain. The objectives of this study were thus to compare CVD risk factors in adolescent CCS with age- and sex-stratified references and examine the association between device-measured PA intensities and CVD risk in adolescent CCS. We hypothesized that higher volume and higher intensity of PA are associated with a favorable CVD risk profile in CCS.

Materials and methods

Study design

This study is part of the international, cross-sectional, multicenter study *Physical Activity in Childhood Cancer Survivors (PACCS)* (24). The PACCS study consists of four work packages (WPs). The current study is based on WP2, which recruited CCS from WP1 from three study sites: Oslo University Hospital, Norway; Haukeland University Hospital, Norway; and University Children's Hospital Basel, Switzerland. Manuals of procedures were developed to ensure standardized data collection across study sites. Participant recruitment and data collection were performed from January 2019 to December 2020.

Participants

Childhood cancer survivors were recruited at their pediatric out-patient clinics when visiting for scheduled follow-up care. Inclusion criteria for the current study (WP2) were participation in WP1, age between 9–18 years, ability to perform a cardio-pulmonary exercise test (CPET), and cancer treatment completed ≥ 1 year prior to recruitment. Participants were excluded if they had language or cognitive difficulties, or a CPET was considered not possible due to physical or cognitive impairments.

We used reference values obtained by Stavnsbo et al. in 2018 as reference material (25). The material includes 5,084 females and 5,133 males aged 6–18 years and we used age- and

sex-stratified reference values of the 9–18-year-olds (n = 5161–9229 in females and n = 5214–9214 in males, depending on the CVD risk factor).

Outcomes: Single cardiovascular disease risk factors and cardiovascular disease risk score

Cardiorespiratory fitness was measured as $VO_{2\text{-peak}}$ ($mL{\cdot}kg^{-1}{\cdot}min^{-1}$) by CPET. Gas exchange was determined by breath-by-breath sampling, averaged over 30-s intervals, through a breathing mask (Hans Rudolph Inc., 2700 series, Kansas City, MO, United States), and $VO_{2\text{-peak}}$ was defined as the highest oxygen uptake during the test and was standardized for body mass. Criteria for aborting the CPET were decreasing systolic blood pressure (SBP) or multiple ventricular extrasystoles during the test. The CPET equipment was volume- and gas calibrated daily to ensure valid measurements, and the tests were performed by a physiotherapist in Bergen and exercise physiologists in Oslo and Basel according to standardized procedures.

In Oslo and Bergen, the CPET was performed by walking and running on a stationary treadmill (Rodby RL2700E, Vänge, Sweden, in Oslo; and Woodway PPS 55 Med, Woodway GmbH, Weil am Rhein, Germany, in Bergen). The breathing mask was connected to a metabolic analyzer (Jaeger Oxycon Pro, Viasys Healthcare GmbH, Hoechberg, Germany, in Oslo; and Jaeger Vyntus CPX, Vyaire Medical GmbH, Hoechberg, Germany, in Bergen). A modified Balke protocol for children was applied (26). Initial workload after habituation to the treadmill was 3 km/h, 4 km/h, and additionally 4% inclination, respectively, for the first 3 min. Thereafter, workload was increased every minute by increasing speed by 1 km/h and inclination by 2% every other minute, respectively. The test was stopped and considered maximal when the participant refused further increase in workload or until subjective exhaustion.

In Basel, the Godfrey cycling protocol was performed using an electronically braked ergometer (Ergoline 800; Pilger, St. Gallen, Switzerland) and a Quark B2 metabolic cart (Cortex MetaLyzer 3B, Leipzig, Germany). Work rate was increased every minute by 15–20 W, depending on participant's height and physical fitness until the minimal cadence of 60 revolutions per minute could not be maintained or subjective exhaustion (27). The CPET protocol was different in Basel due to difference in equipment availability.

Reference values of $VO_{2\text{-peak}}$ were also a combination of treadmill and ergometer cycle tests, where a correction factor of 1.05 was applied for children and adolescents who performed their $VO_{2\text{-peak}}$ test on an ergometer cycle (28). In the current study, $VO_{2\text{-peak}}$ values for participants from Basel were adjusted accordingly.

Systolic and diastolic blood pressure (DBP, mmHg) were measured with an electronic monitor in a seated position after a 5-min rest. Two measurements were performed, and the lowest value was registered.

Body mass was measured non-fasted and in light clothing to the nearest 0.1 kg by a digital scale. Height was measured to the nearest 1 mm by a stadiometer. Body mass index (BMI, kg/m^2) was calculated.

Lipid metabolism was measured as cholesterol [Total-c (mmol/L), high-density lipoprotein cholesterol (HDL-c, mmol/L), ratio between Total-c and HDL-c (Total/HDL), and low-density lipoprotein cholesterol (LDL-c, mmol/L)]. Blood samples were collected in non-fasted state by venous sample in Oslo and Bergen, and by venous or capillary sample in Basel. Samples were analyzed by photometric methods at medical laboratories.

We generated z-scores for all of the above-mentioned single CVD risk factors based on the reference material and followed their guideline published in their **Supplementary material** (25). We first calculated age- and sex-specific reference values based on the published intercepts and beta-coefficients (25). Those reference values were then used to create z-scores based on the following formula: $z\text{-score} = (\text{mean}_{ccs} - \text{mean}_{reference})/\text{SD}_{reference}$. Stavnsbo et al. suggest using (natural) log-transformed values of BMI and Total/HDL to calculate the age- and sex-specific reference values, we thus log-transformed those two variables in our material accordingly. The resulting z-scores were then back-transformed to the original unit of 1 SD for meaningful interpretation (29).

Finally, we calculated a mean continuous CVD risk score = $(\text{inverse}Z_{VO2\text{-peak}} + Z_{BMI} + Z_{SBP} + Z_{Total/HDL})/4$. The CVD risk score was set to missing for participants with < 3 CVD risk factors (n = 1), and were thus omitted from analyses concerning CVD risk score. We calculated a CVD risk score as multiple CVD risk factors have shown to exert a synergetic effect on morbidity and mortality from CVD in later life, as compared to single risk factors (30, 31).

Exposure: Physical activity intensities

A hip-worn accelerometer (ActiGraph GT3X-BT, Pensacola, FL, United States) was used to measure PA. Participants were instructed to wear the monitor for 8 consecutive days and to remove the monitor only for sleep and water-based activities. The accelerometers were initialized at a sampling rate of 30 Hz, and raw files were analyzed at 10-s epoch using the KineSoft analytical software version 3.3.80 (Loughborough, United Kingdom), restricted to hours between 06:00–23:59. Non-wear time was defined as periods of ≥ 20 consecutive minutes of zero counts. Minimum wear time of 8 h/day was required for a valid day, and ≥ 3 valid days were required

for a person to be included in the analyses (**Supplementary Figure 1**). PA in the number of the participant's valid days was averaged to represent their daily PA. Cut-points derived from counts per minute (cpm) were used to categorize the accelerometry data into light-intensity PA (LPA, 100–1999 cpm), moderate-intensity PA (MPA, 2000–5999 cpm), vigorous-intensity PA (VPA, ≥ 6000 cpm), and moderate-to-vigorous-intensity PA (MVPA, ≥ 2000 cpm), respectively (32–34).

Covariates: Age, sex, puberty stage, parental education, and cancer-related characteristics

Puberty stage was determined by the self-reported Pubertal Development Scale questionnaire assessing indices of pubic hair, voice, and facial hair in males; and pubic hair, breast development, and menstruation in females (35). Participants were categorized as pre-pubertal if the participant reported the lowest category for all indices, post-pubertal if the participant reported the highest category for all indices, whereas the remaining participants were categorized as pubertal. Conversion of the original continuous Pubertal Development Scale into a 3-point ordinal scale is shown to be a reliable and valid tool in the pediatric population (36), albeit we are not aware of any validation studies performed in adolescent CCS.

Six categories for parent-reported parental education were collapsed into three categories: (1) 9–10 years; (2) 11–13 years; and (3) > 13 years.

Cancer diagnosis, and a limited number of available key factors from cancer treatment, that were available in conjunction with recruitment of participants, were extracted from medical records: cumulative anthracycline dose (Doxorubicin isotoxic equivalent dose, mg/m^2) (37), cumulative radiation dose (Gy), and high-dose steroids (yes/no) as part of the cancer treatment protocol. Age at diagnosis and time since diagnosis were calculated.

Statistical analyses

Characteristics of participants are expressed as mean ± SD or frequency (proportion), overall and stratified by sex. Comparisons between male and female CCS were made by Welch's *t*-test for unequal variances for continuous variables, and by Chi square tests for categorical variables.

Comparison of CVD risk factors between CCS and references was performed using immediate *t*-tests with unequal variances. Associations between PA intensities and CVD risk factors were assessed using mixed effects linear regression models with study site as random intercept to account for clusters in the data. To adjust for potential confounding, we added covariates to the model (fixed effects) based on a directed acyclic graph drawn in Dagitty version 3.0[1] (38) (**Supplementary Figure 2**). The following "minimal sufficient adjustment set" was identified: age, sex, puberty stage, parental education, age at diagnosis, time since diagnosis, and cancer treatment.

In the crude model, we adjusted only for the cluster variable study site (Model 1). In multivariable models, we additionally adjusted for age, sex, puberty stage and parental education (Model 2), and cancer-related variables (age at diagnosis, cumulative anthracycline dose, cumulative radiation dose, high-dose steroid treatment; Model 3). Time since diagnosis was omitted in Model 3 due to collinearity with age and age at diagnosis. We performed likelihood-ratio tests (LRT) to compare Model 2 and 3 in order to investigate influence of cancer-related characteristics on the PA-CVD risk factor associations. To compare models with LRT, *n* needs to be identical. Thus, missing parental education was defined as own category in the model and missing information on anthracycline dose (n = 9) and radiation dose (n = 1) was set to zero, avoiding loosing participants in analyses due to missing information on covariates. All *P*-values were two-sided, and we considered *P*-values ≤ 0.05 as statistically significant. Analyses were conducted using Stata statistical software release 16.0 (StataCorp LP, College Station, TX, United States).

Ethics

Physical Activity in Childhood Cancer Survivors WP2 was approved by the Norwegian Regional Committee for Medical Research Ethics (project ID 2018/739), the Data protection Officer at Oslo University Hospital, and the Ethics Committee of North-Western and Central Switzerland (project ID 2019-00410). Written informed consent to participate in the current study was collected from all participants/parents.

Results

Study population

Of the 267 eligible invited CCS, 157 (59%) agreed to participate in the study and were included in descriptive analyses; 137 (51%) participants were included in the regression models (**Figure 1**).

The participants were on average 13.4 years old at inclusion and 8.2 years from diagnosis (**Table 1**). Half of the participants

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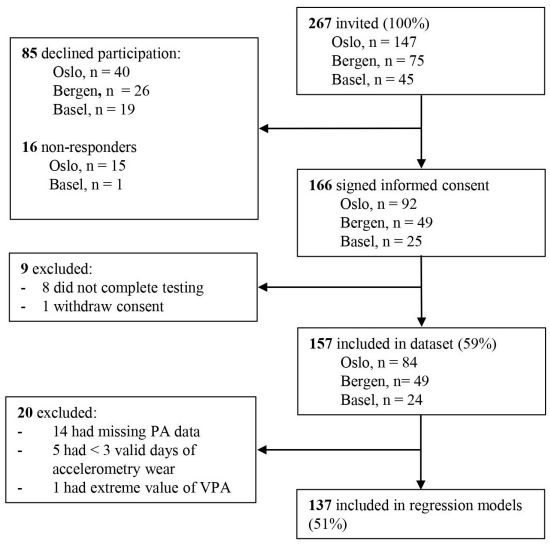

FIGURE 1
Flow chart of the inclusion process in PACCS WP2.

were survivors of leukemia, 78% had received anthracyclines, 29% had received radiotherapy, and 57% had received high-dose steroid treatment as part of their cancer treatment protocol. Females and males were comparable with respect to demographic and cancer-related characteristics, except borderline differences in distribution of puberty stage (18, 73, and 10% of the females were pre-pubertal, pubertal, and post-pubertal, respectively, whereas 27, 70, and 2% of the males were pre-pubertal, pubertal, and post-pubertal, respectively, P_{trend} = 0.077) and proportion experiencing relapse (4% in females vs. 12% in males, P = 0.077).

Basic characteristics were not significantly different between participants and non-participants in WP2 (**Supplementary Tables 1**, **2**), though there was a tendency that fewer participants had experienced relapse compared to non-participants (9 vs. 17%, P = 0.10), and female participants were slightly younger than female non-participants (12.1 vs. 12.9 years, P = 0.11).

Cardiovascular disease risk factors

Male CCS had lower $VO_{2\text{-peak}}$ compared to references [45.4 vs. 49.4 mL·kg^{-1}·min^{-1}, P = 0.001 (**Table 2**)], as well as higher DBP (67 vs. 63 mmHg, P < 0.001) and lower HDL-c (1.35 vs. 1.44 mmol/L, P = 0.012). There were no differences between female CCS and references in any of the CVD risk factors.

Males had a z-score of −0.52 (95% CI, −0.82, −0.22, P = 0.001) for $VO_{2\text{-peak}}$ and 0.14 (95% CI, −0.01, 0.30, P = 0.075) for the CVD risk score (**Figure 2**). Females had a z-score of −0.16 (95% CI, −0.45, 0.12, P = 0.26) for $VO_{2\text{-peak}}$ and 0.02 (95% CI, −0.14, 0.18, P = 0.81) for the CVD risk score.

TABLE 1 Demographic and cancer-related characteristics in adolescent CCS, overall and stratified by sex.

	All (n = 157)	Females (n = 73)	Males (n = 84)	P
Demographic characteristics				
Age at study, years	13.4 ± 2.5	13.2 ± 2.7	13.5 ± 2.4	0.53
Puberty stage				0.077
Pre-pubertal	36 (23)	13 (18)	23 (27)	
Pubertal	112 (71)	53 (73)	59 (70)	
Post-pubertal	9 (6)	7 (10)	2 (2)	
Caucasian ethnicity	146 (93)	68 (93)	78 (93)	0.28
Parental education[a]				0.40
Primary school	6 (6)	3 (8)	3 (5)	
High school	32 (34)	9 (25)	23 (39)	
University or college	57 (60)	24 (67)	33 (56)	
Cancer-related characteristics				
Age at diagnosis, years	5.2 ± 3.4	5.4 ± 3.3	5.1 ± 3.4	0.59
Time since diagnosis, years	8.2 ± 3.6	7.9 ± 3.5	8.4 ± 3.6	0.34
Diagnoses (ICCC-3)				0.25
I Leukemias	78 (50)	39 (53)	39 (46)	
II Lymphoma	16 (10)	4 (5)	12 (14)	
III CNS tumors	18 (11)	7 (10)	11 (13)	
IV–XII other tumors	45 (29)	23 (32)	22 (26)	
Relapse	13 (8)	3 (4)	10 (12)	0.077
Anthracyclines	121 (78)	57 (79)	64 (77)	0.85
Cumulative dose (mg/m^2) (31),[b] (range)	161 ± 90 (45–450)	161 ± 91 (80–450)	161 ± 89 (45–410)	0.82
Radiotherapy	45 (29)	21 (29)	24 (29)	0.98
Cumulative dose (Gy) (range)[c]	33 ± 18 (12–70)	34 ± 20 (12–70)	32 ± 16 (12–54)	0.98
High-dose steroids[d]	90 (57)	42 (58)	48 (57)	0.96

Continuous variables are displayed as mean and standard deviation, categorical variables as frequency and proportion. There are no missing values besides the ones stated in the footnote below. CCS, childhood cancer survivors; CNS, central nervous system; CVD, cardiovascular disease; ICCC-3, International Classification of Childhood Cancer – third edition.
[a]Missing information on parental education for 62 participants.
[b]Missing cumulative anthracycline dose for nine participants.
[c]Missing cumulative radiation dose for one participant.
[d]As part of cancer treatment protocol (yes/no).

Physical activity

In this substudy of PACCS, participants wore their accelerometer, on average, 13 h/day for 6 days. Participants engaged on average in 60 ± 28 min of MVPA/day (**Table 3**).

Associations between physical activity and cardiovascular disease risk factors

The fully adjusted model (Model 3) showed that all PA intensities were associated with $VO_{2\text{-peak}}$, and the coefficients increased in size with higher intensity PA (**Table 4**). A 10-min

TABLE 2 Comparison of single CVD risk factors in CCS vs. references, stratified by sex.

CVD risk factors	Females			Males		
	CCS ($n = 73$)[a]	References (25) ($n = 5161$)[b]	*P*-value	CCS ($n = 84$)[a]	References (25) ($n = 5214$)[b]	*P-value*
$VO_{2\text{-peak}}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	40.1 ± 7.8	41.1 ± 6.6	0.25	45.4 ± 10.8	49.4 ± 7.7	0.001
BMI (kg/m^2)	19.9 ± 3.8	20.0 ± 4.1	0.79	19.8 ± 3.6	20.0 ± 4.0	0.74
ln BMI	2.98 ± 0.18	2.98 ± 0.18	0.99	2.97 ± 0.17	2.97 ± 0.17	0.94
SBP (mmHg)	104 ± 10	105 ± 9	0.55	109 ± 9	109 ± 9	0.75
DBP (mmHg)	63 ± 9	63 ± 8	0.83	67 ± 9	63 ± 8	< 0.001
Total-c (mmol/L)	4.2 ± 0.8	4.3 ± 0.7	0.64	4.0 ± 0.8	4.1 ± 0.7	0.73
HDL-c (mmol/L)	1.47 ± 0.29	1.50 ± 0.32	0.30	1.35 ± 0.30	1.44 ± 0.32	0.012
Total/HDL	3.0 ± 0.8	3.0 ± 0.8	0.75	3.1 ± 0.9	3.0 ± 0.8	0.16
ln Total/HDL	1.06 ± 0.23	1.05 ± 0.24	0.64	1.10 ± 0.28	1.06 ± 0.25	0.15
LDL-c (mmol/L)	2.5 ± 0.8	2.4 ± 0.7	0.058	2.4 ± 0.7	2.2 ± 0.6	0.14

Variables are displayed as mean and standard deviation. BMI, body mass index; CCS, childhood cancer survivors; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein-cholesterol; LDL-c, low-density lipoprotein-cholesterol; ln, natural logarithm; SBP, systolic blood pressure; Total-c, total-cholesterol; VO2-peak, peak oxygen consumption.

[a]CVD risk factors varied from $n = 72$–73 in female CCS and $n = 77$–84 in male CCS.

[b]CVD risk factors varied from $n = 5161$–9229 in female references and $n = 5214$–9214 in male references.

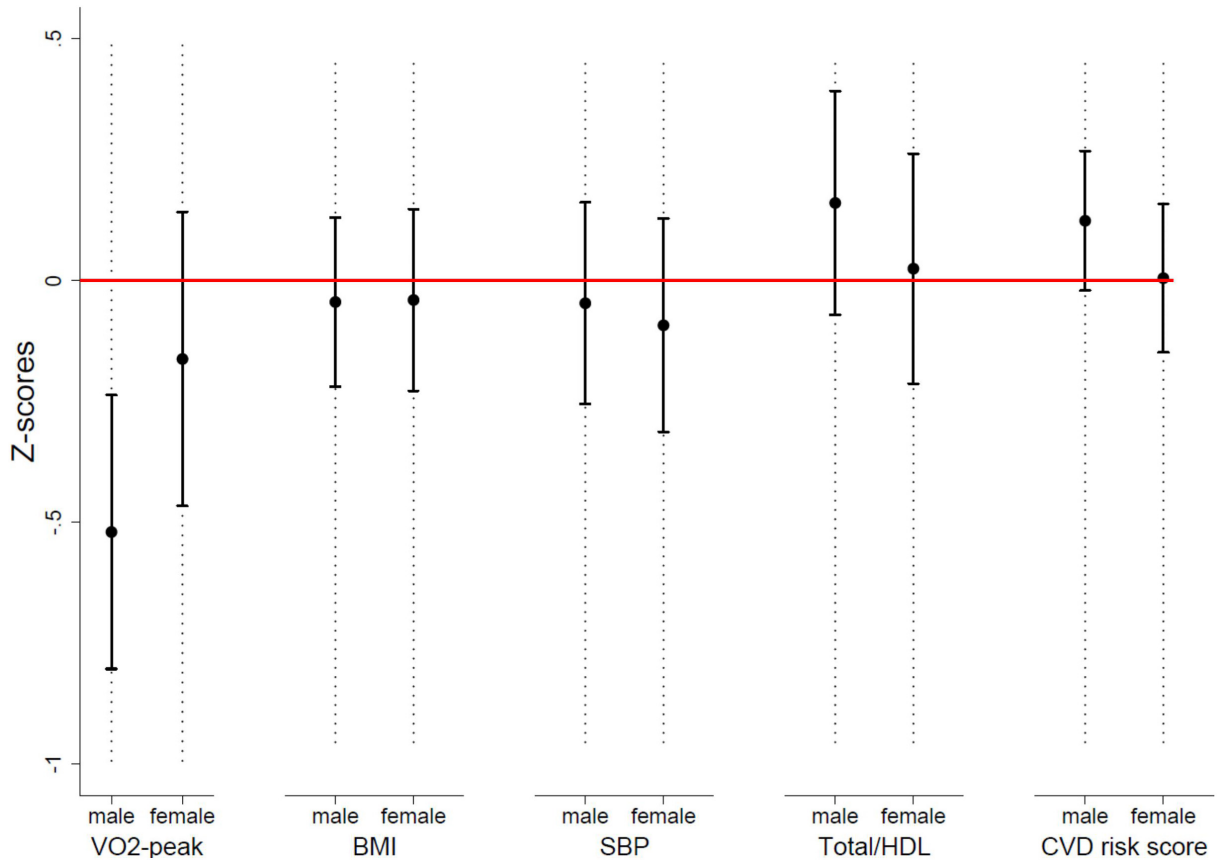

FIGURE 2
Mean *Z*-scores with 95% CI for single CVD risk factors and the CVD risk score, stratified by sex. BMI, body mass index (kg/m^2); CVD, cardiovascular disease; SBP, systolic blood pressure; Total/HDL, total-cholesterol/HDL-cholesterol; VO2-peak, peak oxygen consumption.

increase in LPA, MPA, and VPA was associated with a higher $VO_{2\text{-peak}}$ of 0.5 (95% CI, 0.1–0.8, P = 0.008), 1.0 (95% CI, 0.4–1.6, P = 0.001), and 4.9 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ (95% CI, 2.1–7.7, P = 0.001), respectively. Adding cancer-related variables to the model assessing the association between LPA and $VO_{2\text{-peak}}$ did not alter the strength of the association. However, including cancer-related variables to the model resulted in a significantly better model fit (P_{LRT} comparing models = 0.002). Including cancer-related variables reduced the strength of the association between MPA and $VO_{2\text{-peak}}$ from 1.3 to 1.0 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$; and from 5.6 to 4.9 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ for the association between VPA and $VO_{2\text{-peak}}$ (P_{LRT} comparing models = 0.011 and 0.004 for MPA and VPA, respectively).

Both MPA and VPA were associated with lower Total/HDL (−0.1, 95% CI, −0.1 to −0.0, P = 0.022; and −0.3, 95% CI, −0.6 to −0.1, P = 0.016, respectively), and MPA was additionally associated with lower SBP (-0.9 mmHg, 95% CI, −1.5 to −0.3, P = 0.005). Adding cancer-related variables to the model did not affect the association between PA intensities and Total/HDL or SBP. None of the PA intensities were associated with BMI and including cancer-related variables in the model did not affect the associations.

Also, MPA and VPA were associated with the CVD risk score. A 10-min increase in MPA and VPA were associated with a lower CVD risk score of −0.1 (95% CI, −0.1 to −0.0, P < 0.001), and −0.4 (95% CI, −0.6 to −0.2, P = 0.001), respectively. Adding cancer-related variables to the model did not affect the association between PA intensities and the CVD risk score.

Discussion

Main findings

We found that male adolescent CCS had lower $VO_{2\text{-peak}}$ and HDL-c, and higher DBP and CVD risk score compared to references, in contrast to female adolescent CCS where all CVD risk factors were comparable to references. To our knowledge, this is the first study examining the association between device-measured PA and CVD risk factors in adolescent CCS. We found that PA was associated with single CVD risk factors and the CVD risk score.

TABLE 3 Physical activity intensities in adolescent CCS, overall and stratified by sex.

	All (n = 137)	Females (n = 63)	Males (n = 74)
Physical activity			
LPA (min/day)	175 ± 49	172 ± 41	177 ± 55
MPA (min/day)	55 ± 25	52 ± 20	57 ± 29
VPA (min/day)	5 ± 5	5 ± 5	5 ± 5
MVPA (min/day)	60 ± 28	57 ± 23	62 ± 32

Variables are displayed as mean and standard deviation. CCS, childhood cancer survivors; LPA, low-intensity physical activity; MPA, moderate-intensity physical activity; MVPA, moderate-to-vigorous-intensity physical activity; PA, physical activity; VPA, vigorous-intensity physical activity.

Comparison to other studies

Cardiorespiratory fitness

With respect to the single CVD risk factors, we found that PA at any intensity was positively associated with $VO_{2\text{-peak}}$, and higher intensity PA was inversely associated with Total/HDL. MPA was additionally inversely associated with SBP. Our results are in line with a previous study by Jarvela et al. showing a positive association between self-reported PA and $VO_{2\text{-peak}}$ in young adult survivors of acute lymphoblastic leukemia (15).

Adiposity

Our results conflict with previous studies by Slater et al. showing inverse associations between self-reported PA and adiposity in adolescent and young adult CCS (18, 19). These studies used waist circumference, body fat percentage, subcutaneous and visceral adipose tissue as measures of adiposity, and PA was assessed by questionnaire, which might explain the differences in results. This claim is supported by two other studies in CCS: Tonorezos et al. found an inverse association between device-measured PA and body fat percentage, but not with BMI, in young adult CCS (21); Jarvela et al. found that an increase in PA led to reduced adiposity, measured as waist circumference, waist-to-hip ratio, and body fat percentage, but not with BMI (15). Thus, BMI does not seem like an appropriate measure of adiposity in CCS to detect a potential association with PA. BMI does not distinguish between fat mass and fat-free mass, and studies in CCS have shown that despite having similar BMI z-score as healthy controls, they have deficits in fat-free mass and excesses of fat mass (39).

Blood pressure and lipid metabolism

Jarvela et al. additionally found that an increase in PA resulted in lower SBP and higher HDL-c (15). Our results are in line with these findings. We did not look at the association between measures of PA and HDL-c separately. However, we found an inverse association between PA and ratio of Total/HDL, which might be explained by higher HDL-c. Other cross-sectional studies in CCS have failed to detect these associations (18, 19, 21). This might be due to methodological differences in measuring PA.

Influence of cancer treatment on the association between physical activity and cardiovascular disease risk factors

A recent study by Schindera et al. found a strong association between CRF and CVD risk factors in young adult

TABLE 4 Associations between 10-min increase in PA intensities and CVD risk factors in adolescent CCS.

	10 min LPA (n = 137)			10 min MPA (n = 137)			10 min VPA (n = 137)		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
	β -coefficients with 95% CIs								
$VO_{2\text{-peak}}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)[a]	0.4 (0.0 to 0.7)	0.5 (0.1 to 0.8)	0.5 (0.1 to 0.8)	1.2 (0.6 to 1.8)	1.3 (0.7 to 1.9)	1.0 (0.4 to 1.6)	5.5 (2.5 to 8.6)	5.6 (2.6 to 8.5)	4.9 (2.1 to 7.7)
BMI (kg/m^2)	−0.2 (−0.3 to −0.1)	−0.1 (−0.2 to 0.1)	−0.0 (−0.2 to 0.1)	−0.3 (−0.5 to −0.0)	−0.1 (−0.3 to 0.1)	−0.1 (−0.3 to 0.2)	−1.1 (−2.3 to 0.2)	−0.8 (−2.0 to 0.3)	−0.8 (−2.0 to 0.3)
SBP (mmHg)[a]	−0.5 (−0.8 to −0.1)	−0.1 (−0.5 to 0.3)	−0.1 (−0.5 to 0.2)	−1.0 (−1.6 to −0.3)	−0.8 (−1.4 to −0.2)	−0.9 (−1.5 to −0.3)	−2.2 (−5.7 to 1.2)	−1.8 (−5.0 to 1.3)	−2.0 (−5.1 to 1.2)
Total/HDL[b]	−0.0 (−0.1 to 0.0)	−0.0 (−0.0 to 0.0)	−0.0 (−0.0 to 0.0)	−0.1 (−0.1 to −0.0)	−0.1 (−0.1 to −0.0)	−0.1 (−0.1 to −0.0)	−0.4 (−0.7 to −0.1)	−0.3 (−0.6 to −0.1)	−0.3 (−0.6 to −0.1)
CVD risk score[c]	−0.0 (−0.0 to 0.0)	−0.0 (−0.1 to 0.0)	−0.0 (−0.1 to 0.0)	−0.1 (−0.1 to −0.0)	−0.1 (−0.1 to −0.0)	−0.1 (−0.1 to −0.0)	−0.4 (−0.6 to −0.1)	−0.4 (−0.6 to −0.2)	−0.4 (−0.6 to −0.2)

BMI, body mass index; CCS, childhood cancer survivors; CVD, cardiovascular disease; LPA, low-intensity physical activity; MPA, moderate-intensity physical activity; PA, physical activity; SBP, systolic blood pressure; Total/HDL, ratio of total-cholesterol and high-density lipoprotein-cholesterol; VO2-peak: peak oxygen consumption; VPA, vigorous-intensity physical activity. Adjustments: Model 1 is adjusted for site; Model 2 is additionally adjusted for age, sex, puberty stage, and parental education; Model 3 is additionally adjusted for age at diagnosis, cumulative anthracycline dose, radiation dose, and high-dose steroid treatment (yes/no).

[a]Missing information on VO2-peak (unknown reason) and SBP in two participants.

[b]Missing information on Total/HDL in six participants.

[c]CVD risk score was set to missing for one participant due to < 3 CVD risk factors.

CCS (40). They report that the associations did not change noticeably when adjusting the analyses for cancer treatment. They suggested that survivors may have modified their CVD risk through CRF. Our statistical models were similar, where we compared the associations with- and without including treatment variables as confounders. We found that cancer-related variables reduced the strength of the association between PA and VO_{2-peak}, which might indicate that CCS have smaller increase in $VO_{2\text{-peak}}$ in response to PA than adolescents with no history of cancer. Some potential mechanisms induced by cancer treatment, may be that cardiovascular diseases limit performance during exercise through impairments in systolic and diastolic function, or heart rate response; pulmonary limitations may cause impairments in ventilation and gas exchange; and arterial stiffness and endothelial dysfunction may limit the vascular system (41). We found no impact of cancer-related variables on the association between PA and the other CVD risk factors, suggesting that PA is associated with SBP and Total/HDL independently of former cancer treatment.

Strengths and limitations

The strengths of this study are the inclusion of adolescent CCS, and the use of reliable and valid measurement methods, including device-measured PA and directly measured $VO_{2\text{-peak}}$. We also had access to some key cancer-related characteristics, enabling us to adjust for them in the analyses. Moreover, we recruited participants with a history of various childhood cancer diagnoses. Most previous studies have included participants with a history of acute lymphoblastic leukemia, only. This study has also limitations to be considered. Our analyses assume directional associations, however, associations of cross-sectional data have no real direction. We were thus unable to draw any causal inference due to the cross-sectional design. We did not have fasted blood sample values as the references did. However, Total-c and HDL-c are mainly unaffected by fasted state (42). Moreover, the use of BMI as a measure of adiposity might have reduced the possibility to find an association between PA and adiposity. Self-reporting of puberty stage might be prone to bias, however, a recent study found substantial agreement between Pubertal Development Scale and Tanner stage when each scale was combined into three categories (36), as we did. We failed in finding reference material for HbA1c, and we were thus unable to compare a measure of glucose metabolism, which is a central CVD risk factor, in CCS to references. Lastly, the relatively low inclusion rate (59%) might reflect that an invitation to participate in a study with physical performance testing might appeal more to those who are regularly physically active and may thus have led to selection bias. Even though of no statistical difference, our analysis of non-participants showed that those who had experienced relapse, and females of higher age, were less likely to participate in the current study (WP2).

Conclusion

We found that male adolescent CCS had less favorable values of CVD risk factors compared to references. Moreover, we found higher levels of PA to be associated with a more favorable CVD risk profile in adolescent CCS. This highlights the need to encourage and help adolescent CCS to increase or

maintain their PA level. Whether higher CVD risk is due to lower PA level is yet to be determined. Randomized controlled trials or cohort studies are needed to explore whether increased PA can reduce CVD risk in adolescent CCS.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The study was reviewed and approved by the Regional Committee for Medical and Health Research Ethics (2018/739). Written informed consent to participate in this study was provided by the participants or their legal guardian/next of kin.

Author contributions

MB: formal analysis, investigation, methodology, visualization, writing original draft, and writing – review and editing. SA: conceptualization, funding acquisition, methodology, project administration, supervision, visualization, and writing – review and editing. CR: methodology, supervision, validation, visualization, and writing – review and editing. ER: conceptualization, funding acquisition, project administration, supervision, and writing – review and editing. IT and SK: investigation and writing – review and editing. MG: conceptualization, funding acquisition, investigation, methodology, project administration, supervision, and writing – review and editing. All authors contributed to the article and approved the submitted version.

Funding

This work was funded by the Norwegian Cancer Society (project number 3304) and the Norwegian Research Council (project number 273500).

Acknowledgments

We are grateful to the children and their parents/guardians for giving of their time and effort. It is through their generosity that we were able to complete the study. We thank all members of the PACCS study group not listed as co-authors of this manuscript.

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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.977365/full#supplementary-material

References

1. Miller KD, Fidler-Benaoudia M, Keegan TH, Hipp HS, Jemal A, Siegel RL. Cancer statistics for adolescents and young adults, 2020. *CA Cancer J Clin.* (2020) 70:443–59. doi: 10.3322/caac.21637

2. Schindler M, Belle FN, Grotzer MA, von der Weid NX, Kuehni CE. Childhood cancer survival in Switzerland (1976-2013): time-trends and predictors. *Int J Cancer.* (2017) 140:62–74. doi: 10.1002/ijc.30434

3. Kreftregisteret. *Nasjonalt Kvalitetsregister for Barnekreft, Årsrapport 2020.* Oslo: Kreftregisteret (2021).

4. Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *JAMA.* (2013) 309:2371–81. doi: 10.1001/jama.20136296

5. Alvarez JA, Scully RE, Miller TL, Armstrong FD, Constine LS, Friedman DL, et al. Long-term effects of treatments for childhood cancers. *Curr Opin Pediatr.* (2007) 19:23–31. doi: 10.1097/MOP.0b013e328013c89e

6. Vetsch J, Wakefield CE, Robertson EG, Trahair TN, Mateos MK, Groothenhuis M, et al. Health-related quality of life of survivors of childhood acute lymphoblastic leukemia: a systematic review. *Qual Life Res.* (2018) 27:1431–43. doi: 10.1007/s11136-018-1788-5

7. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American heart association expert panel on population and prevention science; the councils on cardiovascular disease in the young, epidemiology and prevention, nutrition, physical activity and metabolism, high

blood pressure research, cardiovascular nursing, and the kidney in heart disease; and the interdisciplinary working group on quality of care and outcomes research: endorsed by the American academy of pediatrics. *Circulation.* (2006) 114:2710–38. doi: 10.1161/circulationaha.106.179568

8. Armstrong GT, Liu Q, Yasui Y, Neglia JP, Leisenring W, Robison LL, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the childhood cancer survivor study. *J Clin Oncol.* (2009) 27:2328–38. doi: 10.1200/jco.2008.21.1425

9. Poitras VJ, Gray CE, Borghese MM, Carson V, Chaput JP, Janssen I, et al. Systematic review of the relationships between objectively measured physical activity and health indicators in school-aged children and youth. *Appl Physiol Nutr Metab.* (2016) 41:S197–239. doi: 10.1139/apnm-2015-0663

10. Ekelund U, Anderssen SA, Froberg K, Sardinha LB, Andersen LB, Brage S. Independent associations of physical activity and cardiorespiratory fitness with metabolic risk factors in children: the European youth heart study. *Diabetologia.* (2007) 50:1832–40. doi: 10.1007/s00125-007-0762-5

11. Renninger M, Hansen BH, Steene-Johannessen J, Kriemler S, Froberg K, Northstone K, et al. Associations between accelerometry measured physical activity and sedentary time and the metabolic syndrome: a meta-analysis of more than 6000 children and adolescents. *Pediatr Obes.* (2019) 15:e12578. doi: 10.1111/ijpo.12578

12. Jones LW, Liu GT, Armstrong GT, Ness KK, Yasui Y, Devine K, et al. Exercise and risk of major cardiovascular events in adult survivors of childhood hodgkin lymphoma: a report from the childhood cancer survivor study. *J Clin Oncol.* (2014) 32:3643–50. doi: 10.1200/jco.2014.56.7511

13. Smith WA, Li K, Nottage A, Mulrooney DA, Armstrong GT, Lanctot Q, et al. Lifestyle and metabolic syndrome in adult survivors of childhood cancer: a report from the St. Jude lifetime cohort study. *Cancer.* (2014) 120:2742–50. doi: 10.1002/cncr.28670

14. Morales JS, Valenzuela PL, Herrera-Olivares AM, Bano-Rodrigo A, Castillo-Garcia A, Rincon-Castanedo C, et al. Exercise interventions and cardiovascular health in childhood cancer: a meta-analysis. *Int J Sports Med.* (2020) 3:141–53. doi: 10.1055/a-1073-8104

15. Järvelä LS, Kemppainen J, Niinikoski H, Hannukainen JC, Lähteenmäki PM, Kapanen J, et al. Effects of a home-based exercise program on metabolic risk factors and fitness in long-term survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer.* (2012) 59:155–60. doi: 10.1002/pbc.24049

16. Long TM, Rath SR, Wallman KE, Howie EK, Straker LM, Bullock A, et al. Exercise training improves vascular function and secondary health measures in survivors of pediatric oncology related cerebral insult. *PLoS One.* (2018) 13:e0201449. doi: 10.1371/journal.pone.0201449

17. Lemay V, Caru M, Samoilenko M, Drouin S, Alos N, Lefebvre G, et al. Prevention of long-term adverse health outcomes with cardiorespiratory fitness and physical activity in childhood acute lymphoblastic leukemia survivors. *J Pediatr Hematol Oncol.* (2019) 41:e450–8. doi: 10.1097/mph.0000000000001426

18. Slater ME, Ross JA, Kelly AS, Dengel DR, Hodges JS, Sinaiko AR, et al. Physical activity and cardiovascular risk factors in childhood cancer survivors. *Pediatr Blood Cancer.* (2015) 62:305–10. doi: 10.1002/pbc.25276

19. Slater ME, Steinberger J, Ross JA, Kelly AS, Chow EJ, Koves H, et al. Physical activity, fitness, and cardiometabolic risk factors in adult survivors of childhood cancer with a history of hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* (2015) 21:1278–83. doi: 10.1016/j.bbmt.2015.04.007

20. Sloof N, Hendershot E, Griffin M, Anderson L, Marjerrison S. The impact of physical activity on the health of young adult survivors of childhood cancer: an exploratory analysis. *J Adolesc Young Adult Oncol.* (2019) 8:602–9. doi: 10.1089/jayao.2019.0001

21. Tonorezos ES, Robien K, Eshelman-Kent D, Moskowitz CS, Church TS, Ross R, et al. Contribution of diet and physical activity to metabolic parameters among survivors of childhood leukemia. *Cancer Causes Control.* (2013) 24:313–21. doi: 10.1007/s10552-012-0116-6

22. Burchartz A, Anedda B, Auerswald T, Giurgiu M, Hill H, Ketelhut S, et al. Assessing physical behavior through accelerometry – state of the science, best practices and future directions. *Psychol Sport Exerc.* (2020) 49:101703. doi: 10.1016/j.psychsport.2020.101703

23. Adamo KB, Prince SA, Tricco AC, Connor-Gorber S, Tremblay M. A comparison of indirect versus direct measures for assessing physical activity in the pediatric population: a systematic review. *Int J Pediatr Obes.* (2009) 4:2–27. doi: 10.1080/17477160802315010

24. Lie HC, Anderssen SA, Rueegg CS, Raastad T, Grydeland M, Thorsen L, et al. The physical activity and fitness in childhood cancer survivors (PACCS) study: protocol for an international, mixed-methods study. *JMIR Res Protoc.* (2022) 11:e35838. doi: 10.2196/35838

25. Stavnsbo M, Resaland GK, Anderssen SA, Steene-Johannessen J, Domazet L, Skrede T, et al. Reference values for cardiometabolic risk scores in children and adolescents: suggesting a common standard. *Atherosclerosis.* (2018) 278:299–306. doi: 10.1016/j.atherosclerosis.2018.10.003

26. Marinov B, Kostianev S, Turnovska T. Modified treadmill protocol for evaluation of physical fitness in pediatric age group - comparison with Bruce and Balke protocols. *Acta Physiol Pharmacol Bulg.* (2003) 27:47–51.

27. Godfrey S, Davies CT, Wozniak E, Barnes CA. Cardio-respiratory response to exercise in normal children. *Clin Sci.* (1971) 40:419–31. doi: 10.1042/cs0400419

28. Mamen A, Resaland GK, Mo DA, Andersen LB. Comparison of peak oxygen uptake in boys exercising on treadmill and cycle ergometers. *Gazz Med Ital.* (2008) 167:15–21.

29. Roessner U, Nahid A, Chapman B, Hunter A, Bellgard M. Metabolomics – the combination of analytical biochemistry, biology, and informatics. 2nd ed. In: Moo-Young M editor. *Comprehensive Biotechnology*. Cambridge, MA: Academic Press (2011). p. 455.

30. Berenson GS, Srinivasan SR, Bao W, Newman WP, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. the Bogalusa heart study. *N Engl J Med.* (1998) 338:1650–6. doi: 10.1056/nejm199806043382302

31. Kannel WB. Contributions of the Framingham study to the conquest of coronary artery disease. *Am J Cardiol.* (1988) 62:1109–12. doi: 10.1016/0002-9149(88)90558-9

32. Trost SG, Loprinzi PD, Moore R, Pfeiffer KA. Comparison of accelerometer cut points for predicting activity intensity in youth. *Med Sci Sports Exerc.* (2011) 43:1360–8. doi: 10.1249/MSS.0b013e318206476e

33. Andersen LB, Harro M, Sardinha LB, Froberg K, Ekelund U, Brage S, et al. Physical activity and clustered cardiovascular risk in children: a cross-sectional study (the European youth heart study). *Lancet.* (2006) 368:299–304. doi: 10.1016/s0140-6736(06)69075-2

34. Trojano RP, Berrigan D, Dodd KW, Mâsse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc.* (2008) 40:181–8. doi: 10.1249/mss.0b013e31815a51b3

35. Carskadon MA, Acebo C. A self-administered rating scale for pubertal development. *J Adolesc Health.* (1993) 14:190–5. doi: 10.1016/1054-139x(93)90004-9

36. Koopman-Verhoeff ME, Gredvig-Ardito C, Barker DH, Saletin JM, Carskadon MA. Classifying pubertal development using child and parent report: comparing the pubertal development scales to Tanner staging. *J Adolesc Health.* (2020) 66:597–602. doi: 10.1016/j.adohealth.2019.11.308

37. Feijen EAM, Leisenring WM, Stratton KL, Ness KK, van der Pal HJH, Caron HN, et al. Equivalence ratio for daunorubicin to doxorubicin in relation to late heart failure in survivors of childhood cancer. *J Clin Oncol.* (2015) 33:3774–80. doi: 10.1200/jco.2015.61.5187

38. Textor J, van der Zander B, Gilthorpe MS, Liskiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *Int J Epidemiol.* (2016) 45:1887–94. doi: 10.1093/ije/dyw341

39. Weber DR, Leonard MB, Zemel BS. Body composition analysis in the pediatric population. *Pediatr Endocrinol Rev.* (2012) 10:130–9.

40. Schindera C, Zürcher SJ, Jung R, Boehringer S, Balder JW, Rueegg CS, et al. Physical fitness and modifiable cardiovascular disease risk factors in survivors of childhood cancer: a report from the SURfit study. *Cancer.* (2021) 127:1690–8. doi: 10.1002/cncr.33351

41. Berkman AM, Lakoski SG. A review of cardiorespiratory fitness in adolescent and young adult survivors of childhood cancer: factors that affect its decline and opportunities for intervention. *J Adolesc Young Adult Oncol.* (2016) 5:8–15. doi: 10.1089/jayao.2015.0031

42. Nordestgaard BG. A test in context: lipid profile, fasting versus nonfasting. *J Am Coll Cardiol.* (2017) 70:1637–46. doi: 10.1016/j.jacc.2017.08.006

frontiers | Frontiers in Pediatrics

TYPE Review
PUBLISHED 16 September 2022
DOI 10.3389/fped.2022.979292

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Oncology, a section of the journal Frontiers in Pediatrics

RECEIVED 27 June 2022
ACCEPTED 25 August 2022
PUBLISHED 16 September 2022

CITATION
Kohler BE, Sandler CX, Baque E, Bradford NK and Trost SG (2022) Therapeutic exercise interventions in pediatric survivors of brain cancer and other solid tumors: A scoping review. *Front. Pediatr.* 10:979292. doi: 10.3389/fped.2022.979292

Therapeutic exercise interventions in pediatric survivors of brain cancer and other solid tumors: A scoping review

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Background: Improved survival rates for children with solid tumors presents an ongoing challenge of how to maximize quality of survivorship and effectively manage the short- and long-term complications of disease and treatment. To gain an understanding of the extent and nature of research pertaining to therapeutic exercise interventions and identify knowledge gaps, we conducted a scoping review of exercise training studies conducted in pediatric survivors of brain cancer and other solid tumors.

Method: A systematic literature search was performed across four electronic databases. Papers were selected for full-text review if they included participants treated for brain cancer or other solid tumors, with at least 50% of participants aged ≤21 years, evaluated an exercise intervention ≥2-weeks in duration, and were published in an English, peer-reviewed journal. We included the following quantitative study designs; randomized controlled trials, non-randomized trials, and single-arm pre-test-post-test.

Results: Of the 7,482 citations identified, 17 papers met the inclusion criteria (presenting findings from eleven studies). Two studies were randomized controlled trials, five studies were non-randomized controlled trials, and four studies were a single-arm pre-test post-test design. Average age of participants ranged from 7.3–15.5 years, and time since diagnosis ranged from 3 to 70 months. Five studies included participants with brain tumors exclusively, three studies included other solid tumors, and three studies included a mixed sample (brain and other solid tumors). A wide range of exercise modalities were employed, including cycle ergometry, resistance training, sport, yoga, and active gaming. The length of the exercise program ranged from 3–40 weeks and frequency from 3–11 sessions per week. Exercise session duration ranged from 15–180 min, with most studies reporting 30–90-min sessions.

Adherence ranged from 77 to 100%, with none of the studies reporting adverse events. Studies reported improvements in cardiorespiratory fitness, functional strength, physical activity, and quality of life.

Conclusions: A small number of mostly low methodological quality studies have examined the effects of therapeutic exercise in pediatric survivors of solid tumors. Although limited, the extant literature supports the feasibility and safety of therapeutic exercise interventions for pediatric survivors of brain cancer and other solid tumors.

KEYWORDS

children, pediatrics, oncology, solid tumor, physical activity, therapy, survivorship

Introduction

Solid tumors account for approximately 40–60% of cancer diagnoses in children and adolescents (aged 0–21 years) worldwide (1–3). Solid tumor types include tumors of the central nervous system, neuroblastomas, Wilms tumor, Ewing's tumor, rhabdomyosarcoma, soft tissue sarcomas, germ cell tumor and melanomas, and unlike adult cancers, childhood cancers are characterized by their cell of origin, not by their location (4). With advances in surgical intervention, radiotherapy, chemotherapy, and stem cell transplantation, the survival rates of children with solid tumors have increased dramatically over the past several decades, with the current overall 5-year survival rates ranging from 74 to 99% (2, 3). Improved survival rates present an ongoing challenge in survivorship of how to effectively manage the short- and long-term complications acquired from the disease and treatment. Further, the prevention of disabling secondary chronic health conditions, such as cardiovascular disease, metabolic disorders and secondary malignancies is an important factor of care post treatment. In this review, a "survivor" is considered any individual diagnosed and treated for cancer (5).

Pediatric survivors of solid tumors experience a myriad of short- and long-term complications following treatment, as well as late effects following treatment. Common late effects include reduced strength, poor cardiorespiratory fitness, increased fatigue, lowered executive function, and increased pain, consequently making home, school, and recreation activities more challenging (6–11). Quality of life in survivorship is a major concern for patients, families, and clinicians, with survivors of childhood solid tumors reporting a more severe impact of cancer and treatment into adulthood, compared to other cancers (12, 13). With more children than ever surviving solid tumors and living with late effects from the disease and its treatment, there is an urgent need for effective therapies to improve patient outcomes. Physical activity is beneficial for outcomes in both healthy and disease-burdened populations (14). Previous reviews have summarized the research literature on exercise training for mixed pediatric cancer diagnoses (15–18), the combination of adolescent and young adult cancer groups (19, 20), and exercise interventions during the treatment phase (21–23). The results indicate that therapeutic exercise training of sufficient frequency, intensity, and duration can improve cardiorespiratory fitness, muscular strength, fatigue and cognitive functioning (15–17). Additional benefits include improved immune function, reduced days of hospitalization and reduced risk of infection (22). However, the bulk of studies included in these reviews have been conducted in survivors of blood cancers and there is a dearth of research evidence on the efficacy of therapeutic exercise training among pediatric survivors of solid tumors (16, 24). Children with solid tumors differ in their clinical presentation, can receive more intensive treatment combinations of surgery, radiotherapy, and chemotherapy, and thus are likely to respond differently to therapeutic exercise (25–27). To gain a better understanding of the extent and nature of research pertaining to therapeutic exercise programs we conducted a scoping review of exercise training studies conducted in pediatric survivors of brain cancer and other solid tumors.

Methods

Search strategy

A systematic literature search was performed across four electronic databases: Embase, CINAHL, PubMed and Scopus in June 2020, and updated in April 2022. Search terms were developed in consultation with a librarian and based on previously conducted systematic reviews (18, 20, 28). Search terms were deliberately kept broad to ensure the full scope of the research was identified. No limits on publication date were applied. The search strategy contained four key topics: (1) pediatrics and adolescents, (2) solid tumors, (3) physical activity or exercise, and (4) study design (e.g., randomized controlled trials). Details of the search strategies can be found in

the Supplementary material 1. The review is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (29).

Inclusion and exclusion criteria

Papers were selected for full text review based on the following criteria: (1) included participants were treated for a solid tumor including tumors of the central nervous system, neuroblastomas, retinoblastomas, renal tumors, hepatic tumors, malignant bone tumors, soft tissue sarcomas, germ cell tumor and/or melanomas; (2) results were reported separately for solid tumors where studies included blood cancers; (3) at least 50% of participants were aged ≤21 years; (4) evaluated the effects of a physical activity or exercise intervention with a minimum duration of 2 weeks; and (5) published in an English-language, peer-reviewed journal. Papers were excluded if they evaluated an exercise program which was delivered in combination with other therapies (e.g., cognitive behavioral therapy, diet, and nutrition interventions) or if the record was a conference abstract, unpublished theses, commentary, newsletter, protocol, or case study.

Selection of included papers

Search results were exported into EndNote (Version X9), duplicates were removed, and citations (title and abstract) uploaded to online systematic review software (Covidence). Each citation was screened against the inclusion and exclusion criteria by at least two independent reviewers (BK, and either EB or CS) in two stages: (1) title and abstract screening and (2) full-text screening. Discrepancies were resolved by a third reviewer (EB or CS). In addition, a hand search of references lists of included papers was undertaken.

Data extraction

A data extraction table was developed by all authors to collate relevant information about the study design, sample size, tumor type(s), exercise training (location, supervision, frequency, intensity, duration and modes), and reported outcomes. Data extraction for one paper were completed collectively by all authors before one author (BK) completed data extraction for all remaining studies. Methodological quality was assessed independently by two authors (BK, and either EB or CS) using the Physiotherapy Evidence Database Scale (PEDro) (30). Any discrepancies were resolved through consensus. Scores of < 4 were considered "poor", 4 to 5 were considered "fair", 6 to 8 were considered "good" and 9 to 10 were considered "excellent" (31).

Results

Search results

After removal of duplicates, the search identified a total of 7,482 papers. Following title and abstract screening, 212 were selected for full-text review. Of this number, 17 papers presenting findings from 11 studies met the eligibility criteria and were included for data extraction (see Figure 1).

Study characteristics

Supplementary material 2 provides a detailed summary of the 17 papers. All papers were published between 2014 and 2021. Five of the eleven studies were conducted in North America (32–39), five conducted in Europe (40–47), and one conducted in Asia (48). Two studies were randomized controlled trials (40–42, 47), five studies were non-randomized trials with a control condition (32–36, 39, 45, 46), and four studies were single-arm pre-test post-test studies (37, 38, 43, 44, 48). Five studies conducted assessments immediately post-intervention only (37, 38, 44, 46, 48), five studies conducted follow-ups at 2–6-months post-intervention (32–36, 39–42, 47), and one study conducted follow-up assessments at 12-months post-intervention (43, 45). In single-arm pre-test post-test studies, the sample size ranged between nine (38) and 88 participants (44). In studies with a control group, total sample size ranged between 13 (41, 42) and 57 (39), with control group sample sizes ranging between seven (41, 42) and 35 (32). The average participant age ranged from 7.3 years (38) to 15.5 years (45). Time since diagnosis ranged from 3 months (45) to 70 months (33–36). Five studies included participants with brain cancer exclusively (33–38, 41, 42, 48), three studies included other solid tumors (32, 39, 40, 47), and three studies included mixed sample with brain cancer and other solid tumors (43–46). Specific tumor types included astrocytoma, medulloblastoma, ependymoma, juvenile pilocytic astrocytoma, craniopharyngioma, germ cell tumor, retinoblastoma, choroid plexus carcinoma, glioma, osteosarcoma, Ewing's sarcoma, chondroblastoma, soft tissue sarcomas, neuroblastoma, and Wilms tumor. Based on the PEDro scoring, four papers were rated as "poor" (37, 39, 43, 44), eight papers as "fair" (33–36, 38, 45, 46, 48), four papers as "good" (32, 41, 42, 47), and one paper as "excellent" (40).

Exercise interventions

Five studies evaluated exercise programs post-treatment (33–38, 41–44) and six studies evaluated exercise programs

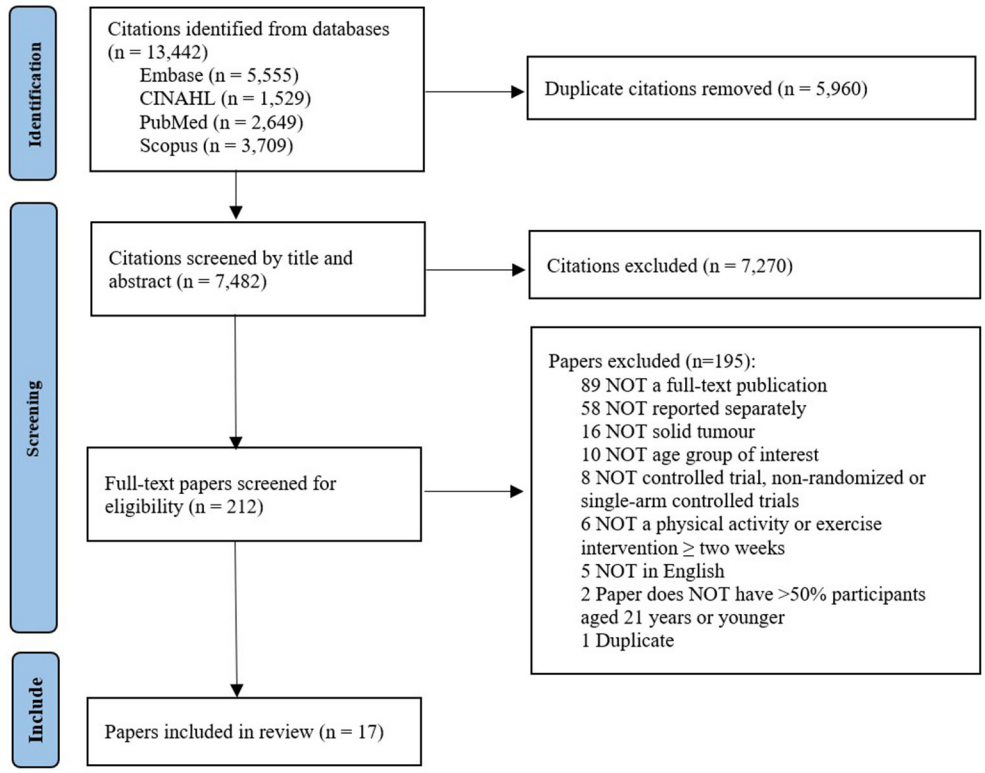

FIGURE 1
Flow chart of included and excluded papers.

during treatment (32, 39, 40, 45–48). Six studies examined the effects of a hospital inpatient program (39, 40, 43–48), two examined combined outpatient and home-based programs (33–36, 38), two examined home-based programs (37, 41, 42), and one study examined the effects of a combined hospital inpatient and outpatient program (32). Nine studies evaluated individual exercise programs delivered one-on-one (32, 37–42, 45–48), with the remaining two studies evaluating programs that combined individual and group-based exercise (33–36, 43, 44). In all eleven studies, the exercise program was supervised or remotely coached by a trained health professional (e.g., nurse, physiotherapist, exercise physiologist or trained exercise leader).

Multiple modes or types of exercise were reported across the eleven studies, including aerobic exercise (cycle ergometry, sports, active games) (32–36, 40, 45–47), resistance training (32, 40, 45–47), stretching (32, 45), yoga (48), and active video gaming (41, 42). One study evaluated the efficacy of physical activity goal setting and self-monitoring with an activity tracker (37). One study employed constraint-induced movement therapy (CIMT), which required participants to wear a removable cast on the unaffected arm and engage in task-specific training using the affected arm (38). One study utilized a staged coaching program during routine clinic visits to identify barriers to physical activity and prescribe physical activity and resources accordingly (39). Seven studies reported utilizing adult-like exercise programs (e.g., treadmills, cycle ergometry, resistance training) and/or competitive games/sports (e.g., basketball, relay running, dodgeball) (32–36, 39, 40, 45–48).

The length of the exercise program ranged from 3 weeks (38) to 40 weeks (45), with four studies opting for 10–12 week intervention periods (32–37, 41, 42). Exercise frequency ranged from three (32–36, 40, 45–48) to 11 (43, 44) sessions per week. Two studies did not report frequency (37, 39). The duration of the exercise program ranged from 15 min (45) to 180 min (38), with most studies reporting 30- to 90-min sessions (32–36, 40–48). Seven studies did not report exercise intensity (37–39, 41–44, 46, 48). Studies that reported intensity prescribed moderate-to-high intensity exercise determined by percentage of peak heart rate (33–36), age-predicted heart rate maximum (32, 40, 47), or Borg ratings of perceived exertion (RPE) (45). Resistance training comprised 1–3 sets of 6–15 repetitions for major muscle groups (32, 40, 45).

Adherence was operationally defined differently across studies. Six studies defined adherence as the number of sessions attended divided by the number prescribed, adherence ranged from 77 to 100% (32–36, 38, 41, 42, 45, 48). One study defined

adherence as the number of prescribed exercises completed, where 68% of participants completed >90% of prescribed exercises (40, 47). One study defined adherence as the number of weeks the participant met or exceeded their goal, reported to be 69% (37). Three studies did not report adherence (43, 44, 46). Six of the eleven studies monitored adverse events (32–37, 40, 45, 48), with no adverse events reported.

Outcomes

A total of nine different outcomes were measured across the 17 papers. The most commonly measured outcomes were physical activity (n = 6) (37, 39–41, 43, 45), QoL (n = 6) (37–40, 43, 46), motor performance (n = 5) (35, 38, 41, 42, 44), cardiorespiratory fitness (n = 4) (34, 35, 37, 40), and brain structure and function (n = 4) (33, 34, 36, 42). There were multiple measures used for each outcome. Physical activity was measured by wearable devices, including step counters (37) and accelerometers (39, 40, 43–45, 47); and/or by self-report questionnaires, including the Godin-Leisure-Time Exercise Questionnaire (37, 39). Motor performance was measured by the Bruininks-Osterestsky Test of Motor Performance (35, 41), the Assessment of Motor and Process Skills (42), gait analysis (44), balance (44), and three upper limb function measures (38). Cardiorespiratory fitness was measured by the Six-Minute Walk Test (34, 37) and/or by a graded exercise test with spirometry (35, 40). According to the International Classification of Functioning, Disability and Health (ICF), studies assessed impairment- or activity-related outcomes; no specific participation-related outcomes were reported, except for QoL (49, 50).

Exercise programs that involved a combination of aerobic and resistance training (n = 5) (32, 40, 43–47) resulted in improvements in strength (40), functional mobility (32, 40), physical activity (43, 45), QoL (43), balance (44), immune function (47) and bone mass (45). Exercise programs that involved aerobic training only (n = 1) (33–36) resulted in improvements in cardiorespiratory fitness (34, 35), brain structure and function (33, 34, 36), and motor performance (35, 41). Active gaming (n = 1) (41, 42) resulted in improvements in physical activity (41), cognitive function (42), coordination (41), and activities of daily living to a score above the cut-off for independent living (42). Goal setting and self-monitoring daily step counts (n = 1) (37) resulted in improvements in cardiorespiratory fitness, QoL and fatigue. CIMT (n = 1) (38) resulted in improvements in the amount and quality of hemiplegic arm use, general fatigue, and sleep/rest fatigue sub-domain scores. Yoga (n = 1) (48) resulted in improvement in parent-reported child symptoms (appetite, pain, headache, sleep, physical activity, fatigue). A staged nurse-led coaching program resulted in no changes to physical activity, and results showed a significant increase in fatigue at 6 months (39).

Discussion

Compared to other cancer types, only a small number of studies have examined the effects of therapeutic exercise in pediatric survivors of solid tumors. Studies conducted to date vary considerably in methodological quality, exercise modalities, program duration, and clinical endpoints. The available evidence, although limited, supports the feasibility and safety of therapeutic exercise in this patient group, but well-designed trials are needed to assess the efficacy of such programs.

This review identified a small number of studies of mostly low methodological quality. Over a third (36%) of studies did not have a control group, and only five papers (29%) scored good-excellent quality on the PEDro Scale. Furthermore, over half of the studies (55%) evaluated small samples (n = <30), thus limiting statistical power. Brain cancer and other solid tumor diagnoses are relatively rare and the recruitment process is time- and resource-intensive, making it difficult to recruit the sample sizes required for adequately powered studies (51). Most studies did not include extended follow-up periods (>3 months) thus, the long-term effectiveness of the interventions, remains unclear. To address these methodological limitations, adequately powered multi-site studies employing rigorous study designs and long-term follow-up are needed. Alternative study design and analytic approaches also need to be explored to address limitations of small sample sizes (i.e., single-subject study designs) (52, 53).

The age of participants, tumor type, and time since diagnosis varied considerably across studies. Participants were, however, mostly "school-aged" (i.e., 5–18 years), highlighting an absence of studies involving young children aged 0 to 5 years. This is despite almost half (47%) of all childhood cancers diagnosed between the ages of 0 to 4 years (2). Early childhood is a crucial period of growth and development, where minimizing the impact of impairments, optimizing neuroplasticity, and enhancing rehabilitation is critical (54, 55). More research is needed to investigate the effects of therapeutic exercise in children with solid tumors during early childhood.

Children with brain cancer (e.g., medulloblastoma) were more frequently studied than other solid tumors, likely due the higher prevalence rates and high levels of treatment complications and long-term impairments (13). Challenges in crossing the blood-brain barrier mean that treatment for CNS tumors differ to that of other solid tumors, with brain cancer treated with more surgery and radiation-focused treatments compared to other solid tumors, which are more often treated with a rigorous regimen of surgery and chemotherapy (56, 57). Children with bone tumors in particular, (e.g., osteosarcoma) have their own unique experiences and needs, often effected by amputations, disability and poorer QoL (7, 58). Currently there is a near-absence of evidence investigating the role exercise may play in the survivorship phase of these children. As this group of children present different clinically, and undergo

different treatment regimes, they may also respond differently to exercise. Regardless of the diagnoses, providing supportive care throughout the course of a child's acute treatment and survivorship is critical in achieving optimal outcomes.

The exercise programs varied by setting, level of supervision, length, and exercise modalities. Most studies delivered the exercise program in hospital-based settings, with few utilizing home-based programs. No studies delivered the exercise program in a community-based setting such as recreational halls, and parks. Whilst hospitals may be rich in resources (e.g., qualified staff, specific equipment), they also place additional challenges on children and their families. Hospitals can be inconvenient and expensive for travel, and for those children in the post-treatment phase, returning to hospital can induce fear and anxiety (59). The appropriate exercise setting is therefore crucial and may influence adherence, enjoyment, and long-term participation. To better meet the needs of children with solid tumors and their families, future research should investigate the effectiveness of patient-centered therapeutic exercise programs delivered in community-based settings.

Most programs included in this review involved face-to-face supervision by a trained exercise professional. Some patients and their families prefer flexible and convenient modes of intervention delivery (e.g., face-to-face at home, telehealth, mobile-health apps), which may enhance exercise adherence and long-term sustainability of program outcomes (59, 60). While supervised exercise may be initially required for monitoring safety and ensuring program fidelity, these remote delivery modes warrant investigation to delineate what is the most feasible and effective for children and their families who desire alternative delivery modes (e.g., children living in remote communities).

Studies in this review predominantly used adult-based exercise modalities and prescription closely aligned with generic American College of Sports Medicine guidelines (61). Few studies employed play- or game-based exercise, which is more likely to be engaging and motivating for children (62). Children are not little adults, and exercise programs for young children should be designed and implemented in a developmentally appropriate manner. Exercise interventions will likely be more effective and result in sustainable improvements in habitual physical activity, movement competence, and functional capacity if they are play- or game-based. Evaluations of developmentally appropriate play-based exercise programs in pediatric survivors of brain and other solid tumors are urgently needed to determine its effectiveness in this clinically unique patient group.

There was a notable lack of studies evaluating patient-centered, personalized exercise programs (63, 64), with multiple programs ($n = 5$) assessing traditional 'impairment-based' exercise interventions (32–36, 40, 45–47, 50). Programs of this type are based on the expectation that remediating impairments will lead to improved participation in their activities of choice. However, such interventions typically report poor participation outcomes in pediatric cohorts (65, 66). Intrinsically-motivated behavior (e.g., regular physical activity) is theorized to be influenced by three basic psychological needs; autonomy, perceived competence, and relatedness (67, 68). Autonomy-supportive environments encourage intrinsic motivation for sustainable behavior change through fulfillment of these basic psychological needs (69, 70). An example of fostering an autonomy-supportive environment is goal setting, whereby goals are set collaboratively by the patients and their families to be meaningful, individualized, and sensitive to the patient's clinical presentation and preferences. There is evidence supporting the effectiveness of goal-directed interventions to improve motor performance, physical activity and QoL in other pediatric groups (e.g., children with cerebral palsy, muscular dystrophy, or intellectual disability), which may be more conducive to long-term improvements (71–73). There are a small number of published study protocols advocating for the use of goal-directed interventions (74–76).

Although some outcomes were assessed in multiple studies, the measures used to assess these outcomes varied considerably. This finding is consistent with the conclusions of recent reviews on assessment of physical function in pediatric cancer patients (77–79). Outcomes measures were predominantly impairment-focused and lacked participation-level outcomes, based on the ICF framework. To improve the consistency, comparability, and transparency of study findings, future studies should adopt a more standardized approach to outcome selection and reporting. Future studies should also include participation-based outcomes such as the Participation and Environment Measure for Children and Youth (80) or participation-focused goal-directed measures, including the Canadian Occupational Performance Measure (81) or the Goal Attainment Scale (82).

Considering the relatively small number of studies and the wide range of outcomes and measures utilized across studies, it was not feasible to conduct a quantitative synthesis of the results. Nevertheless, across studies, therapeutic exercise was associated with improvements in cardiorespiratory fitness, habitual physical activity, muscle strength, functional mobility, motor performance, body composition and QoL. There were no reported adverse events from participation in therapeutic exercise. This suggests that therapeutic exercise is a potentially safe and feasible intervention for improving the QoL and wellbeing in pediatric survivors of brain cancer and other solid tumors; however, higher grade evidence is needed to make firm conclusions about the effectiveness of therapeutic exercise in this patient group and formal clinical recommendations.

This review has several strengths. It is the first scoping review of exercise training studies conducted in pediatric survivors of brain cancer and other solid tumors. The review was completed according to the PRISMA_ScR guidelines. An extensive search for articles was conducted across four databases, with no limitation on publication date. To supplement this

search, an extensive manual search of all included articles was conducted. The review and extraction processes were rigorous. Titles and abstracts and full -text citations were reviewed by two independent authors and all citations were independently checked for accuracy after extraction. Opposing these strengths were some limitations. It is possible that not all relevant publications were identified through the systematic search and cross-reference searches. For example, papers published in languages other than English or in the gray literature were not included in the review. Despite most participants being "school-aged", a small of number of studies included participants who were 18 years or over.

Conclusion

This scoping review provides the first synthesis on the extent and nature of research pertaining to therapeutic exercise programs conducted in pediatric survivors of brain cancer and other solid tumors. Compared to blood cancer types, a small number of studies have examined the effects of therapeutic exercise in pediatric survivors of solid tumors. The methodological quality of studies conducted to date has been low (i.e., non-randomized study designs, no control group, small sample sizes) and have limited follow-up (e.g., greater than 6 months). Most of the research has been conducted in brain cancer survivors, with the bulk of studies evaluating highly structured supervised exercise programs delivered in hospital settings. The role of therapeutic exercise in children with other solid tumors, such as osteosarcoma and Ewing's sarcomas, has received limited research attention, particularly in relation to QoL in survivorship. Few studies employed play- or game-based exercise programs, instead utilizing adult-based modalities and prescription. There were multiple measures used for each outcome, with a paucity of standardized outcomes measures administered across papers. Although limited, the extant research supports the feasibility and safety of therapeutic exercise for children with solid tumors before, during and after treatment. Nonetheless, significant knowledge gaps were identified. Future research should address the major gaps in the literature, including the evaluation of developmentally appropriate play-based physical activity interventions for children aged 5 years and under; the feasibility, acceptability, and potential efficacy of exercise programs delivered in of different settings (e.g., home and community-based settings) and delivery channels (e.g., telehealth and apps). To improve the quality of evidence, collaborative, multi-site studies are needed to ensure that trials are adequately powered to detect clinically meaningful changes in outcomes.

Author contributions

ST, CS, EB, and BK were responsible for the conceptualization and design of the study. CS, EB, and BK screened citations and critically appraised included papers. BK completed data extraction and drafted the manuscript, which was critically reviewed by ST, CS, EB, and NB. All authors read and approved the final manuscript.

Funding

This review is supported by a project grant from the Children's Brain Cancer Centre through the Children's Hospital Foundation (CCABCR010). The funders had no role in the design of the study or preparation of the manuscript, and will remain separate for data collection, analysis, and interpretation of the data.

Acknowledgments

We would like to acknowledge the contributions of the library staff at Queensland University of Technology for their assistance with search strategy development. CS is supported by Cancer Institute NSW Early Career Fellowship (2021/ECF1310).

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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.979292/full#supplementary-material

References

1. Ljungman G, Jakobson A, Behrendtz M, Ek T, Friberg LG, Hjalmars U, et al. Incidence and survival analyses in children with solid tumours diagnosed in Sweden between 1983 and 2007. *Acta Paediatr.* (2011) 100:750–7. doi: 10.1111/j.1651-2227.2010.02122.x

2. Youlden D, Aitken J. *Childhood Cancer in Australia 1983–2015.* Brisbane, Australia: Cancer Council Australia. (2019).

3. Lacour B, Guyot-Goubin A, Guissou S, Bellec S, Désandes E, Clavel J. Incidence of childhood cancer in France: National Children Cancer Registries, 2000–2004. *Eur J Cancer Prevent.* (2010) 19:173–81. doi: 10.1097/CEJ.0b013e32833876c0

4. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer, third edition. *Cancer.* (2005) 103:1457–67. doi: 10.1002/cncr.20910

5. Denlinger CS, Carlson RW, Are M, Baker KS, Davis E, Edge SB, et al. Survivorship: introduction and definition. *JNCCN.* (2014) 12:34–45. doi: 10.6004/jnccn.2014.0005

6. Ness KK, Mertens AC, Hudson MM, Wall MM, Leisenring WM, Oeffinger KC, et al. Limitations on physical performance and daily activities among long-term survivors of childhood cancer. *Ann Intern Med.* (2005) 143:639–47. doi: 10.7326/0003-4819-143-9-200511010-00007

7. Bekkering WP, Vliet Vlieland TP, Koopman HM, Schaap GR, Bart Schreuder HW, Beishuizen A, et al. Functional ability and physical activity in children and young adults after limb-salvage or ablative surgery for lower extremity bone tumors. *J Surg Oncol.* (2011) 103:276–82. doi: 10.1002/jso.21828

8. Riggs L, Bouffet E, Laughlin S, Laperriere N, Liu F, Skocic J, et al. Changes to memory structures in children treated for posterior fossa tumors. *J Int Neuropsychol Soc.* (2014) 20:168–80. doi: 10.1017/S135561771300129X

9. Piscione PJ, Bouffet E, Mabbott DJ, Shams I, Kulkarni AV. Physical functioning in pediatric survivors of childhood posterior fossa brain tumors. *Neuro Oncol.* (2014) 16:147–55. doi: 10.1093/neuonc/not138

10. Marina N, Hudson MM, Jones KE, Mulrooney DA, Avedian R, Donaldson SS, et al. Changes in health status among aging survivors of pediatric upper and lower extremity sarcoma: a report from the childhood cancer survivor study. *Arch Phys Med Rehabil.* (2013) 94:1062–73. doi: 10.1016/j.apmr.2013.01.013

11. Fernandez-Pineda I, Hudson MM, Pappo AS, Bishop MW, Klosky JL, Brinkman TM, et al. Long-term functional outcomes and quality of life in adult survivors of childhood extremity sarcomas: a report from the St.Jude Lifetime Cohort Study. *J Cancer Survivorship.* (2017) 11:1–12. doi: 10.1007/s11764-016-0556-1

12. Ness KK, Leisenring WM, Huang S, Hudson MM, Gurney JG, Whelan K, et al. Predictors of inactive lifestyle among adult survivors of childhood cancer. *Cancer.* (2009) 115:1984–94. doi: 10.1002/cncr.24209

13. Ness KK, Hudson MM, Ginsberg JP, Nagarajan R, Kaste SC, Marina N, et al. Physical performance limitations in the Childhood Cancer Survivor Study cohort. *J Clin Oncol.* (2009) 27:2382. doi: 10.1200/JCO.2008.21.1482

14. Strong WB, Malina RM, Blimkie CJR, Daniels SR, Dishman RK, Gutin B, et al. Evidence based physical activity for school-age youth. *J Pediatr.* (2005) 146:732–7. doi: 10.1016/j.jpeds.2005.01.055

15. Morales J, Valenzuela PL, Olivares AM, Baño-Rodrigo A, Castillo-García A, Rincon C, et al. Exercise Interventions and Cardiovascular Health in Childhood Cancer: a Meta-Analysis. International *J* Sports Medicine. 2020;41. doi: 10.1055/a-1073-8104

16. Braam KI, van der Torre P, Takken T, Veening MA, van Dulmen-den Broeder E, Kaspers GJ. Physical exercise training interventions for children and young adults during and after treatment for childhood cancer. *Cochr Datab System Rev.* (2016) 3:CD008796. doi: 10.1002/14651858.CD008796.pub3

17. Wurz A, McLaughlin E, Lategan C, Chamorro Viña C, Grimshaw SL, Hamari L, et al. The international Pediatric Oncology Exercise Guidelines (iPOEG). *Transl Behav Med.* (2021) 11:1915–22. doi: 10.1093/tbm/ibab028

18. Ospina PA, McNeely ML, A. Scoping Review of Physical Therapy Interventions for Childhood Cancers. *Physiother Canada.* (2019) 71:287–96. doi: 10.3138/ptc.2018-13.pp

19. Caru M, Levesque A, Rao P, Dandekar S, Terry C, Brown V, et al. A scoping review to map the evidence of physical activity interventions in post-treatment adolescent and young adult cancer survivors. *Crit Rev Oncol Hematol.* (2022) 171:103620. doi: 10.1016/j.critrevonc.2022.103620

20. Brunet J, Wurz A, Shallwani SM, A. scoping review of studies exploring physical activity among adolescents and young adults diagnosed with cancer. *Psychooncology.* (2018) 27:1875–88. doi: 10.1002/pon.4743

21. Rustler V, Hagerty M, Daeggelmann J, Marjerrison S, Bloch W, Baumann FT. Exercise interventions for patients with pediatric cancer during inpatient acute care: A systematic review of literature. *Pediatric Blood Cancer.* (2017) 64:e26567. doi: 10.1002/pbc.26567

22. Beller R, Bennstein SB, Götte M. Effects of exercise interventions on immune function in children and adolescents with cancer and HSCT recipients - a systematic review. *Front Immunol.* (2021) 12:746171. doi: 10.3389/fimmu.2021.746171

23. Santos SDS, Moussalle LD, Heinzmann-Filho JP. Effects of physical exercise during hospitalization in children and adolescents with cancer: a systematic review. *Rev Paulista de Pediatria.* (2020) 39:e2019313. doi: 10.1590/1984-0462/2021/39/2019313

24. Donnan BM, Webster T, Wakefield CE, Dalla-Pozza L, Alvaro F, Lavoipierre J, et al. What about school? Educational challenges for children and adolescents with cancer the educational and developmental. *Psychologist.* (2015) 32:23–40. doi: 10.1017/edp.2015.9

25. Casey DL, Cheung N-KV. Immunotherapy of pediatric solid tumors: treatments at a crossroads, with an emphasis on antibodies. *Cancer Immunol Res.* (2020) 8:161–6. doi: 10.1158/2326-6066.CIR-19-0692

26. Merchant TE, Kortmann R-D. *Pediatric Radiation Oncology*. 1st ed Cham: Springer International Publishing. (2018). doi: 10.1007/978-3-319-43545-9_1

27. Hayat MA. *Pediatric Cancer, Volume 2 Teratoid/Rhabdoid, Brain Tumors, and Glioma.* 1st ed. 2012. ed. Dordrecht: Springer Netherlands. (2012). doi: 10.1007/978-94-007-2957-5

28. Gmelig Meyling C, Verschuren O, Rentinck IR, Engelbert RHH, Gorter JW. Physical rehabilitation interventions in children with acquired brain injury: a scoping review. *Dev Med Child Neurol.* (2021). doi: 10.1111/dmcn.14997

29. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med.* (2018) 169:467–73. doi: 10.7326/M18-0850

30. Moseley AM, Herbert RD, Sherrington C, Maher CG. Evidence for physiotherapy practice: A survey of the Physiotherapy Evidence Database (PEDro). *Austr J Physiother.* (2002) 48:43–9. doi: 10.1016/S0004-9514(14)60281-6

31. Cashin AG, McAuley JH. Clinimetrics: Physiotherapy Evidence Database (PEDro) Scale. *J Physiother.* (2020) 66:59. doi: 10.1016/j.jphys.2019.08.005

32. Corr AM, Liu W, Bishop M, Pappo A, Srivastava DK, Neel M, et al. Feasibility and functional outcomes of children and adolescents undergoing preoperative chemotherapy prior to a limb-sparing procedure or amputation. *Rehabil Oncol.* (2017) 35:38–45. doi: 10.1097/01.REO.0000000000000050

33. Cox E, Bells S, Timmons BW, Laughlin S, Bouffet E, de Medeiros C, et al. A controlled clinical crossover trial of exercise training to improve cognition and neural communication in pediatric brain tumor survivors. *Clin Neurophysiol.* (2020) 131:1533–47. doi: 10.1016/j.clinph.2020.03.027

34. Riggs L, Piscione J, Laughlin S, Cunningham T, Timmons BW, Courneya KS, et al. Exercise training for neural recovery in a restricted sample of pediatric brain tumor survivors: a controlled clinical trial with crossover of training versus no training. *Neuro Oncol.* (2017) 19:440–50. doi: 10.1093/neuonc/now177

35. Piscione PJ, Bouffet E, Timmons B, Courneya KS, Tetzlaff D, Schneiderman JE, et al. Exercise training improves physical function and fitness in long-term paediatric brain tumour survivors treated with cranial irradiation. *Eur J Cancer.* (2017) 80:63–72. doi: 10.1016/j.ejca.2017.04.020

36. Szulc-Lerch KU, Timmons BW, Bouffet E, Laughlin S, de Medeiros CB, Skocic J, et al. Repairing the brain with physical exercise: Cortical thickness and brain volume increases in long-term pediatric brain tumor survivors in response to a structured exercise intervention. *Neuroimage-Clin.* (2018) 18:972–85. doi: 10.1016/j.nicl.2018.02.021

37. Ovans J, Hooke MC, Bendel AE, Tanner L. Physical therapist coaching to improve physical activity in children with brain tumors: a pilot study. *Pediatr Phys Ther.* (2018) 30:310–7. doi: 10.1097/PEP.0000000000000531

38. Sparrow J, Zhu L, Gajjar A, Mandrell BN, Ness KK. Constraint-induced movement therapy for children with brain tumors. *Pediat Phys Ther.* (2017) 29:55–61. doi: 10.1097/PEP.0000000000000331

39. Hooke MC, Hoelscher A, Tanner LR, Langevin M, Bronas UG, Maciej A, et al. Kids are moving: a physical activity program for children with cancer. *J Pediatr Oncol Nursing.* (2019) 36:379–89. doi: 10.1177/1043454219858607

40. Fiuza-Luces C, Padilla JR, Soares-Miranda L, Santana-Sosa E, Quiroga JV, Santos-Lozano A, et al. Exercise intervention in pediatric patients with solid tumors: the physical activity in pediatric cancer trial. *Med Sci Sports Exerc.* (2017) 49:223–30. doi: 10.1249/MSS.0000000000001094

41. Sabel M, Sjolund A, Broeren J, Arvidsson D, Saury JM, Blomgren K, et al. Active video gaming improves body coordination in survivors of childhood brain tumours. *Disabil Rehabil.* (2016) 38:2073–84. doi: 10.3109/09638288.2015.1116619

42. Sabel M, Sjolund A, Broeren J, Arvidsson D, Saury JM, Gillenstrand J, et al. Effects of physically active video gaming on cognition and activities of daily living in childhood brain tumor survivors: a randomized pilot study. *Neuro-Oncol Pract.* (2017) 4:98–110. doi: 10.1093/nop/npw020

43. Müller C, Krauth K, Gerß J, Rosenbaum D. Physical activity and health-related quality of life in pediatric cancer patients following a 4-week inpatient rehabilitation program. *Suppor Care Cancer.* (2016) 24:3793–802. doi: 10.1007/s00520-016-3198-y

44. Müller C, Rosenbaum D, Krauth KA. Prospective evaluation of postural control and gait in pediatric patients with cancer after a 4-week inpatient rehabilitation program. *Am J Phys Med Rehabil.* (2017) 96:646–53. doi: 10.1097/PHM.0000000000000729

45. Müller C, Winter C, Boos J, Gosheger G, Hardes J, Vieth V, et al. Effects of an exercise intervention on bone mass in pediatric bone tumor patients. *Int J Sports Med.* (2014) 35:696–703. doi: 10.1055/s-0033-1358475

46. Spreafico F, Barretta F, Murelli M, Chisari M, Gattuso G, Terenziani M, et al. Positive impact of organized physical exercise on quality of life and fatigue in children and adolescents with cancer. *Front Pediatr.* (2021) 9:627876. doi: 10.3389/fped.2021.627876

47. Fiuza-Luces RC, Padilla SJ, Valentín JJ, Santana-Sosa JE, Santos-Lozano JA, Sanchis-Gomar JF, et al. Effects of exercise on the immune function of pediatric patients with solid tumors: insights from the PAPEC randomized trial. *Am J Phys Med Rehabil.* (2017) 96:831–7. doi: 10.1097/PHM.0000000000000757

48. Govardhan HB, Nelson N, Khaleel IA, Kumar A, Roy M, Divyashree S, et al. Effect of yoga on the symptomps response in pediatric brain tumor in-patients undergoing chemo and radiotherapy. *Oncol Radiother.* (2019) 1:034–8.

49. McDougall J, Wright V, Rosenbaum P. The ICF model of functioning and disability: incorporating quality of life and human development. *Dev Neurorehabil.* (2010) 13:204–11. doi: 10.3109/17518421003620525

50. International Classification of Functioning. *Disability and Health Children and Youth Version ICF-CY.* Albany: World Health Organization. (2006).

51. Bradford N, Cashion C, Condon P, Rumble S, Bowers A. Recruitment principles and strategies for supportive care research in pediatric oncology. *BMC Med Res Methodol.* (2021) 21:178. doi: 10.1186/s12874-021-01371-1

52. Kazdin AE. *Single-Case Research Designs: Methods for Clinical and Applied Settings.* 2nd ed New York: Oxford University Press. (2011).

53. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ.* (2009) 338:b2393. doi: 10.1136/bmj.b2393

54. Novak I, Morgan C. High-risk follow-up: Early intervention and rehabilitation. *Handb Clin Neurol.* (2019) 162:483–510. doi: 10.1016/B978-0-444-64029-1.00023-0

55. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *J Speech, Language, Hear Res.* (2008) 51:S225–S39. doi: 10.1044/1092-4388(2008/018)

56. Power EA, Rechberger JS, Gupta S, Schwartz JD, Daniels DJ, Khatua S. Drug delivery across the blood-brain barrier for the treatment of pediatric brain tumors – An update. *Adv Drug Deliv Rev.* (2022) 185:114303. doi: 10.1016/j.addr.2022.114303

57. Reed DR, Hayashi M, Wagner L, Binitie O, Steppan DA, Brohl AS, et al. Treatment pathway of bone sarcoma in children, adolescents, and young adults. *Cancer.* (2017) 123:2206–18. doi: 10.1002/cncr.30589

58. Bekkering WP, Vliet Vlieland TP, Koopman HM, Schaap GR, Schreuder HW, Beishuizen A, et al. Quality of life in young patients after bone tumor surgery around the knee joint and comparison with healthy controls. *Pediatric Blood Cancer.* (2010) 54:738–45. doi: 10.1002/pbc.22439

59. Ross WL, Le A, Zheng DJ, Mitchell H-R, Rotatori J, Li F, et al. Physical activity barriers, preferences, and beliefs in childhood cancer patients. *Support Care Cancer.* (2018) 26:2177–84. doi: 10.1007/s00520-017-4041-9

60. Wright M. Physical activity participation and preferences: developmental and oncology-related transitions in adolescents treated for cancer. *Physiother Canada.* (2015) 67:292–9. doi: 10.3138/ptc.2014-25LHC

61. Liguori G, Feito Y, Fountaine C, Roy B. *ACSM's Guidelines for Exercise Testing and Prescription*. Eleventh ed Philadelphia: Wolters Kluwer. (2022).

62. Okely AD, Ghersi D, Loughran SP, Cliff DP, Shilton T, Jones RA, et al. A collaborative approach to adopting/adapting guidelines. The Australian 24-hour movement guidelines for children (5–12 years) and young people (13–17 years): An integration of physical activity, sedentary behaviour, and sleep. *Int J Behav Nutr Phys Activity*. (2022) 19:1–21. doi: 10.1186/s12966-021-01236-2

63. Mead N, Bower P. Patient-centredness: a conceptual framework and review of the empirical literature. *Soc Sci Med.* (2000) 51:1087–110. doi: 10.1016/S0277-9536(00)00098-8

64. Wijma AJ, Bletterman AN, Clark JR, Vervoort S, Beetsma A, Keizer D, et al. Patient-centeredness in physiotherapy: What does it entail? A systematic review of qualitative studies. *Physiother Theory Pract.* (2017) 33:825–40. doi: 10.1080/09593985.2017.1357151

65. Adair B, Ullenhag A, Keen D, Granlund M, Imms C. The effect of interventions aimed at improving participation outcomes for children with disabilities: a systematic review. *Dev Med Child Neurol.* (2015) 57:1093–104. doi: 10.1111/dmcn.12809

66. Reedman S, Boyd RN, Sakzewski L. The efficacy of interventions to increase physical activity participation of children with cerebral palsy: a systematic review and meta-analysis. *Dev Med Child Neurol.* (2017) 59:1011–8. doi: 10.1111/dmcn.13413

67. Deci EL, Ryan RM. Self-determination theory in health care and its relations to motivational interviewing: a few comments. *Int J Behav Nutr Phys Act.* (2012) 9:24. doi: 10.1186/1479-5868-9-24

68. Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. *Am Psychol.* (2000) 55:68. doi: 10.1037/0003-066X.55.1.68

69. Michie S, van Stralen MM, West R. The behaviour change wheel: A new method for characterising and designing behaviour change interventions. *Implementation Sci.* (2011) 6:42. doi: 10.1186/1748-5908-6-42

70. Blackburn NE, Wilson JJ, McMullan II, Caserotti P, Giné-Garriga M, Wirth K, et al. The effectiveness and complexity of interventions targeting sedentary behaviour across the lifespan: a systematic review and meta-analysis. *Int J Behav Nutr Phys Activity.* (2020) 17:53. doi: 10.1186/s12966-020-00957-0

71. Novak I, McIntyre S, Morgan C, Campbell L, Dark L, Morton N, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. *J Develop Med Child Neurol.* (2013) 55:885–910. doi: 10.1111/dmcn.12246

72. Willis C, Nyquist A, Jahnsen R, Elliott C, Ullenhag A. Enabling physical activity participation for children and youth with disabilities following a goal-directed, family-centred intervention. *Res Dev Disabil.* (2018) 77:30–9. doi: 10.1016/j.ridd.2018.03.010

73. Palisano RJ, Chiarello LA, King GA, Novak I, Stoner T, Fiss A. Participation-based therapy for children with physical disabilities. *Disabil Rehabil.* (2012) 34:1041–52. doi: 10.3109/09638288.2011.628740

74. Grimshaw S, Taylor N, Conyers R, Shields N. Promoting positive physical activity behaviours for children and adolescents with cancer: development of the canmove intervention using the behaviour change wheel. *Pediatr Blood Cancer.* (2021) 68:S352.

75. Kohler BE, Baque E, Sandler CX, Brookes DSK, Terranova CO, Rixon M, et al. Physical ACTivity in Survivorship (PACTS): study protocol for a randomized controlled trial evaluating a goal-directed therapeutic exercise program in pediatric posterior fossa brain tumor survivors. *BMC Pediatr.* (2021) 21:105. doi: 10.1186/s12887-021-02566-7

76. Brown MC, Araújo-Soares V, Skinner R, Glaser AW, Sarwar N, Saxton JM, et al. Using qualitative and co-design methods to inform the development of an intervention to support and improve physical activity in childhood cancer survivors: a study protocol for BEing Active after ChildhOod caNcer (BEACON). *BMJ Open.* (2020) 10:e041073. doi: 10.1136/bmjopen-2020-041073

77. Söntgerath R, Däggelmann J, Kesting SV, Rueegg CS, Wittke T-C, Reich S, et al. Physical and functional performance assessment in pediatric oncology: a systematic review. *Pediatr Res.* (2022) 91:743–56. doi: 10.1038/s41390-021-01523-5

78. Grimshaw SL, Taylor NF, Mechinaud F, Shields N. Assessment of physical function in children with cancer: A systematic review. *Pediatr Blood Cancer*. (2018) 65:e27369-n/a. doi: 10.1002/pbc.27369

79. Shank J, Chamorro-Viña C, Guilcher GMT, Langelier DM, Schulte F, Culos-Reed SN. Evaluation tools for physical activity programs for childhood cancer: a scoping review. *J Pediatr Oncol Nurs*. (2020) 37:163–79. doi: 10.1177/1043454219891987

80. Coster W, Bedell G, Law M, Khetani MA, Teplicky R, Liljenquist K, et al. Psychometric evaluation of the participation and environment measure for children and youth. *Dev Med Child Neurol*. (2011) 53:1030–7. doi: 10.1111/j.1469-8749.2011.04094.x

81. Law M, Polatajko H, Pollock N, McColl MA, Carswell A, Baptiste S. Pilot testing of the Canadian Occupational Performance Measure: clinical and measurement issues. *Canad J Occup Ther*. (1994) 61:191–7. doi: 10.1177/000841749406100403

82. Steenbeek D, Ketelaar M, Galama K, Gorter JW. Goal attainment scaling in paediatric rehabilitation: a critical review of the literature. *Dev Med Child Neurol*. (2007) 49:550–6. doi: 10.1111/j.1469-8749.2007.00550.x

frontiers | Frontiers in Pediatrics

TYPE Perspective
PUBLISHED 27 September 2022
DOI 10.3389/fped.2022.980257

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Oncology, a section of the journal Frontiers in Pediatrics

RECEIVED 28 June 2022
ACCEPTED 01 September 2022
PUBLISHED 27 September 2022

CITATION
Pouplier A, Larsen HB, Christensen J, Schmidt-Andersen P, Winther H and Fridh MK (2022) The rehabilitation including structured active play (RePlay) model: A conceptual model for organizing physical rehabilitation sessions based on structured active play for preschoolers with cancer. *Front. Pediatr.* 10:980257. doi: 10.3389/fped.2022.980257

The rehabilitation including structured active play (RePlay) model: A conceptual model for organizing physical rehabilitation sessions based on structured active play for preschoolers with cancer

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Anti-cancer treatments, as well as cancer itself, reduce children's cardiorespiratory fitness, muscle strength, and gross motor functions. Early rehabilitation programs, including physical activity for childhood cancer patients, can counteract these adverse effects. Previous studies of school-aged children (6–18 years old) indicate that physical activity, including aerobic and resistance training, is safe, feasible, and effective. The goal of structured physical activity rehabilitation for preschool children (1–5 years old) is to support gross motor development and opportunities to move freely in various ways. Specific rehabilitation for preschoolers diagnosed with cancer is needed to promote physical-, social-, and personal development. This paper introduces a conceptual model—The RePlay (Rehabilitation including structured active play) Model—for organizing physical rehabilitation sessions based on structured active play for preschoolers with cancer. The theory and empirically based model combine knowledge of early childhood development, play, physical activity and rehabilitation for children with cancer, and cancer treatment. With this model, we propose how to structure rehabilitation sessions, including goal-oriented, age-sensitive, fun movement activities that facilitate preschoolers to develop gross motor skills while enhancing their social and personal skills, through four core principles: (1) ritual practices, (2) reinforcement of movement through repetition, (3) development through appropriate challenge, and (4) adjusting activities to accommodate

treatment-related side effects. This model holds promise for use with preschoolers diagnosed with cancer, as it is scalable and pragmatic and accounts for the children's fluctuating physical capacity and daily wellbeing during cancer treatment.

KEYWORDS

pediatric oncology, preschoolers, rehabilitation, structured active play, physical activity, gross motor skills, social skills, personal skills

Introduction

The combination of anti-cancer treatments, infections, long-term bed rest, and cancer itself reduces the cardiorespiratory fitness, muscle strength, and gross motor functions (e.g., jumping, running, throwing) of children with cancer (1–4). These impairments become evident early in treatment, leading to physical inactivity and increasing the risk of delaying important gross motor development milestones in early childhood (5). Moreover, these impairments affect long-term physical health (6, 7). Thus, early initiated rehabilitation programs are warranted for children with cancer to ameliorate the physical consequences of cancer itself and of anti-cancer treatments. Accordingly, The International Pediatric Oncology Exercise Guidelines (iPOEG) recommend children with cancer to be physically active and do what they can, when they can (8). Rehabilitation programs focusing on cardiorespiratory fitness and muscle strength have been tested for children with cancer from 4 years of age (3, 9–12). Of these studies including children with cancer, the most structured exercise interventions followed well-established guidelines for aerobic- and resistance training sessions developed for healthy populations (13, 14). These sessions included 30–40 min of aerobic/endurance training followed by ∼30 min of resistance training, including one to three sets of 6–15 repetitions for major muscle groups, with progressive exercise volume over time (10, 12). Rehabilitation programs for older children and adolescents with cancer are unsuitable for preschool children, as preschoolers are motivated to be physically active because of their need to play, learn new skills, express themselves, and interact with others (15). Furthermore, health benefits are seldom a motivating factor for children with cancer (16). Instead, they underline the social aspect of physical activity as motivating (17). A new approach involving physical activity programs based on different principles and guidelines is warranted for preschoolers with cancer (age 1–5 years).

Physical activity in early childhood is positively associated with gross motor development, and there is a positive relationship between the development of gross motor skills, social cognition, language, and social interactions (18, 19). Accordingly, a rehabilitation program for preschoolers should include gross motor skills-, social-, and personal development, as these are interdependent (15, 20, 21). Children explore their capabilities, themselves, and others, through movement and play. They discover their movement possibilities, forming their confidence in movement and an "I can" mentality (22). Play is the children's arena for engaging and interacting with the world around them. It allows children to develop physically, socially, and personally within a world they can master with creativity and imagination (15, 23). They realize the ability to make something happen, and a distinction between instinctive movement and willful movement occurs (22).

Sufficient development of gross motor skills through movement is fundamental for: (a) engaging in social and physical activity during childhood, (b) ensuring the development of more complex movement skills, and (c) participation in physical activities throughout life (18, 24, 25). A way to achieve this is for the children to participate in structured physical activity facilitated by adults (e.g., parents, healthcare professionals, exercise professionals, teachers) and in the form of structured active play (15, 26).

In this paper, we introduce a conceptual model—The RePlay (Rehabilitation including structured active play) Model—for organizing physical rehabilitation sessions based on structured active play for preschoolers with cancer.

Development of the rehabilitation including structured active play (RePlay) model

The RePlay Model is based on knowledge of early childhood development (25–31), physical activity-based rehabilitation interventions for children with cancer during treatment (2, 3, 17, 32–36), and empirically based experience with structured active play with healthy preschoolers and their parents.

The concept of structured active play used in this paper refers specifically to instructor-led (e.g., parents, healthcare professionals, exercise professionals, teachers) sessions of goal-oriented, age-sensitive, fun movement activities that facilitate preschoolers to develop gross motor skills while enhancing their social and personal skills (20, 23, 37). Structured active play allows children to develop positive attitudes to physical activity, which is essential for: (1) gross motor development (e.g., learning to jump, run, and throw), ensuring

movement possibilities and participation in physical activity, (2) social development (e.g., learning to take turns, being patient, working together) ensuring good relationships and participation in activities with others, and (3) personal development (e.g., self-esteem, realizing abilities, confidence in movement) ensuring motivation for being physically active and taking on new challenges (37, 38). To ensure all three aspects in structured active play for children with cancer, we decided on four core principles for the model: (1) ritual practices, (2) reinforcement of movement through repetition, (3) development through appropriate challenge, and (4) adjusting activities to accommodate treatment-related side effects. The principles were defined from literature about childhood development. The principles were discussed among the author group with backgrounds in human physiology, humanities and social sport sciences, physiotherapy, sociology, and several years of experience within the field of exercise and childhood oncology. In the following, the four core principles is elaborated and why they are important to the rehabilitation of preschool children with cancer. A summary of the four core principle is presented in **Table 1**.

Ritual practices

In early childhood, rituals help to guide behavior and support development. They contribute to a predictable structure and a secure environment in everyday life (27, 28). Children with cancer and their families experience disruptions to their daily activities and routines, as the treatment is characterized by lack of continuity, and they experience constant adjustment of old routines and the establishment of new ones (39, 40). Accordingly, creating routines around physical activity and a predictable structure is important, especially for preschoolers with cancer.

Intentional rituals ease the approach to the routine of structured active play. This is achieved by including a repeated beginning and ending ritual, hereby creating the frame around the sessions and creating certainty and familiarity for the children. The rituals thus symbolize the transition into and out of the structured active play sessions. The rituals have a social (rather than physical) purpose. They are done in a circle, whereby the participants (i.e., children, parents, instructors) can all see each other and feel seen. This creates an inclusive environment in which we start and end together. A starting and ending ritual could be a song which is performed with added movements. Following the starting ritual and preceding the ending rituals should be a known activity—a familiar, active play activity. This known activity is one with which the children are familiar and that everyone can master independently. The known activity ensures that every child feels they can participate, even if functional levels vary from child to child. These activities are core elements that will ensure that physical activity becomes a routine with recognizable and repeated elements and where all sessions begin and end with a successful experience for all children.

TABLE 1 A summary of the four core principles.

A summary of four core principles				
Principle	**1 Ritual practices**	**2 Reinforcement of movement through repetition**	**3 Development through appropriate challenge**	**4 Adjusting activities to accommodate treatment-related side effects**
Reasoning	Creating a routine around the structured active play with a ritual creates familiarity.	Gross motor development and gross motor skills need to be sustained through repetition, also to maintain an "I can"-mentality around movement.	The child must be challenged in new activities and gross motor functions to develop new movement skills. However, the challenge must be appropriate	Anti-cancer treatment leads to substantial variation in the children's daily physical capacity and motivation.
What it does	Familiar rituals create certainty for the children, as well as an inclusive environment in which we start and end together.	Repetition–both through activity and movement type–will reinforce movement possibilities and ensure confidence in and sustainability of movement.	Too many activities that are too simple can promote boredom, where too many activities that are too challenging become frustrating and create the "I can't" feeling. Activities with appropriate challenges will evoke motivation and development.	Adjusting known or new activities from session to session can be necessary to ensure participation and that the challenge is still appropriate.
How it is done	Including a starting and ending ritual which is the same every session.	Performing known activities and repetition of movement patterns, including known and new gross motor skills.	Most of the main active play activities within a session should be appropriately challenging (i.e., in the zone of proximal development.)	It can be duration adjustments, but also regressing or progressing activities to a suitable motor development level.

Reinforcement of movement through repetition

The repeated rituals and known activities create familiar routines for the children. However, repetitions also reinforce movement. Gross motor functions are developed through guidance (verbal or physical), encouragement, and practice (25, 37). Children discover movement possibilities and corporeal powers through movement. This forms confidence in moving and creates an "I can"-mentality (22). If gross motor development is not sustained, early movement failures can result, leading to physical inactivity (37). This affects the child's self-esteem, feeling of mastery, and movement possibilities—leading to an "I can't"-mentality (22, 25, 37). Mastery experiences are essential for our belief in our abilities and self-efficacy, and continued success reinforces this belief (29, 30). Repetition of movement patterns, including known and new gross motor skills, will reinforce movement possibilities and sustain known gross motor skills and develop new ones. Children with cancer experience changes in their physical capabilities, movement possibilities, and associated self-esteem (41). They may experience their body letting them down and consequently find themselves being unable to do what they did before cancer and what other children can do (41). The children's changes in experiences from movement possibilities to movement impossibilities can change their "I can" to "I can't" (22). Hence, repeated activities through routines and repeated movement patterns ensure confidence in- and sustainability of movement. This can be exemplified with the obstacle course as an activity that is repeated from session to session, where it is possible for the child to practice and advance their abilities on the course. It can also be e repeated movement pattern like throwing several balls again and again in the same activity. When an activity or movement pattern is repeated it creates an opportunity for the child to gain continued successes in a known activity.

Development through appropriate challenge

Repetition and mastery experiences are closely linked to the third principle of development through appropriate challenge. Appropriately challenging a child's current level of gross motor function elicits physical adaptations, also known as progressive overload (42). The child must be challenged in new activities and gross motor functions to develop new movement skills and avoid monotonous activities, leading to demotivation. If the current level of gross motor function is not disrupted by progressive overload, adaptations will not occur (42). Appropriate challenges require encouragement and guidance to support the child in mastering the challenge (25, 29–31, 37). "Appropriate challenge" refers to Lev Vygotsky's concept of the zone of proximal development (31). **Figure 1** depicts a model based on already existing interpretations of the zone of proximal development (31, 43, 44). Too many activities that are too simple and already within mastery (green zone) can promote boredom. In contrast, excessively complex and challenging activities become frustrating and create the "I can't" feeling (red zone). Ultimately, this leads to mastery inexperience and no development of new skills (31). Activities with appropriate challenges will evoke motivation and development. An appropriate challenge is placed in the zone of proximal development (yellow zone), where the activity or skill is too complex for the child to master independently but manageable with guidance from a knowledgeable other (i.e., parent, healthcare professional, or peer) (31).

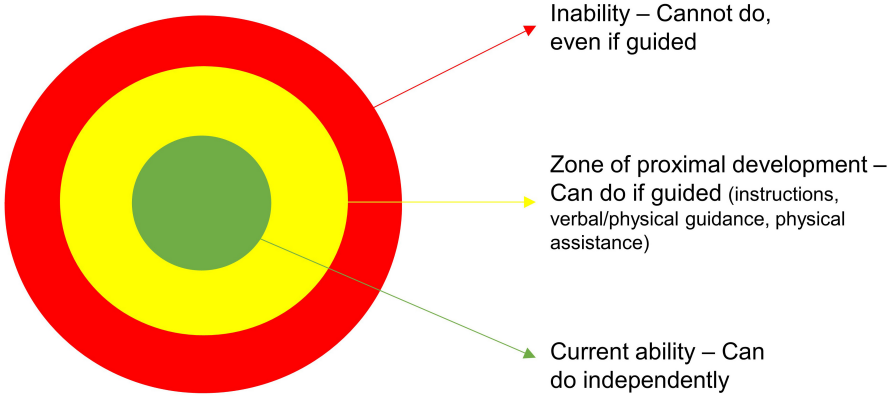

FIGURE 1
Zone of proximal development. This figure, including the colors, is based on already existing interpretations of the theory "Zone of proximal development" (31, 43, 44). In the zone of proximal development, there is a spectrum of level of guidance needed for the child to be able to do the activity (i.e., instructions, verbal/physical guidance, and physical assistance).

In the zone of proximal development, there is a spectrum of how much guidance is needed for the child to master the activity: instructions, verbal/physical guidance, or physical assistance. The social interactions are essential to learn new gross motor skills, as participating in the same activities and seeing others participate in the same activity can increase the feeling of mastery and an "if they can do it, I can do it"-mentality (22, 29, 30).

Main active play activities are the core of structured active play sessions. Here, the children's gross motor functions are challenged to either sustain or develop new movement skills. Main active play activities with repetition and guidance support the child to master experiences in known activities and new challenges. It is possible to adjust a known activity to challenge the child further, but still be within the zone of proximal development and with a sense of mastery through familiarity. For example, the child might have mastered an obstacle course with low obstacles. To challenge the child further an adjustment of the known activity is done by adding a balancing beam lifted from the ground. However, the child might now require instructions or physical guidance by showing the child how to balance over the beam, or physical assistance by holding the child's hand. In activities within the zone of proximal development with more than one child, the relative challenge can vary from child to child in the same activity; where one child needs instructions, another needs physical guidance. However, all children can participate with different level of guidance. Furthermore, the social interactions reinforce social development, as the knowledgeable peers must show patience, wait their turn, or even offer their support to children requiring guidance.

Adjusting activities to accommodate treatment-related side effects

The fourth principle is fundamental in childhood oncology. Anti-cancer treatment leads to substantial variation in the children's daily physical capacity and motivation. Corticosteroids are commonly used to treat several childhood cancers—causing an altered body composition (i.e., increased fat mass, myopathy and reduced muscle mass), reduced muscle strength and adverse psychological side effects (45–47), which affects the children's motivation and possibility to engage in structured active play. Moreover, the children can also experience dizziness, fatigue, and nausea affecting their daily physical capacity (48). This variation in physical capacity is also associated with severe neuropathic pain and peripheral neurotoxicity (i.e., a burning or prickling sensation in the peripheral limbs, sensory loss, numbness, muscle weakness, and pain) caused by chemotherapeutic agents, such as vincristine (49, 50). The severity of these symptoms can vary within hours, and they often limit the children's physical capabilities and motivation daily. Thus, daily considerations of safety parameters (i.e., hemoglobin >5.0 mmol/l; platelets >10 billion/l at moderate to intense activities; no active diarrhea, coughing, or cold; temperature $<38.0°C$; no severe comorbidities) along with physician clearing the patient for physical activity, to ensure that the children can participate in exercise and to ensure to proper adjustments are warranted. Adjusting known or new activities can then be necessary from session to session (and even within sessions) to ensure that the challenge remains within the zone of proximal development. Additionally, adjusting the duration of the entire session and/or the duration or number of main active play activities can become necessary. Consequently, the length of time of the active play session and main active play activities are proportional to the daily wellbeing of the participating children. Due to the nature of cancer treatment, this means regressing activities to a lower (but suitable) motor development level or level of energy expenditure in periods with restricting side effects and progressing activities in periods with fewer side effects. Practically, this is done by: (1) decreasing/increasing the demands of the activity (fewer/more limbs involved, execution with decreased/increased range of motion, or more extensive/minor base of support), (2) use of/no use of external support (e.g., from parents, instructor), (3) use of/no use of a more static execution of activities, and (4) decrease/increase of time spent in the structured active play activities.

For example, a child who is already familiar with the obstacle course as an activity but experiences an acute worsening of their physical capacity in the following session can still obtain a feeling of mastery and the will to complete a course. This can be done by adjusting the activity with: (a) more accessible (e.g., smaller, less movable) elements, (b) added assistance from parents, such as holding their hands, or (c) both. With these adjustments, the child can participate in the same activity and maintain the "I can"-mentality.

The rehabilitation including structured active play (RePlay) model

With The RePlay Model (**Figure 2**), we propose how to structure rehabilitation sessions, including goal-oriented, age-sensitive, fun movement activities that facilitate preschoolers to develop gross motor skills while enhancing their social and personal skills through the four core principles described above: (1) ritual practices, (2) reinforcement of movement through repetition, (3) development through appropriate challenge, and (4) adjusting activities to accommodate treatment-related side effects. The model was designed to depict how the level of challenge is relative, and the time used in each section of the session is proportional and can vary from day to day, depending on the child's daily physical capacity and wellbeing.

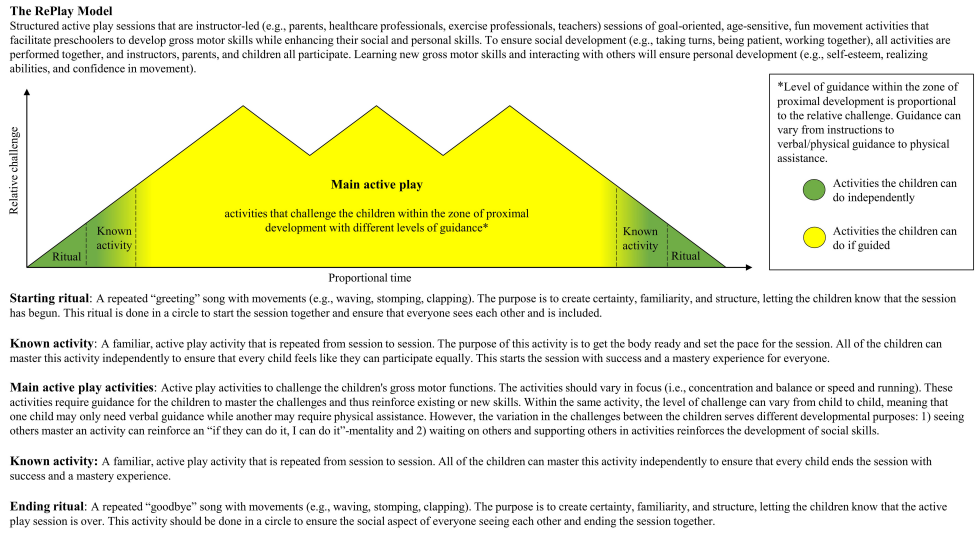

FIGURE 2
The RePlay model.

In **Supplementary File 1**, a version of the model can be found with practical examples of activities.

Discussion and future directions

The RePlay Model was developed to provide a framework to organize a rehabilitation session aimed at supporting gross motor-, social-, and personal development in preschool children with cancer (aged 1–5 years) during treatment. These children experience impaired gross motor function (1, 4) during treatment and are at risk of delaying or missing important developmental milestones in early childhood (5). Consequently, they require early initiated and continuous rehabilitation throughout their treatment trajectory. Following the principles of disrupting the child's current level of gross motor function through appropriate challenges and progressive overload (i.e., to elicit physical adaptations and gross motor function development) (42) is complex due to the side effects connected to the toxic nature of anti-cancer treatment. Safety parameters must be verified daily to determine participation in the rehabilitation sessions and activities must be adjusted to the child's fluctuating wellbeing. Instead of viewing appropriate challenge of activities as a linear progress, we present a model that considers adjustments of activities to the child's daily physical capabilities. The RePlay Model can be carried out by adults who have received instruction in it. The model is also applicable for children with all levels of gross motor function, for planning both individual- and group sessions, and can be integrated into most settings (e.g., hospital settings, home settings, school settings, outdoor settings). However, the model is not designed to monitor feasibility, adherence, and progression to physical activity interventions. Development of gross motor skills is central for preschool children and occurs through play. Consequently, well-established approaches for monitoring feasibility, adherence, and progression in physical activity interventions (e.g., heart rate, repetitions, resistance, rate of perceived exhaustion) is not suitable. We propose that registering time spent in each structured active play session, time spent in each activity, and percentage of overall time spent in main active play activities are suitable outcomes for evaluating feasibility and adherence within The RePlay Model. It is recommended that younger children (aged 1–5 years) are physically active at least 60 min each day, but preferably up to several hours (15, 51). Of this, 30–60 min should be structured physical activity facilitated by an adult (15). This also applies for children with cancer, however, iPOEG states that day-to-day differences must be taken into account and children should move when they can, as much as they can (8, 51). We propose a suitable timeframe for the model is between the 30 and 60 min with 75% of the time spent in main active play activities where the children are appropriately challenged on their current level. Progression can be monitored by registering and describing the change in the complexity of the main active play activities. This can be done by differentiating the activities in categories of levels of gross motor skills where activities are color-coded according to the child's achieved gross motor skill level (34, 52, 53). This description can help define the intensity and difficulty of each section of the session which cannot be described with usual parameters used for older children, adolescents, or adults. The RePlay model then might be used to track progression in an intervention as an addition to the validated gross motor assessment tools.

Children develop while they play, and all children want to play, even when undergoing anti-cancer treatment. An observational study showed that preschool children with cancer still play when they are negatively affected by anti-cancer treatment, but unstructured play becomes sedentary with the increasing severity of side effects (54). Thus, families of preschool children with cancer need support to engage in physical activity as structured active play during treatment to maintain gross motor-, social, and personal development. With preschool children, structured physical activity can be challenging. The RePlay Model is based on the world of the children and their approach to movement. Here, play, social interactions, rituals, repetition, and appropriate challenges are key components to being physically active. This approach helps to keep the children motivated to engage in active play. It is unlikely that you can motivate every child with the same play activities every session, as children are curious and driven by curiosity and imagination (23, 26). The possibility to improvise is therefore necessary within a structured frame to maintain motivation. To achieve this flexibility, however, researchers risk reducing the reproducibility of a physical activity intervention. In our opinion, The RePlay Model provides a structured framework for organizing and describing rehabilitation for preschool children with cancer in a reproducible manner, but still with the flexibility needed for this patient group. However, this remains to be investigated.

Already known structured exercise programs for children with cancer are designed using progressive exercise regimes including both aerobic- and resistance exercises (3, 9, 10, 12). In most studies of exercise programs for children and adolescents with cancer, the researchers modify the exercises according to the physical capacity of the child based on daily variability (3, 9, 10, 12), showing how, despite the intent, exercise with children and adolescents with cancer is difficult to structure similarly for each session. The RePlay Model therefore gives healthcare professionals and parents a structure for organizing a rehabilitation session that can help to sustain and stimulate the child's gross motor-, social- and personal development, even during hospitalization and active anti-cancer treatment.

The fundamental principles of The RePlay Model can theoretically be transferred to other groups of children, as play, rituals, repetition, and appropriate challenges are principles of general early childhood development. This also includes settings where gross motor, social, and personal development are the target in general (e.g., daycare, physical education classes). However, future research is needed to investigate the feasibility in these settings.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

AP, HW, and MKF drafted the model and the manuscript. All authors actively and substantially contributed to the final design of the model, contributed, read, and approved the final version.

Funding

This work was a part of the Childhood Oncology Network Targeting Research, Organization & Life expectancy (CONTROL), supported by the Danish Cancer Society (R-257-A14720) and the Danish Childhood Cancer Foundation (2019-5934). Furthermore, this study was supported explicitly by individual grants from the Danish Cancer Society (R-284-A16272-20-S15, R296-A16956, R327-A18909, and R335-A19468) and the Danish Childhood Cancer Foundation (2019-5947, 2020-6756, and 2021-7400). Funding sources played no role in the design or conduct of the study, collection of data, analysis, interpretation of results, preparation, review, approval of the manuscript, or decision to submit the manuscript for publication.

Acknowledgments

We would like to thank Jens Schmidt-Andersen for the illustrations used in **Supplementary File 1**.

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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.980257/full#supplementary-material

References

1. Ness KK, Kaste SC, Zhu L, Pui CH, Jeha S, Nathan PC, et al. Skeletal, neuromuscular and fitness impairments among children with newly diagnosed acute lymphoblastic leukemia. *Leuk Lymphoma.* (2015) 56:1004–11. doi: 10.3109/10428194.2014.944519

2. Thorsteinsson T, Larsen HB, Schmiegelow K, Thing LF, Krustrup P, Pedersen MT, et al. Cardiorespiratory fitness and physical function in children with cancer from diagnosis throughout treatment. *BMJ Open Sport Exerc Med.* (2017) 3:e000179. doi: 10.1136/bmjsem-2016-000179

3. Nielsen MKF, Christensen JF, Frandsen TL, Thorsteinsson T, Andersen LB, Christensen KB, 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.* (2020) 18:175. doi: 10.1186/s12916-020-01634-6

4. Vainionpää L. Clinical neurological findings of children with acute lymphoblastic leukaemia at diagnosis and during treatment. *Eur J Pediatr.* (1993) 152:115–9. doi: 10.1007/BF02072486

5. Nijhof SL, Vinkers CH, van Geelen SM, Duijff SN, Achterberg EJM, van der Net J, et al. Healthy play, better coping: The importance of play for the development of children in health and disease. *Neurosci Biobehav Rev.* (2018) 95:421–9. doi: 10.1016/j.neubiorev.2018.09.024

6. Oeffinger KC, Mertens AC, Sklar CA. Chronic health conditions in adult survivors of childhood cancer. *Oncol Times.* (2007) 29:26. doi: 10.1097/01.COT.0000265629.30194.8e

7. Ness KK, Mertens AC, Hudson MM, Wall MM, Leisenring WM, Oeffinger KC, et al. Limitations on physical performance and daily activities among long-term survivors of choldhood cancer. *Ann Intern Med.* (2005) 143:639–48. doi: 10.7326/0003-4819-143-9-200511010-00007

8. Wurz A, Mclaughlin E, Lategan C, Chamorro Vinã C, Grimshaw SL, Hamari L, et al. The international pediatric oncology exercise guidelines (iPOEG). *Transl Behav Med.* (2021) 11:1915–22. doi: 10.1093/tbm/ibab028

9. Stössel S, Neu MA, Wingerter A, Bloch W, Zimmer P, Paret C, et al. Benefits of exercise training for children and adolescents undergoing cancer treatment: Results from the randomized controlled MUCKI trial. *Front Pediatr.* (2020) 8:243. doi: 10.3389/fped.2020.00243

10. Fiuza-Luces C, Padilla JR, Soares-Miranda L, Santana-Sosa E, Quiroga JV, Santos-Lozano A, et al. Exercise intervention in pediatric patients with solid tumors: The physical activity in pediatric cancer trial. *Med Sci Sports Exerc.* (2017) 49:223–30. doi: 10.1249/MSS.0000000000001094

11. Lanfranconi F, Zardo W, Moriggi T, Villa E, Radaelli G, Radaelli S, et al. Precision-based exercise as a new therapeutic option for children and adolescents with haematological malignancies. *Sci Re.* (2020) 10:1–13. doi: 10.1038/s41598-020-69393-1

12. Morales JS, Santana-Sosa E, Santos-Lozano A, Baño-Rodrigo A, Valenzuela PL, Rincón-Castanedo C, et al. Inhospital exercise benefits in childhood cancer: A prospective cohort study. *Scand J Med Sci Sport.* (2020) 30:126–34. doi: 10.1111/sms.13545

13. Braith RW. Role of exercise in rehabilitation of cancer survivors. *Pediatr Blood Cancer.* (2005) 44:595–9. doi: 10.1002/pbc.20354

14. Faigenbaum AD, Kraemer WJ, Blimkie CJR, Jeffreys I, Micheli LJ, Nitka M, et al. Youth resistance training: Updated position statement paper from the national strength and conditioning association. *J Strength Cond Res.* (2009) 23:60–79. doi: 10.1519/JSC.0b013e31819df407

15. Virgilio SJ, Clements R. *Active start : A statement of physical activity guidelines for children from birth to age 5*. 3rd Editio ed. Baltimore, MD: SHAPE America (2020). 48 p.

16. Petersen NN, Hansson H, Lie HC, Brinkkjær M, Graungaard B, Hamilton Larsen M, et al. A qualitative study of young childhood cancer survivors and their parents' experiences with treatment-related late effects in everyday life post-treatment. *J Adv Nurs.* (2022) 78:858–68. doi: 10.1111/jan.15073

17. Thorsteinsson T, Schmiegelow K, Thing LF, Andersen LB, Helms AS, Ingersgaard MV, et al. Classmates motivate childhood cancer patients to participate in physical activity during treatment: A qualitative study. *Eur J Cancer Care.* (2019) 28:1–10. doi: 10.1111/ecc.13121

18. Timmons BW, Leblanc AG, Carson V, Gorber SC, Dillman C, Janssen I, et al. Systematic review of physical activity and health in the early years (aged 0-4 years). *Appl Physiol Nutr Metab.* (2012) 37:773–92. doi: 10.1139/h2012-070

19. Leonard HC, Hill EL. Review: The impact of motor development on typical and atypical social cognition and language: A systematic review. *Child Adolesc Ment Health.* (2014) 19:163–70. doi: 10.1111/camh.12055

20. Pellegrini AD, Smith PK. Physical activity play: The nature and function of a neglected aspect of play. *Child Dev.* (1998) 69:577–98. doi: 10.1111/j.1467-8624.1998.tb06226.x

21. National Association for Sport and Physical Education. *Active Start: A statement of Physical Activity Guidelines For Children From Birth To Age 5*. 2nd ed. Reston, VA: NASPE (2011).

22. Sheets-Johnstone M. *The primacy of movement. In: The primacy of movement expanded second edition*. 2nd ed. Amsterdam: John Benjamins Publishing Company (2011). p. 113–52. doi: 10.1075/aicr.82

23. Ginsburg KR, Shifrin DL, Broughton DD, Dreyer BP, Milteer RM, Mulligan DA, et al. The importance of play in promoting healthy child development and maintaining strong parent-child bonds. *Pediatrics.* (2007) 119:182–91. doi: 10.1542/peds.2006-2697

24. Wrotniak BH, Epstein LH, Dorn JM, Jones KE, Kondilis VA. The relationship between motor proficiency and physical activity in children. *Pediatrics* (2006) 118:e1758–65. doi: 10.1542/peds.2006-0742

25. Clark JE. On the problem of motor skill development. *J Phys Educ Recreat Danc.* (2007) 78:39–44. doi: 10.1080/07303084.2007.10598023

26. Zosh JM, Hirsh-Pasek K, Hopkins EJ, Jensen H, Liu C, Neale D, et al. Accessing the inaccessible: Redefining play as a spectrum. *Front Psychol.* (2018) 9:1124. doi: 10.3389/fpsyg.2018.01124

27. Gillespie L, Petersen S. Rituals and routines: Supporting infants and toddlers and their families. *Young Child.* (2012) 67:76–8. doi: 10.1093/sleep/32.5.599

28. Spagnola M, Fiese BH. Family routines and rituals. *Encycl Hum Relat.* (2013) 20:284–99. doi: 10.1097/01.IYC.0000290352.32170.5a

29. Bandura A. Self-efficacy: Towards a unifying theory of behavioral change. *Psychol Rev.* (1977) 84:191–215. doi: 10.1037//0033-295x.84.2.191

30. Bandura A. *Self-efficacy: The exercise of control*. New York, NY: Freeman (1997).

31. Vygotsky L. *Mind in society: The development of higher psychological processes*. Cambridge, MA: Harvard University Press (1978).

32. Thorsteinsson T, Helms AS, Adamsen L, Andersen LB, Andersen KV, Christensen KB, et al. Study protocol: Rehabilitation including social and physical activity and education in children and teenagers with cancer (RESPECT). *BMC Cancer.* (2013) 13:544. doi: 10.1186/1471-2407-13-544

33. Schmidt-Andersen P, Fridh MK, Müller KG, Pouplier A, Hjalgrim LL, Faigenbaum AD, et al. Integrative neuromuscular training in adolescents and children treated for cancer (INTERACT): Study protocol for a multicenter, two-arm parallel-group randomized controlled superiority trial. *Front Pediatr.* (2022) 10:833850. doi: 10.3389/fped.2022.833850

34. Pouplier A, Winther H, Christensen J, Schmidt-Andersen P, Zhang H, Frandsen TL, et al. Rehabilitation including structured active play for preschoolers with cancer (RePlay)—Study protocol for a randomized controlled trial. *Front Pediatr.* (2022) 10:834512. doi: 10.3389/fped.2022.834512

35. Nielsen MKF, Christensen JF, Frandsen TL, Thorsteinsson T, Andersen LB, Christensen KB, et al. Testing physical function in children undergoing intense cancer treatment—a RESPECT feasibility study. *Pediatr Blood Cancer.* (2018) 65:1–9. doi: 10.1002/pbc.27100

36. Nybro, N, Hanne P, Larsen B, Pouplier A, Andersen PS, Thorsteinsson T, et al. Childhood cancer survivors' and their parents' experiences with participation in a physical and social intervention during cancer treatment: A RESPECT study. *J Adv Nurs.* (2022) 00:1–11. doi: 10.1111/jan.15381

37. Garcia C, Garcia L, Floyd J, Lawson J. Improving public health through early childhood movement programs. *J Phys Educ Recreat Danc.* (2002) 73:27–31. doi: 10.1080/07303084.2002.10605876

38. Henderson K, Glancy M, Little S. Putting the fun into physical activity. *J Phys Educ Recreat Danc.* (1999) 70:43–5. doi: 10.1080/07303084.1999.10605706

39. Darcy L, Knutsson S, Huus K, Enskar K. The everyday life of the young child shortly after receiving a cancer diagnosis, from both children's and parent's perspectives. *Cancer Nurs.* (2014) 37:445–56. doi: 10.1097/NCC.0000000000000114

40. Hildenbrand AK, Clawson KJ, Alderfer MA, Marsac ML. Coping with pediatric cancer: Strategies employed by children and their parents to manage cancer-related stressors during treatment. *J Pediatr Oncol Nurs.* (2011) 28:344–54. doi: 10.1177/1043454211430823

41. Darcy L, Enskär K, Björk M. Young children's experiences of living an everyday life with cancer – A three year interview study. *Eur J Oncol Nurs.* (2019) 39:1–9. doi: 10.1016/j.ejon.2018.12.007

42. Faigenbaum AD, Lloyd RS, Oliver JL. *Essentials of youth fitness*. Champaign, IL: Human Kinetics (2019).

43. Senninger T. *Abenteuer leiten – in abenteuern lernen*. Münster: Ökotopia Verlag (2000).

44. Andersen MM. *Meaningful experiences. Developmental processes for adolescents and adults with cerebral palsy through resilience based, social sport– and movement initiatives*. Copenhagen: University of Copenhagen (2020).

45. Stuart FA, Segal TY, Keady S. Adverse psychological effects of corticosteroids in children and adolescents. *Arch Dis Child.* (2005) 90:500–6. doi: 10.1136/adc.2003.041541

46. Arpe MLH, Rørvig S, Kok K, Mølgaard C, Frandsen TL. The association between glucocorticoid therapy and BMI z-score changes in children with acute lymphoblastic leukemia. *Support Care Cancer*. (2015) 23:3573–80. doi: 10.1007/s00520-015-2718-5

47. Natsui K, Tanaka K, Suda M, Yasoda A, Sakuma Y, Ozasa A, et al. High-dose glucocorticoid treatment induces rapid loss of trabecular bone mineral density and lean body mass. *Osteoporos Int.* (2006) 17:105–8. doi: 10.1007/s00198-005-1923-3

48. Hooke MC, Linder LA. Symptoms in children receiving treatment for cancer—Part I: Fatigue, sleep disturbance, and nausea/vomiting. *J Pediatr Oncol Nurs.* (2019) 36:244–61. doi: 10.1177/1043454219849576

49. Carozzi VA, Canta A, Chiorazzi A. Chemotherapy-induced peripheral neuropathy: What do we know about mechanisms? *Neurosci Lett*. (2015) 596:90–107. doi: 10.1016/j.neulet.2014.10.014

50. Nielsen MKF, Larsen HB, Schmiegelow K, Christensen JF. Muscle dysfunction in childhood cancer: Biological mechanisms and implications for long-term survivorship. *EMJ Oncol.* (2016) 4:78–85.

51. Götte M, Söntgerath R, Gauß G, Wiskemann J, Buždon M, Kesting S. A national implementation approach for exercise as usual care in pediatric and adolescent oncology: Network activeoncokids. *Pediatr Exerc Sci.* (2022):1–8. doi: 10.1123/pes.2021-0218 [Epub ahead of print].

52. University of Minnesota. *Developmental skills for ages 4 to 5 years*. Minnesota: Fairview Health Services (2010).

53. University of Minnesota. *Developmental skills for ages 2 to 3 years*. Minnesota: Fairview Health Services (2010). p. 3–6.

54. Almqvist L, Hellnäs P, Stefansson M, Granlund M. "I can play!" young children's perceptions of health. *Pediatr Rehabil.* (2006) 8491:275–84. doi: 10.1080/13638490500521303

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 13 October 2022
DOI 10.3389/fped.2022.980890

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Oncology, a section of the journal Frontiers in Pediatrics

RECEIVED 29 June 2022
ACCEPTED 05 September 2022
PUBLISHED 13 October 2022

CITATION
Grimshaw SL, Taylor NF, Conyers R and Shields N (2022) Promoting positive physical activity behaviors for children and adolescents undergoing acute cancer treatment: Development of the CanMOVE intervention using the Behavior Change Wheel. *Front. Pediatr.* 10:980890. doi: 10.3389/fped.2022.980890

Promoting positive physical activity behaviors for children and adolescents undergoing acute cancer treatment: Development of the CanMOVE intervention using the Behavior Change Wheel

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Background: Increasing participation in physical activity has the potential to improve outcomes for children and adolescents with cancer during treatment and into survivorship. The aim of this study is to outline the theoretical process behind development of CanMOVE, a behavior change intervention designed to increase physical activity for children and adolescents with cancer.

Study design: This study followed a theoretical design process consistent with the Behavior Change Wheel to inform the design of a complex intervention.

Materials and methods: The three stages of the Behavior Change Wheel intervention design process include: (1) understanding physical activity behavior within the pediatric cancer setting, (2) identifying potential intervention functions, and (3) identifying appropriate behavior change and implementation strategies. Qualitative and behavior change literature relevant to the pediatric cancer treatment setting were used to inform each stage.

Results: An individualized and flexible approach to physical activity promotion that considers intrinsic factors specific to the child/adolescent and their environment is required. Fifteen behavioral change strategies were identified to form the intervention components of CanMOVE. Implementation strategies were identified to build motivation, opportunity and capacity toward increasing physical activity behaviors. Key intervention components of CanMOVE include standardized assessment and monitoring (physical activity, physical function, and health-related quality of life), provision of an activity

monitor to both child/adolescent and parent, and one-on-one capacity building sessions with a healthcare professional. Capacity building sessions include education, goal setting, an active supervised physical activity session, barrier identification and problem solving, and action planning.

Conclusion: CanMOVE is a novel approach to physical activity promotion in the pediatric cancer treatment setting. The use of a theoretical intervention design process will aid evaluation and replication of CanMOVE when it is assessed for feasibility in a clinical setting. The design process utilized here can be used as a guide for future intervention development.

KEYWORDS

cancer, child, adolescent, physical activity, Behavior Change Wheel, complex intervention development

Introduction

Childhood cancer and its treatment can cause adverse physical effects (1–5), evident from as early as one week following diagnosis (6). Muscle loss, reduced fitness, fatigue, and motor impairment are prevalent among children and adolescents undergoing acute cancer therapy. These adverse effects are not limited to the acute treatment phase. Adults who have undergone childhood cancer treatment display high levels of sedentary behavior, can experience lifelong disability and impairment, and are at an increased risk of chronic disease and premature mortality (7–9). A growing number of childhood cancer survivors are reaching adulthood, which increases the burden of these adverse outcomes (10). Intervening early could work to mitigate these negative effects and promote improved physical function and wellbeing in the immediate and long-term.

Physical activity is vital to health and development (11, 12), yet, children and adolescents undergoing acute cancer treatment are less active than their age-matched peers (13, 14). Children and adolescents can receive intensive cancer treatments over the course of many months (15). Over this time, adverse treatment effects can compromise a child's ability to be physically active and functionally independent. For this population, physical activity has a role to play in managing treatment-related effects, preventing (or minimizing) declines in physical function and mental health, maintaining physical literacy skills and promoting active lifestyles (16, 17). Managing these negative factors through proactive physical activity promotion could help to maximize their physical function and participation during cancer treatment. This could in turn have a positive impact on long term health outcomes, such as reducing the risk of physical impairment, metabolic syndrome and cardiovascular morbidity (18, 19). There is growing evidence to support the benefits of physical activity for children with cancer (20–22), yet the barriers to physical activity in this setting are complex, and there is little consensus regarding how to implement feasible, equitable and sustainable interventions (23, 24).

Physical activity encompasses any bodily movement resulting in energy expenditure (25). As a sub-section of physical activity, literature supports the benefits of supervised exercise (26–30). Supervised exercise interventions have strong attendance and adherence rates, and numerous systematic reviews report its safety and benefits (20, 24, 31–33). However, supervised exercise often target impairments alone, and tie physical activity engagement to the presence of a trained professional. They are also costly. In treatment centers with a high volume of annual cases it can be challenging, from a funding perspective, to provide such services to all families throughout treatment. Promoting physical activity in its broadest sense, from a behavior change perspective, could help families to independently incorporate more physical activity into their daily routine (34–36). This has the potential to alleviate reliance on supervised exercise sessions alone, allowing a more nuanced and targeted approach to service delivery; whereby, more intensive support is provided to children/adolescents if, and when, it is needed.

Complex interventions comprise several interacting and flexible components, have a number of varying outcomes and involve complex behaviors (37). Physical activity is a complex behavior (38); for positive change, complex interventions that consider individual and environmental factors are required (38–40). Implementing strategies that target physical activity behavior using complex intervention design strategies are yet to be thoroughly explored in the acute pediatric cancer setting. There are examples of complex physical activity interventions within the acute cancer treatment setting (41–44), yet these examples either lack a clear theoretical underpinning or fail to

incorporate strategies that target the child/adolescent and their social and physical environment.

The UK's Medical Research Council approach to complex intervention design requires a transparent, and systematic process that articulates the theoretical basis for the intervention (45). Interventions are commonly designed without formal analysis of the behavior to be targeted, nor the theorized mechanism of action. The theoretical underpinning of a complex intervention describes how the intervention is expected to work through outlining the expected causal pathways between the intervention components, the expected outcomes and how contextual factors might influence these (46). Defining and undertaking a theoretical approach to intervention design has many benefits. It helps researchers analyze the problem, understand how an intervention can work, assess effectiveness and ultimately improves replicability and clinical implementation of results (47). Interventions designed *via* a theoretical process are considered to be more effective in leading to lasting change (48).

The Behavior Change Wheel is a framework that integrates 19 existing behavior change frameworks into one model. The components of the Behavior Change Wheel can be used to explain physical activity behavior (49), and to guide intervention design. This framework can be applied across any type of behavior and setting (50), and has been used in various health contexts to design complex physical activity interventions (51–54). The Behavior Change Wheel necessitates consideration of what internal conditions specific to the individual, and their social and physical environment need to be in place for the target behavior to be achieved (50). The COM-B component of the Behavior Change Wheel provides the method for understanding the behavior theoretically. Other theoretical frameworks such as The Transtheoretical Model of Behavior Change, Health Promoting Behavior, Theory of Planned Behavior, and Health Belief Model are commonly cited in the context of complex intervention design. These models can be helpful to predict, explain or describe behavior, yet have limitations for intervention design as they do not require in-depth analysis of the target behavior, nor link theoretical constructs to mechanisms of change (50). The Behavior Change Wheel helps researchers design interventions through linking potential intervention components with the target behavior, population and environment in which they will be delivered (48).

The Behavior Change Wheel was used here to design a complex intervention to promote positive changes in physical activity behavior specifically for children and adolescents receiving acute cancer treatment. This paper outlines the theoretical process undertaken. The decision-making process that led to the resultant intervention "CanMOVE" will be described in terms of the behavior change techniques selected and their mode of delivery. CanMOVE will subsequently be piloted for feasibility.

Materials and methods

The Behavior Change Wheel was the theoretical framework used to inform the design of CanMOVE (50). This intervention aimed to target school aged children (5–16 years) who were undergoing acute cancer treatment. The definition of acute cancer treatment includes hematopoietic stem cell transplantation and all treatment phases except the 'maintenance phase' of leukemia therapy. The research team members worked collaboratively through the three stages of this design process outlined below (**Figure 1**).

Stage 1: Understand the behavior (steps 1–4)

Steps 1–3 define the problem and identify a specific behavior to change. Steps 1–3 were pre-determined prior to undergoing this design process. As described in the introduction, CanMOVE aims to proactively attenuate the negative physical health and participation restrictions observed for children with cancer. The target behavior, physical activity, was determined based on available evidence outlining that children and adolescents undergoing cancer treatment are less physically active than age-matched peers, and the potential positive effects of improved physical engagement (7, 8, 13, 14).

Step 4 analyzed what needs to change in a person, and their environment to facilitate change in the target behavior. The central components of the Behavior Change Wheel, the COM-B model, guided analysis within this step. The COM-B model proposes that for someone to undertake a particular behavior they need to be physically and psychologically *capable*, process the want or need to undertake the behavior *(motivation)*, and have the social and physical *opportunity* to engage in the behavior (50). Each of these components were evaluated on their potential contribution to physical activity behavior specifically for children and adolescents in the acute cancer setting. Data from our qualitative study were used to inform this evaluative process (55). Data were analyzed thematically, first via an inductive process to identify emergent themes, and second via a deductive process whereby the resultant themes were mapped to each of the COM-B components. Results from additional relevant qualitative literature that included insights from child and adolescent perspectives were also used (56–58). Based on the identified reasons for reduced levels of physical activity, a list of potential pathways to create change was generated.

Stage 2: Identify intervention options (steps 5 and 6)

Stage 2 determines the types of intervention functions and policy categories that could be applied to bring about change in

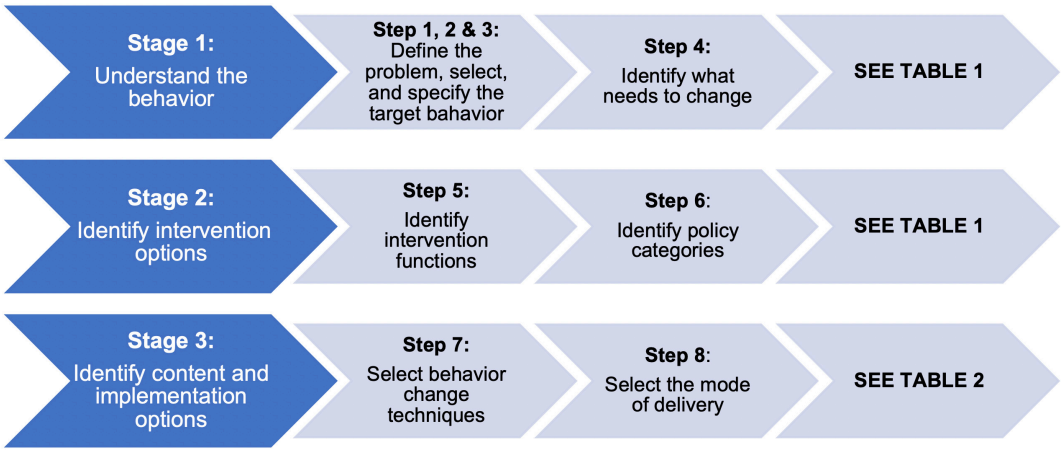

FIGURE 1
Behavior Change Wheel stages of intervention design.

the target behavior. Intervention functions represent the type of intervention to be implemented and policy categories are decisions made by authorities concerning those interventions (50). Factors identified in stage 1 as contributing to physical activity behavior were mapped to potential intervention functions. This process ensures intervention techniques target the specific population and their environment. For example, skills training may be appropriate where there is a lack of skill but will be less helpful if a lack of motivation to perform the skill is the underlying reason for the behavior (48). Identifying potential policy category strategies was beyond the scope of this study.

Stage 3: Identify content and implementation options (steps 7 and 8)

Using the intervention functions identified in stage 2, stage 3 involved selecting behavioral change techniques that could form the different components of the intervention. Behavior change techniques are the "active ingredients" selected to comprise the intervention and facilitate a change in behavior. Clear identification and definition of the behavioral change techniques selected is key to the analysis of how an intervention works; it allows the researcher to accurately describe the intervention, and aids identification of the specific techniques effective in altering behavior (59). The CALO-RE (Coventry, Aberdeen, and London – Refined) taxonomy was used to define the selected behavior change techniques as it was specifically designed to describe physical activity and healthy eating interventions (59).

For each of the selected behavior change strategies, it was then decided how they will be delivered to the target population. Selection of behavior change techniques and their delivery mode was informed through evidence-based analysis of literature relevant to physical activity in the acute cancer treatment setting and physical activity behavior change theory. It was through this decision-making process – identifying which behavior change techniques to use, and the most effective mode of delivery – that the components of CanMOVE were determined.

Results

Stage 1: Understand the behavior (steps 1–4)

A summary of how each of the COM-B components (capability, motivation, opportunity) contribute to physical activity behavior within the acute pediatric cancer setting can be viewed in **Table 1.** Results from Stage 1 highlight the diverse nature of the barriers and facilitators to physical activity that exist.

Challenges to physical activity can vary from one child to another depending on their environment, cancer type, support network, treatment regimen, emotional and physical states. In addition, barriers to physical activity can change for each individual child over the course of their acute treatment phase, which can span many months (55). A child/adolescent's capacity to engage in physical activity can be limited by physical impairments caused by treatment side effects but also through a lack of knowledge, fear, and impaired mental health. Motivation can be impacted through spending large amounts of time in the hospital environment (both in-patient and out-patient setting), reduced physical ability, a loss of independence and freedom, and a lack of joy with movement. Opportunities to be physically active can be restricted through experiencing isolation from friends and family, residing in unstimulating environments, restricted participation in daily routines and not

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TABLE 1 Behavior Change Wheel stage 1 and 2.

		Stage 1		Stage 2
COM-B behavioral determinants		**Reasons for inactivity (55–58)**	**What can be changed?**	**Intervention functions***
Capability	Psychological	Lack of knowledge: why and how to be physically active, potential benefits and risks Reduced mental capacity and stamina Mental health issues: lost confidence, embarrassment, fear, anger	Provide education regarding benefits of physical activity Practical demonstration about safe physical activity Identify mental health issues and initiate prompt referral for management services for support	Education, modeling, training, enablement
	Physical	Reduced physical ability and function: strength, balance, co-ordination, physical impairment Treatment side effects: medically unwell, fatigue, nausea, pain	Identify declines in function and initiate prompt referral to physiotherapy for assessment and treatment Identify unwanted treatment side effects and initiate prompt referral to medical team for review for management	Enablement
Motivation	Reflective	Foreign hospital environment No routine or access to independent ADLs No desire to be physically active Loss of independence and choice Lack of joy with movement Unaware of current level of physical activity (possibly reduced) Unaware of current level of function (possibly reduced)	Facilitate changes to the physical environment to promote physical activity Provide feedback on activity and sedentary behavior Provide feedback on physical function Provide support, encouragement and positive feedback Provide incentive to be physically active	Training, persuasion, incentivization, environmental restructuring
	Automatic	Negative values and beliefs toward physical activity during cancer treatment Perceived risk No perceived benefit Conflicting priorities Reduced self-efficacy toward physical activity	Education regarding potential benefits of physical activity Dispel fears regarding risks of physical activity Education and demonstration on how to safely be physically active	Education, modeling
Opportunity	Physical	Medically imposed physical restriction to movement Medical attachments Need for mobility aid use Lack of environmental cues Unstimulating environment Lack of engaging equipment Lack of space Restrictive hospital rules and policy Lack of access to previous sporting activities and environments	Facilitate changes to the physical environment to promote physical activity: access to other environments, access to toys and equipment, time detached from medical equipment, restrict sedentary activities Provision of appropriate mobility aids	Training, environmental restructuring, restriction
	Social	Lack of positive modeling and social cues Lack of social interaction Lack of availability of specialized services and staff Negative parental values and beliefs toward physical activity Reduced parental capacity – mentally and physically Values of treatment team not aligned with physical activity	Education provided to other oncology HCP about the importance of physical activity Facilitate social interactions on the ward, attendance to groups Increase social support: friends, family, staff Provide education parents and treating team about the benefits of physical activity and how to facilitate it Engage parents and treating staff in strategies to overcome physical activity	Education, training, environmental restructuring,

ALDs, activities of daily living; HCP, healthcare professional.

*Behavior Change Wheel intervention functions (50): Education, increasing knowledge or understanding. Persuasion, using communication to induce positive or negative feelings or stimulate action; Incentivization, creating expectation of reward; Coercion, creating an expectation of punishment or cost; Training, imparting skills; Restriction, using rules to reduce the opportunity to engage in the target reducing the behavior; Environmental restructuring, changing the physical or social context; Modeling, providing an example for people to aspire to or imitate; Enablement, increasing means/reducing barriers to increase capability or opportunity.

having access to sports equipment or toys (55–58). To address the unique characteristics of each child/adolescent and their context, multi-layered, individualized and flexible solutions are needed. Solutions need to acknowledge the heterogeneity of this population. They also need to consider the variability that exists for a child as they move through different treatment phases and have varying medical and support needs.

Many factors identified in the COM-B model are not immediately modifiable. For example, the physical layout of a ward or day oncology unit, the necessity of medical treatments, intravenous lines, resource availability, infection risks and hospital policies. In identifying potential pathways to create behavior change, focus was given to identifying ways to maximize physical activity within these constraints.

Stage 2: Identify intervention options (steps 5 and 6)

A summary of the identified intervention functions can be viewed in **Table 1.** Education, modeling, training, enablement, providing incentives and environmental restructuring (50) were identified as approaches that could affect physical activity behavior.

Stage 3: Identify content and implementation options (steps 7 and 8)

Based on stage 1 and 2, 15 behavioral change strategies to implement within CanMOVE were identified. **Table 2** outlines CanMOVE's intervention components, how they will be delivered, and the behavior change techniques selected. Also depicted are how each component is linked to the previously identified intervention functions.

"Goal setting" and "self-monitoring" were identified as key strategies. Reduced motivation and self-efficacy are commonly reported barriers to physical activity (60). Giving children and adolescents the means to set goals and monitor progress in real time creates a sense of control that is rarely afforded in other aspects of their care (61). For delivery, activity monitors were selected. Activity monitors can also be used to apply a variety of behavior change techniques (62, 63). They are increasingly used within the pediatric settings (42, 64–67) and literature supports their use in motivating physical activity behavior, especially as part of a broader intervention plan (68). Using activity monitors to quantify physical activity via daily steps provides children/adolescents with a means to approximate the amount of physical activity they undertake in real-time. It is acknowledged that daily steps are one representation of physical activity, not taking account of other parameters such as intensity and frequency. However, daily steps are an accessible means by which to set and monitor physical activity goals (69). Rather than offering support that relies upon extrinsic motivation and staff supervision, activity monitors can facilitate intrinsic motivation through providing a means to self-manage behavior.

"Demonstration" was another key behavioral change strategy identified. For children and adolescents with cancer, an experience of physical impairment and reduced opportunity for activity has the potential to lead to a belief they are unable, or it is unsafe, to engage in physical activity. Through education and participating in an active demonstration session with a trained healthcare professional, opportunities for positive movement experiences can be identified. This builds confidence in a child/adolescent's own ability to move.

"Planned social support," "barrier identification and problem solving," and "action planning" were also identified (70–73). Parental support is a key determinant of physical activity behavior in children and adolescents (74, 75). In the cancer treatment setting, negative perceptions toward physical activity can be reinforced by parents leading to perpetuating the sick role of the child/adolescent and a belief physical activity is unsafe (76). Parents can play a strong protective and advocacy role in the care of their child with cancer (77). In order to utilize this influential role, involvement of the family unit was identified as important. Facilitating opportunity for families to collaborate with their child/adolescent as a team gives control over how they engage with physical activity, enabling formulation of self-determined solutions specific to their interests and family context.

Through "environmental restructuring," CanMOVE aims to encourage members of the medical multidisciplinary team to engage in a child/adolescent's physical activity goals. The priorities that exist within an organization can impact a child/adolescent's physical activity (78). Providing a means for other members of the treatment team to engage could result in additional motivation and opportunity for physical activity through facilitating changes in work practices and routines.

The intervention: CanMOVE

The name "CanMOVE" was selected to promote the idea that even in the context of acute cancer treatment, children and adolescents can be physically active. It is a flexible, individualized intervention tailored to suit the unique, and often changing, context of each child/adolescent. The intervention includes three phases run over 10 weeks: Assessment, Monitoring and Feedback (4 weeks), Capacity Building (2 weeks) and Consolidation (4 weeks) (**Figure 2**). The program is designed to be implemented by a healthcare professional, termed the "CanMOVE HCP." This professional will have specific training in exercise and rehabilitation for children with cancer, such as an exercise physiologist or physiotherapist. The intent is for CanMOVE to run parallel to existing hospital or community-based therapy services. Where

TABLE 2 Behavior Change Wheel stage 3.

Intervention component	Mode of delivery	COM-B behavioral determinant	Intervention function*	CALO-RE BCT (59)
Phase 1 Assessment, monitoring and feedback				
Standardized assessment of physical function, physical activity and HRQOL	Complete standardized assessments at two time points	Motivation	Education, persuasion	Provide feedback on performance
Provide feedback on performance on standardized assessments	One-on-one session with participant/parent and trial CanMOVE HCP	Motivation	Persuasion	Provide feedback on performance
Refer to specialized services as indicated	± Referral to services			Plan social support
Phase 2 Capacity building: Theme 1 "Let's find a reason for you to be physically active"				
Provide written and verbal education regarding physical activity definition, benefits, evidence-based standards and recommendations	One-on-one session with participant/parent and CanMOVE HCP	Capability, motivation	Education, training, persuasion	Provide information about health consequences of behavior in general Provide information about health consequences of behavior to the individual
Set a steps per day goal	Provide activity monitor to participant: set steps/day target on device and visually display goal in environment	Motivation	Persuasion, incentivization	Goal setting (behavior) Environmental restructure Teach to use prompts
Provide capability to self-monitor steps/day	Child/adolescent to wear activity monitor at wrist Set prompts on activity monitor to indicate progress toward goal (50, 75, and 100% celebrations)	Motivation	Persuasion, incentivization	Prompt self-monitoring of behavior Provide feedback on performance
Engage family in goal attainment	Provide activity monitor to parent to wear and work together with child/adolescent to achieve steps/day goal	Motivation	Persuasion	Plan social support
Engage treating team in goal attainment	Visually display steps/day goal in environment Record steps/days goal in medical record	Motivation	Persuasion	Plan social support
Capacity building: Theme 2 "Let's explore how you can be more physically active"				
Brainstorming of possible ways to be physically active in current setting	One-on-one session with participant/parent and CanMOVE HCP	Capability, motivation	Enablement	Provide information on where and when to perform the behavior
Supervised participation in physical activity		Capability, motivation, opportunity	Training, enablement	Model/demonstrate the behavior
Capacity building: Theme 3 "Let's make a physical activity plan"				
Review steps/day data and provide positive reinforcement	One-on-one session with participant/parent and CanMOVE HCP	Motivation	Persuasion, incentivization	Prompting focus on past success Prompt rewards contingent on effort or progress toward behavior Prompt review of behavioral goals
Identify individual barriers to physical activity and discuss possible solutions		Motivation, opportunity	Persuasion, incentivization	Barrier identification and problem solving
Set a new steps per day goal based on prior results		Motivation	Persuasion, incentivization	Goal setting (behavior)
Create an action plan to achieve steps/day goal (see Table 3 for example action plan items)		Motivation, opportunity	Motivation, opportunity	Action planning
Provide support to carry out action plan	CanMOVE HCP allocated 1 h/week to assist implementation of action plan items	Motivation, opportunity	Motivation, opportunity	Action planning
Phase 3 Consolidation sessions 1–4 (Repeat Theme 3 weekly)				

BCT, behavior change technique; CALO-RE, Coventry, Aberdeen, and London – Refined; HCP; healthcare professional, HRQOL, health-related quality of life.

*Behavior Change Wheel intervention functions (50): Education, increasing knowledge or understanding; Persuasion, using communication to induce positive or negative feelings or stimulate action; Incentivization, creating expectation of reward; Coercion, creating an expectation of punishment or cost; Training, imparting skills; Restriction, using rules to reduce the opportunity to engage in the target reducing the behavior; Environmental restructuring, changing the physical or social context; Modeling, providing an example for people to aspire to or imitate; Enablement, increasing means/reducing barriers to increase capability or opportunity.

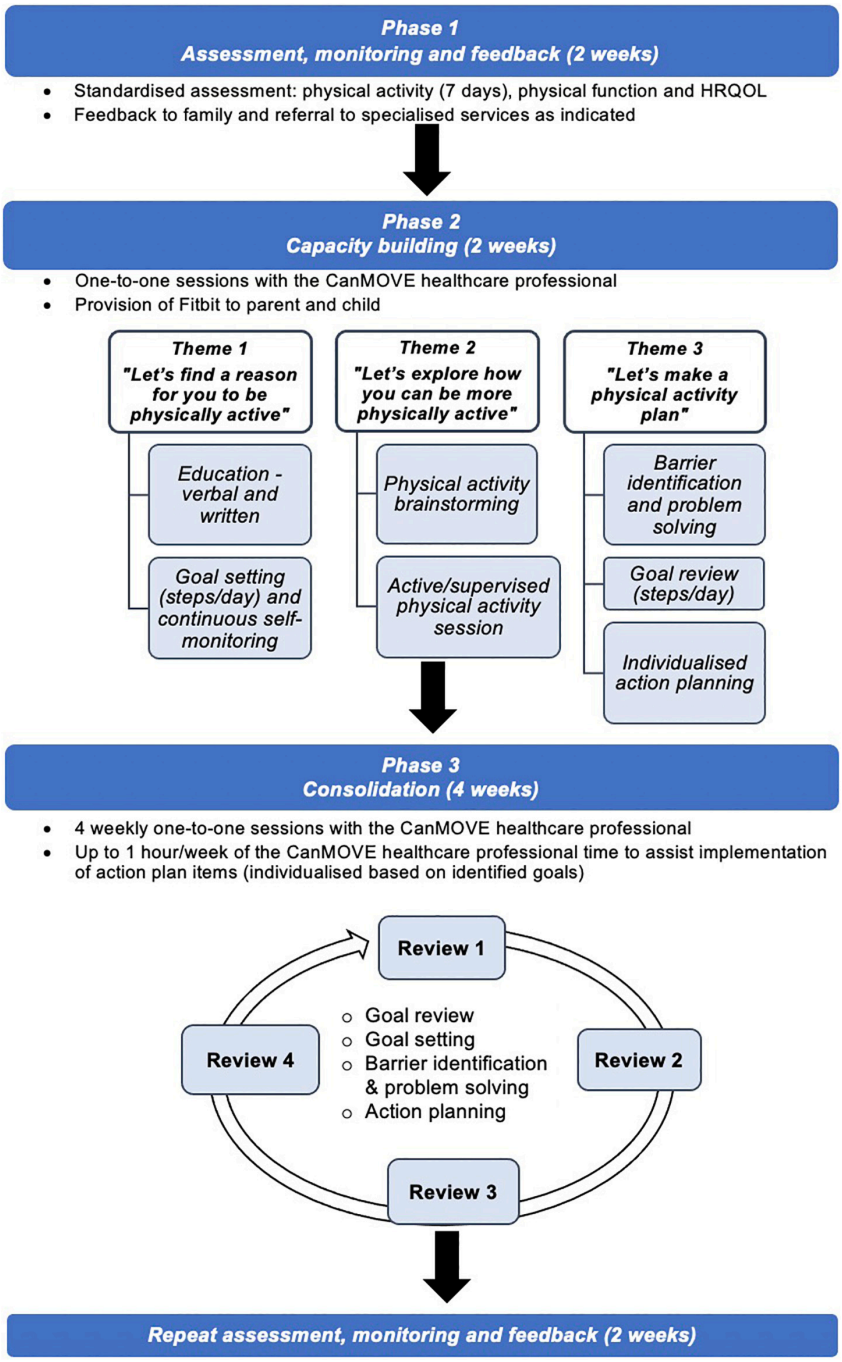

FIGURE 2
CanMOVE intervention model.

appropriate CanMOVE sessions can be conducted remotely to accommodate both the home and hospital environment, and overcome any isolation restrictions.

Phase 1: Assessment, monitoring, and feedback

This phase occurs at the beginning (2 weeks) and the end of the intervention (2 weeks). It includes objective assessment of physical activity, physical function (e.g., gross motor skills, cardiovascular function, functional tasks) and health-related quality of life (HRQOL). Each assessment outcome is discussed with the child/adolescent and their parent to build self-awareness of their current level of physical activity and learn about factors contributing to it (i.e., physical function and mental health). Assessing across two time points provides

an opportunity to highlight and celebrate any improvements overtime. The assessment of physical function also provides opportunity to identify impairments requiring more intensive therapeutic input. In this phase, referrals can be made to additional services, for instance in the case of a vincristine neuropathy. There is insufficient evidence to support the selection of outcome measures to assess physical function in this population (79). Further psychometric analysis is required to inform the selection of assessment tools that may be utilized in this phase.

Phase 2: Capacity building

Theme 1: "Let's find a reason for you to be physically active"

Theme 1 explores self-identified motivations toward physical activity. Education is individually tailored to identify motivating factors for them, and their parent/s. Here the CanMOVE HCP seeks to define the broad nature of physical activity, re-framing it as something that is achievable, fun, and part of the everyday routine. The benefits of physical activity are also discussed, specifically in the context of cancer treatment. A booklet specifically about physical activity and cancer treatment is provided (80). At the conclusion of the session, the child/adolescent is asked to identify 1–3 reasons why being physically active is important and beneficial for them.

The child/adolescent and one parent are provided with an activity monitor which is used to set an individualized daily step target. The daily steps target will act to broadly represent their participation in physical activity throughout the day. Together the child/adolescent and parent work toward their daily target. The initial daily step goal is formulated collaboratively taking into consideration results from the baseline assessment and current medical management. Progress toward their goal can be monitored continuously in real-time via the activity monitor. The daily step goal will be displayed in their hospital room (or at home) and communicated to the treating team via their medical record and multi-disciplinary team meetings.

Theme 2: "Let's explore how you can be more physically active"

Theme 2 involves collaboratively brainstorming how the child/adolescent can be more physically active in their environment, whether that be at home or in the hospital setting. Within this session children will be encouraged to reflect upon what physical activity is, what they currently do, what they are able to do, and what they would like to do. In doing so, the child/adolescent is supported to identify new ways they can introduce physical activity opportunities into their daily routine. Identified strategies will aim to reflect the broad nature of 'physical activity' (25). For example, this may include activities of daily living, play, a structured exercise routine, sports skills, walking, and/or planned social interactions and hobbies that can incorporate incidental physical activity.

The child/adolescent will then participate in a physical activity session with the CanMOVE HCP. Activities completed will be tailored to the child/adolescent's interests, treatment, abilities, and safety restrictions. Only activities the child/adolescent can carry out independently (or with the assistance of their parent) will be incorporated. If equipment, toys, technology, or active gaming are used, they must be readily available to the child/adolescent for independent use. This session aims to offer a positive movement experience that is fun and build confidence in their ability to move.

Theme 3: "Let's make a physical activity plan"

Theme 3 aims to devise a physical activity plan in partnership with the child/adolescent and parent/s. Within this session, progress toward their daily step goal is reviewed. Positive reinforcement is provided in response to the child/adolescent making attempts to achieve the daily step goal. A list of barriers and facilitators to goal attainment are formulated. Factors that are within their realm of control are identified and potential solutions brainstormed. Here the daily step goal can be altered to make it more achievable or to motivate a challenge, a decision to be made in the context of upcoming treatment plans. An action plan will be formulated to work toward the daily steps target. Action plan items will comprise individualized strategies to assist in overcoming identified barriers. Tasks will be agreed upon and implemented by the child/adolescent and parent. The aim here is to support families to make independent choices regarding how the child/adolescent chooses to move, and motivate a shift toward a more physically active daily routine.

In addition, the CanMOVE HCP will allocate one hour to assist implementation of action plan items over the course of the following week. Action plan items will involve the broader treating medical and nursing team where able. An example of a barrier identification and action plan can be viewed in **Table 3**. In cases where psychological or physical impairments are identified and cannot be addressed adequately within the scope of the CanMOVE program, the CanMOVE HCP will collaborate with specialized therapy services and referrals made as indicated.

Phase 3: Consolidation

Four "consolidation" sessions will be conducted to evaluate and modify intervention strategies based on their success in bringing about behavior change. Each week the daily steps data for the previous week will be discussed and a new goal set for the coming week. The daily step goal will aim to increase each week. However, to ensure goals are achievable, it may be maintained or decreased based on individual circumstances, such as upcoming hospital admissions/discharges, medical

TABLE 3 Example barriers and action plan items.

Barriers	Potential action plan items	Carried out by
Admitted on hospital ward – unsure how to be physically active, nothing to do	Loan equipment/games/toys to encourage physical activity in line with interests Facilitate a plan for regular time outdoors/off ward with medical team Develop a plan to restrict screen time Plan social visits with friends and family	Child/adolescent, parent, CanMOVE HCP CanMOVE HCP/medical and nursing team Child/adolescent, parent Child/adolescent, parent
	Attend team meetings and facilitate opportunities to be physically active through existing services, i.e., play therapy Carry out additional supervised physical activity sessions to increase confidence and promote independence	CanMOVE HCP CanMOVE HCP
	Plan ADLs to participate in (etc. dressing, showering, making own snacks) Facilitate interaction with other children on the ward Develop and schedule independent exercise program based on needs and interests Start a physical activity routine, e.g., ADLs, walking, independent exercises, sport activities/games	Child/adolescent, parent CanMOVE HCP, nursing team, parent Child/adolescent, parent, CanMOVE HCP Child/adolescent, parent, CanMOVE HCP
Fatigue and nausea with current treatment	Plan rest time Education on pacing	Child/adolescent, parent, CanMOVE HCP Child/adolescent, parent, CanMOVE HCP
Tripping when walking	Discus with medical team need for physiotherapy referral for additional assessment and management	CanMOVE HCP, medical team, hospital physiotherapists
Lack of motivation to get up and move	Display prompts and cues to encourage physical activity Discuss goal with nursing staff and encourage their involvement in supporting their goal attainment	CanMOVE HCP CanMOVE HCP, medical and nursing team
Long periods of time on intravenous line	Schedule line-free time with nursing staff	CanMOVE HCP, medical and nursing team

ADLs, activities of daily living; HCP, healthcare professional.

treatments and/or setbacks. Any new barriers and facilitators identified will be discussed. Success of action plan strategies will be reviewed, and items removed or added as indicated. An additional one hour of CanMOVE HCP time can be used to assist in carrying out action plan items each week.

Outcomes

The primary outcome of the CanMOVE intervention is to facilitate change in physical activity behavior in children undergoing acute cancer treatment. There may be additional potential benefits if CanMOVE is implemented in a clinical setting. The potential short- and long-term outcomes, along with their theorized mechanisms of action can be found in **Figure 3**. Prior to clinical implementation, CanMOVE must first be piloted for feasibility and undergo further development to ensure safety, acceptability, and optimum efficacy.

Discussion

CanMOVE is a complex intervention that takes a novel and proactive approach to physical activity promotion. With a focus on behavior change, CanMOVE aims to promote positive movement experiences and maximize the family's capacity toward physical activity. The design process was transparent, theory-driven and informed by qualitative data. The Behavior Change Wheel process necessitated a deep understanding of the target behavior, population and environment (50). Although time consuming, developing a clear behavioral diagnosis specific to the desired population ensured all subsequent design decisions were relevant to the population. The result is an intervention that targets specific physical activity challenges faced by children and adolescents within the acute cancer treatment setting. Intervention strategies identified for CanMOVE promote physical activity as necessary, enjoyable, and achievable in the acute cancer treatment setting. This

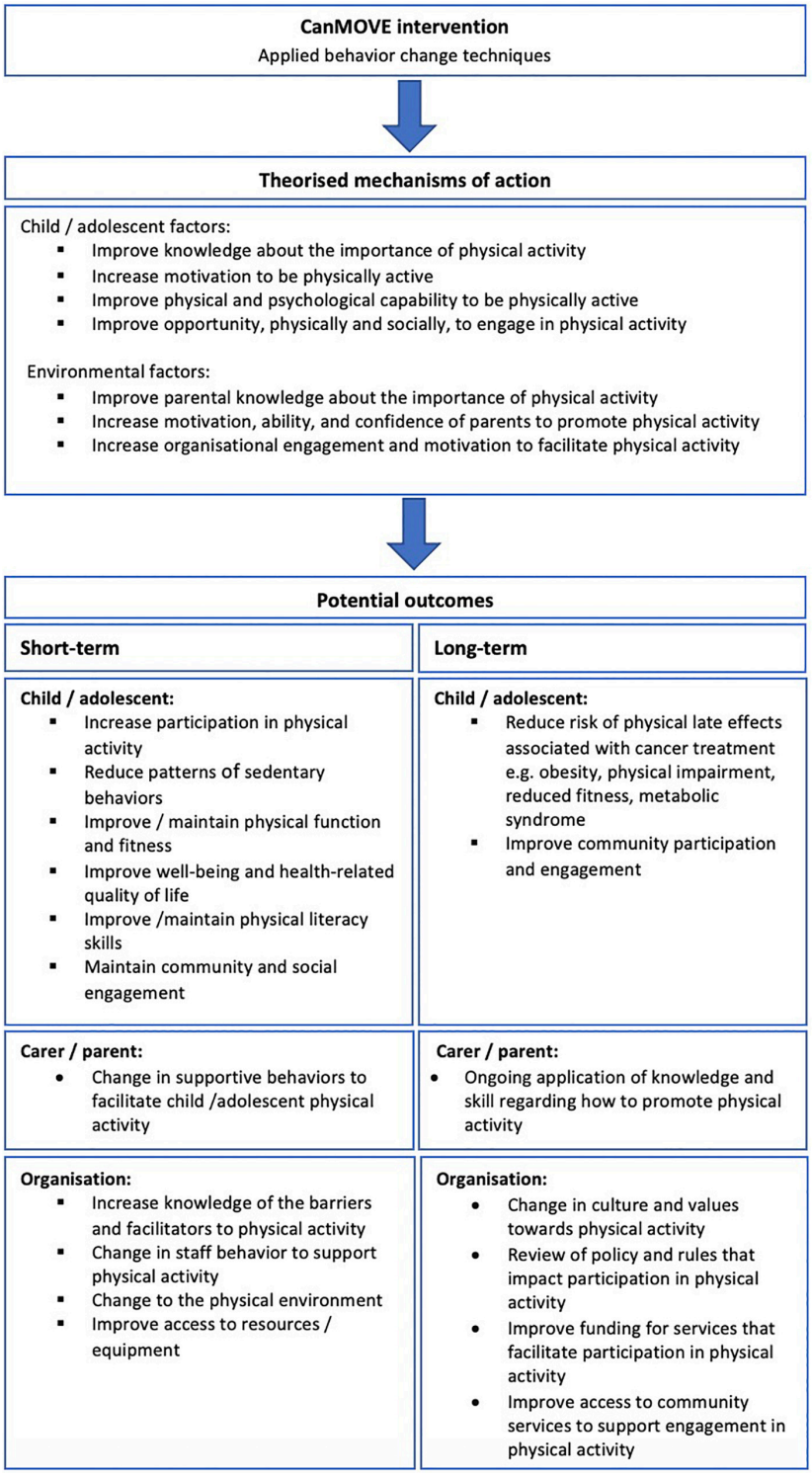

FIGURE 3
Outcomes.

perspective is in-line with recently released physical activity guidelines for children with cancer (81). Given the complex determinants of physical activity behavior for children with cancer, it is important to acknowledge that CanMOVE is only one element within a multi-system approach required to promote physical activity for this population.

CanMOVE seeks to complement, rather than replace specialized therapy services that provide physical assessment, intervention, and rehabilitation. Without the availability of therapists to address treatment related physical impairments (for example post-surgical impairments, myopathy and neuropathy), children and adolescents with compromised physical function will find it challenging to be physically active. CanMOVE incorporates a mechanism whereby physical function is monitored, with referrals made on a need basis. This approach ensures physical impairments are identified and treated promptly, while maximizing the efficiency of specialized service provision. Success, however, relies upon the selection of psychometrically robust outcome measures (79), and adequate services in place to provide additional therapy as needed. Given the protracted nature of acute cancer treatment, the provision of monitoring and follow up after the completion of CanMOVE is another consideration. The Stoplight program is an example of a clinical service that utilizes monitoring and targeted exercise provision with positive results (82).

Treating organizations have a role to play to ensure hospital environments, professional services and staff values are conducive to physical activity engagement. The social-ecological model provides a framework to describe the multiple levels of influence to be considered in working toward the promotion of positive health behaviors (83). In addition to addressing factors on an individual and interpersonal level, there is a need for change at the organizational level. CanMOVE invites treating teams to participate in a child/adolescent's physical activity promotion, yet there are other positive changes an organization could make to support physical activity. These changes fall within the policy categories of the Behavior Change Wheel, such as environmental planning, service provision and a review of hospital guidelines (50). For example, often equipment and spaces that promote physical activity are not readily available to families. Altering treatment environments to allow space and independent access to equipment is a positive change that could promote physical activity. Other examples include education programs for nursing staff on physical activity promotion, including physical activity goals into medical treatment plans, and a review of hospital polies that restrict physical activity.

Feasibility evaluation is a vital step in the complex intervention design process (37). Prior to implementation, CanMOVE will be assessed for feasibility in a non-randomized pilot study (84) against criteria designed by Bowen et al. (85). The undertaking of a theoretical approach to intervention design will aid this evaluation. Without clearly defined "active ingredients" of the intervention, understanding what worked, and how, can be difficult to isolate. A comprehensive analysis of feasibility, utilizing qualitative and quantitative data (86), enables a deeper understanding of intervention elements such as: which were implemented successfully, which were effective, and the potential mechanisms underlying any observed changes in behavior. It also works to answer questions such as how well an intervention fits within a clinical setting and how acceptable it is. Addressing these questions is essential to inform future intervention development decisions and clinical implementation strategies. In depth analysis of the barriers and facilitators to physical activity reported by participants during the pilot study will also help the inform future intervention development decisions, and guide potential changes to the environment and services. Future design considerations for CanMOVE will include when to time the intervention, which outcome measures to use, how to engage the multi-disciplinary team, and how changes of behavior changes may be maintained over the entire length of acute treatment and into survivorship (87).

CanMOVE endeavors to promote positive physical activity experiences through maximizing a child/adolescent's capacity, motivation and opportunities for movement. It aims to change how parents, children and adolescents think about physical activity. Results will ultimately inform the implementation of services within the pediatric cancer setting. This type of intervention, however, cannot stand alone. Meaningful change relies upon organizations providing specialized services and environments that promote and facilitate participation in physical activity. The theoretical design process underpinning the design of CanMOVE is an important stepping-stone toward understanding how to improve physical activity participation for children and adolescents in this setting. It also has potential application to other pediatric chronic health populations where physical activity participation is challenged in the hospital setting.

Data availability statement

The original contributions presented in this study are included in the article, further inquiries can be directed to the corresponding author.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Funding

This work was supported by an Australian Government Research Training Program Scholarship through La Trobe University, a Ph.D. top-up scholarship through the Murdoch Children's Research Institute, and a research grant provided through the charity organisation Little Big Steps.

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.

The handling editor declared a past co-authorship with one of the authors SG.

Publisher's note

References

1. Deisenroth A, Söntgerath R, Schuster AJ, von Busch C, Huber G, Eckert K, et al. Muscle strength and quality of life in patients with childhood cancer at early phase of primary treatment. *Pediatr Hematol Oncol.* (2016) 33:393–407.

2. Elmantaser M, Stewart G, Young D, Duncan R, Gibson B, Ahmed S. Skeletal morbidity in children receiving chemotherapy for acute lymphoblastic leukaemia. *Arch Dis Child.* (2010) 95:805–9.

3. Fuemmeler BF, Pendzich MK, Clark K, Lovelady C, Rosoff P, Blatt J, et al. Diet, physical activity, and body composition changes during the first year of treatment for childhood acute leukemia and lymphoma. *J Pediatr Hematol Oncol.* (2013) 35:437–43. doi: 10.1097/MPH.0b013e318279cd3e

4. Lavoie Smith EM, Li L, Chiang C, Thomas K, Hutchinson RJ, Wells EM, et al. Patterns and severity of vincristine-induced peripheral neuropathy in children with acute lymphoblastic leukemia. *J Peripher Nerv Syst.* (2015) 20:37–46.

5. Thorsteinsson T, Larsen HB, Schmiegelow K, Thing LF, Krustrup P, Pedersen MT, et al. Cardiorespiratory fitness and physical function in children with cancer from diagnosis throughout treatment. *BMJ Open Sport Exerc Med.* (2017) 3:e000179. doi: 10.1136/bmjsem-2016-000179

6. Ness KK, Kaste SC, Zhu L, Pui CH, Jeha S, Nathan PC, et al. Skeletal, neuromuscular and fitness impairments among children with newly diagnosed acute lymphoblastic leukemia. *Leuk Lymphoma.* (2015) 56:1004–11. doi: 10.3109/10428194.2014.944519

7. Bhakta N, Liu Q, Ness KK, Baassiri M, Eissa H, Yeo F, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude lifetime cohort study (SJLIFE). *Lancet.* (2017) 390:2569–82.

8. Ness KK, Leisenring WM, Huang S, Hudson MM, Gurney JG, Whelan K, et al. Predictors of inactive lifestyle among adult survivors of childhood cancer: a report from the childhood cancer survivor study. *Cancer.* (2009) 115:1984–94.

9. Smith WA, Li C, Nottage KA, Mulrooney DA, Armstrong GT, Lanctot JQ, et al. Lifestyle and metabolic syndrome in adult survivors of childhood cancer: a report from the St. Jude lifetime cohort study. *Cancer.* (2014) 120:2742–50.

10. Baade PD, Youlden DR, Valery PC, Hassall T, Ward L, Green AC, et al. Trends in incidence of childhood cancer in Australia, 1983–2006. *Br J Cancer.* (2010) 102:620–6. doi: 10.1038/sj.bjc.6605503

11. Carson V, Stone M, Faulkner G. Patterns of sedentary behavior and weight status among children. *Pediatr Exerc Sci.* (2014) 26:95–102.

12. Pellegrini AD, Smith PK. Physical activity play: the nature and function of a neglected aspect of play. *Child Dev.* (1998) 69:577–98.

13. Lam KK, Li WH, Chiu SY, Chan GC. The impact of cancer and its treatment on physical activity levels and quality of life among young Hong Kong Chinese cancer patients. *Eur J Oncol Nurs.* (2016) 21:83–9. doi: 10.1016/j.ejon.2016.01.007

14. Winter C, Müller C, Brandes M, Brinkmann A, Hoffmann C, Hardes J, et al. Level of activity in children undergoing cancer treatment. *Pediatr Blood Cancer.* (2009) 53:438–43.

15. Hochhauser D, Tobias JS. *Cancer and Its Management*. Somerset: John Wiley & Sons, Incorporated (2014).

16. Stout NL, Baima J, Swisher AK, Winters-Stone KM, Welsh J. A systematic review of exercise systematic reviews in the cancer literature (2005-2017). *PM R.* (2017) 9:S347–84. doi: 10.1016/j.pmrj.2017.07.074

17. Myers RM, Balsamo L, Lu X, Devidas M, Hunger SP, Carroll WL, et al. A prospective study of anxiety, depression, and behavioral changes in the first year after a diagnosis of childhood acute lymphoblastic leukemia. *Cancer.* (2014) 120:1417–25. doi: 10.1002/cncr.28578

18. White J, Flohr JA, Winter SS, Vener J, Feinauer LR, Ransdell LB. Potential benefits of physical activity for children with acute lymphoblastic leukaemia. *Dev Neurorehabil.* (2005) 8:53–8.

19. Friedman DN, Tonorezos ES, Cohen P. Diabetes and metabolic syndrome in survivors of childhood cancer. *Horm Res Paediatr.* (2019) 91:118–27.

20. Morales JS, Valenzuela PL, Rincón-Castanedo C, Takken T, Fiuza-Luces C, Santos-Lozano A, et al. Exercise training in childhood cancer: a systematic review and meta-analysis of randomized controlled trials. *Cancer Treat Rev.* (2018) 70:154–67. doi: 10.1016/j.ctrv.2018.08.012

21. Klika R, Tamburini A, Galanti G, Mascherini G, Stefani L. The role of exercise in pediatric and adolescent cancers: a review of assessments and suggestions for clinical implementation. *J Funct Morphol Kinesiol.* (2018) 3:7.

22. Baumann FT, Bloch W, Beulertz J. Clinical exercise interventions in pediatric oncology: a systematic review. *Pediatr Res.* (2013) 74:366–74.

23. Wurz A, Daeggelmann J, Albinati N, Kronlund L, Chamorro-Vina C, Culos-Reed SN. Physical activity programs for children diagnosed with cancer: an international environmental scan. *Support Care Cancer.* (2019) 27:1153. doi: 10.1007/s00520-019-04669-5

24. Grimshaw SL, Taylor NF, Shields N. The feasibility of physical activity interventions during the intense treatment phase for children and adolescents with cancer: a systematic review. *Pediatr Blood Cancer.* (2016) 63:1586–93. doi: 10.1002/pbc.26010

25. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep.* (1985) 100:126–31.

26. Corr AM, Liu W, Bishop M, Pappo A, Srivastava DK, Neel M, et al. Feasibility and functional outcomes of children and adolescents undergoing preoperative chemotherapy prior to a limb-sparing procedure or amputation. *Rehabil Oncol.* (2017) 35:38–45.

27. Fiuza-Luces C, Padilla JR, Soares-Miranda L, Santana-Sosa E, Quiroga JV, Santos-Lozano A, et al. Exercise intervention in pediatric patients with solid tumors: the physical activity in pediatric cancer trial. *Med Sci Sports Exerc.* (2017) 49:223–30.

28. Gohar SF, Comito M, Price J, Marchese V. Feasibility and parent satisfaction of a physical therapy intervention program for children with acute lymphoblastic leukemia in the first 6 months of medical treatment. *Pediatr Blood Cancer.* (2011) 56:799–804. doi: 10.1002/pbc.22713

29. Hartman A, te Winkel ML, van Beek RD, de Muinck Keizer-Schrama SM, Kemper HC, Hop WC, et al. 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) 53:64–71. doi: 10.1002/pbc.21942

30. Winter C, Müller C, Hardes J, Gosheger G, Boos J, Rosenbaum D. The effect of individualized exercise interventions during treatment in pediatric patients with a malignant bone tumor. *Support Care Cancer.* (2013) 21:1629–36.

31. Zucchetti G, Rossi F, Chamorro Vina C, Bertorello N, Fagioli F. Exercise program for children and adolescents with leukemia and lymphoma during treatment: a comprehensive review. *Pediatric Blood Cancer.* (2018) 65:e26924.

32. Rustler, V, Hagerty M, Daeggelmann J, Marjerrison S, Bloch W, Baumann FT. Exercise interventions for patients with pediatric cancer during inpatient acute care: a systematic review of literature. *Pediatr Blood Cancer.* (2017) 64:e26567 doi: 10.1002/pbc.26567

33. Braam KI, van der Torre P, Takken T, Veening MA, van Dulmen-den Broeder E, Kaspers GJL. Physical exercise training interventions for children and young

adults during and after treatment for childhood cancer. *Cochrane Libr.* (2013) 4:CD008796.

34. Wurz A, McLaughlin E, Chamorro Viña C, Grimshaw SL, Hamari L, Götte M, et al. Advancing the field of pediatric exercise oncology: research and innovation needs. *Curr Oncol.* (2021) 28:619–29. doi: 10.3390/curroncol28010061

35. Brown MC, Sharp L, Sniehotta FF, Skinner R, Araújo-Soares V. The development of health behaviour change interventions for childhood cancer survivors: the need for a behavioural science approach. *Pediatr Blood Cancer.* (2020) 67:e28500.

36. Cross A, Howlett N, Sheffield D. Social ecological interventions to increase physical activity in children and young people living with and beyond cancer: a systematic review. *Psychol Health.* (2020) 35:1477–96. doi: 10.1080/08870446.2020.1759601

37. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new medical research council guidance. *BMJ.* (2008) 337:a1655. doi: 10.1136/bmj.a1655

38. Buchan DS, Ollis S, Thomas NE, Baker JS. Physical activity behaviour: an overview of current and emergent theoretical practices. *J Obes.* (2012) 2012:546459. doi: 10.1155/2012/546459

39. Imms C. Children with cerebral palsy participate: a review of the literature. *Disabil Rehabil.* (2008) 30:1867–84.

40. Ferreira I, Van Der Horst K, Wendel-Vos W, Kremers S, Van Lenthe FJ, Brug J. Environmental correlates of physical activity in youth – a review and update. *Obes Rev.* (2007) 8:129–54.

41. Cox CL, Zhu L, Kaste SC, Srivastava K, Barnes L, Nathan PC, et al. Modifying bone mineral density, physical function, and quality of life in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer.* (2017) 65:e26929. doi: 10.1002/pbc.26929

42. Götte M, Kesting SV, Gerss J, Rosenbaum D, Boos J. Feasibility and effects of a home-based intervention using activity trackers on achievement of individual goals, quality of life and motor performance in patients with paediatric cancer. *BMJ Open Sport Exerc Med.* (2018) 4:e000322. doi: 10.1136/bmjsem-2017-000322

43. Lam KKW, Li WHC, Chung OK, Ho KY, Chiu SY, Lam HS, et al. 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) 101:1947–56. doi: 10.1016/j.pec.2018.07.008

44. Nielsen MKF, Christensen JF, Frandsen TL, Thorsteinsson T, Andersen LB, Christensen KB, 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.* (2020) 18:175. doi: 10.1186/s12916-020-01634-6

45. Skivington K, Matthews L, Simpson S, Craig P, Baird J, Blazeby J, et al. A new framework for developing and evaluating complex interventions: update of medical research council guidance. *BMJ.* (2021) 374:n2061. doi: 10.1136/bmj.n2061

46. O'Cathain A, Croot L, Duncan E, Rousseau N, Sworn K, Turner KM, et al. Guidance on how to develop complex interventions to improve health and healthcare. *BMJ Open.* (2019) 9:e029954. doi: 10.1136/bmjopen-2019-029954

47. Michie S, Abraham C. Interventions to change health behaviours: evidence-based or evidence-inspired? *Psychol Health.* (2004) 19:29–49.

48. Michie S, Johnston M, Francis J, Hardeman W, Eccles M. From theory to intervention: mapping theoretically derived behavioural determinants to behaviour change techniques. *Appl Psychol.* (2008) 57:660–80.

49. Willmott TJ, Pang B, Rundle-Thiele S. Capability, opportunity, and motivation: an across contexts empirical examination of the COM-B model. *BMC Public Health.* (2021) 21:1014. doi: 10.1186/s12889-021-11019-w

50. Michie S, Van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci.* (2011) 6:1–12.

51. Kinnear FJ, Wainwright E, Bourne JE, Lithander FE, Hamilton-Shield J, Searle A. The development of a theory informed behaviour change intervention to improve adherence to dietary and physical activity treatment guidelines in individuals with familial hypercholesterolaemia (FH). *BMC Health Serv Res.* (2020) 20:27. doi: 10.1186/s12913-019-4869-4

52. Martin, R, Murtagh EM. An intervention to improve the physical activity levels of children: design and rationale of the 'active classrooms' cluster randomised controlled trial. *Contemp Clin Trials.* (2015) 41:180–91. doi: 10.1016/j.cct.2015.01.019

53. Murtagh E, Barnes A, McMullen J, Morgan P. Mothers and teenage daughters walking to health: using the behaviour change wheel to develop an intervention to improve adolescent girls' physical activity. *Public Health.* (2018) 158:37–46. doi: 10.1016/j.puhe.2018.01.012

54. Webb J, Foster J, Poulter E. Increasing the frequency of physical activity very brief advice for cancer patients. Development of an intervention using the behaviour change wheel. *Public Health.* (2016) 133:45–56. doi: 10.1016/j.puhe.2015.12.009

55. Grimshaw SL, Taylor NF, Mechinaud F, Conyers R, Shields N. Physical activity for children undergoing acute cancer treatment: a qualitative study of parental perspectives. *Pediatr Blood Cancer.* (2020) 67:e28264.

56. Lam KK, Ho Cheung William L, Ho KY, Chung OK, Chan CF. Factors contributing to the low physical activity level for Hong Kong Chinese children hospitalised with cancer: an exploratory study. *J Clin Nurs.* (2017) 26:190–201. doi: 10.1111/jocn.13495

57. Gotte M, Kesting S, Winter C, Rosenbaum D, Boos J. Experience of barriers and motivations for physical activities and exercise during treatment of pediatric patients with cancer. *Pediatr Blood Cancer.* (2014) 61:1632–7.

58. Thorsteinsson T, Schmiegelow K, Thing LF, Andersen LB, Helms AS, Ingersgaard MV, et al. Classmates motivate childhood cancer patients to participate in physical activity during treatment: a qualitative study. *Eur J Cancer Care (Engl).* (2019) 28:e13121.

59. Michie S, Ashford S, Sniehotta FF, Dombrowski SU, Bishop A, French DP. A refined taxonomy of behaviour change techniques to help people change their physical activity and healthy eating behaviours: the CALO-RE taxonomy. *Psychol Health.* (2011) 26:1479–98. doi: 10.1080/08870446.2010.540664

60. Bar-Mor G, Bar-Tal Y, Krulik T, Zeevi B. Self-efficacy and physical activity in adolescents with trivial, mild, or moderate congenital cardiac malformations. *Cardiol Young.* (2000) 10:561–6. doi: 10.1017/S1047951100008829

61. Gibbins J, Steinhardt K, Beinart H. A systematic review of qualitative studies exploring the experience of parents whose child is diagnosed and treated for cancer. *J Pediatr Oncol Nurs.* (2012) 29:253–71. doi: 10.1177/1043454212452791

62. Lyons EJ, Lewis ZH, Mayrsohn BG, Rowland JL. Behavior change techniques implemented in electronic lifestyle activity monitors: a systematic content analysis. *J Med Internet Res.* (2014) 16:e192. doi: 10.2196/jmir.3469

63. Mercer K, Li M, Giangregorio L, Burns C, Grindrod K. Behavior change techniques present in wearable activity trackers: a critical analysis. *JMIR Mhealth Uhealth.* (2016) 4:e40. doi: 10.2196/mhealth.4461

64. Le A, Mitchell HR, Zheng DJ, Rotatori J, Fahey JT, Ness KK, et al. A home-based physical activity intervention using activity trackers in survivors of childhood cancer: a pilot study. *Pediatr Blood Cancer.* (2017) 64:387–94. doi: 10.1002/pbc.26235

65. Hooke MC, Gilchrist L, Tanner L, Hart N, Withycombe JS. Use of a fitness tracker to promote physical activity in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer.* (2016) 63:684–9. doi: 10.1002/pbc.25860

66. Mendoza JA, Baker KS, Moreno MA, Whitlock K, Abbey-Lambertz M, Waite A, et al. A fitbit and facebook mHealth intervention for promoting physical activity among adolescent and young adult childhood cancer survivors: a pilot study. *Pediatr Blood Cancer.* (2017) 64:e26660. doi: 10.1002/pbc.26660

67. Schofield L, Mummery WK, Schofield G. Effects of a controlled pedometer-intervention trial for low-active adolescent girls. *Med Sci Sports Exerc.* (2005) 37:1414–20. doi: 10.1249/01.mss.0000174889.89600.e3

68. Sullivan AN, Lachman ME. Behavior change with fitness technology in sedentary adults: a review of the evidence for increasing physical activity. *Front Public Health.* (2017) 4:289. doi: 10.3389/fpubh.2016.00289

69. Kraus WE, Janz KF, Powell KE, Campbell WW, Jakicic JM, Troiano RP, et al. Daily Step counts for measuring physical activity exposure and its relation to health. *Med Sci Sports Exerc.* (2019) 51:1206–12. doi: 10.1249/MSS.0000000000001932

70. Michie S, Abraham C, Whittington C, McAteer J, Gupta S. Effective techniques in healthy eating and physical activity interventions: a meta-regression. *Health Psychol.* (2009) 28:690–701. doi: 10.1037/a0016136

71. Greaves CJ, Sheppard KE, Abraham C, Hardeman W, Roden M, Evans PH, et al. Systematic review of reviews of intervention components associated with increased effectiveness in dietary and physical activity interventions. *BMC Public Health.* (2011) 11:119. doi: 10.1186/1471-2458-11-119

72. Kahn EB, Ramsey LT, Brownson RC, Heath GW, Howze EH, Powell KE, et al. The effectiveness of interventions to increase physical activity. A systematic review. *Am J Prev Med.* (2002) 22:73–107. doi: 10.1016/S0749-3797(02)00434-8

73. Rhodes RE, Pfaeffli LA. Mediators of physical activity behaviour change among adult non-clinical populations: a review update. *Int J Behav Nutr Phys Act.* (2010) 7:1–11. doi: 10.1186/1479-5868-7-37

74. Trost SG, Loprinzi PD. Parental influences on physical activity behavior in children and adolescents: a brief review. *Am J Lifestyle Med.* (2011) 5:171–81. doi: 10.1177/1559827610387236

75. Golan M. Parents as agents of change in childhood obesity – from research to practice. *Int J Pediatr Obes.* (2006) 1:66–76. doi: 10.1080/17477160600644272

76. Le A, Li F, Mitchell HR, Kadan-Lottick N. Exercise practices, preferences, and barriers in the pediatric oncology population. *Pediatr Blood Cancer.* (2015) 62:2177–84. doi: 10.1186/s12913-016-1423-5

77. Kars MC, Duijnstee MSH, Pool A, Van Delden JJM, Grypdonck MHF. Being there: parenting the child with acute lymphoblastic leukaemia. *J Clin Nurs.* (2008) 17:1553–62. doi: 10.1111/j.1365-2702.2007.02235.x

78. Keats MR, Culos-Reed SN, Courneya KS. An examination of the beliefs, attitudes and counselling practices of paediatric oncologists toward physical activity: a provincial survey. *Paediatr Child Health.* (2007) 12:289–93. doi: 10.1093/pch/12.4.289

79. Grimshaw SL, Taylor NF, Mechinaud F, Shields N. Assessment of physical function in children with cancer: a systematic review. *Pediatr Blood Cancer.* (2018) 65:e27369. doi: 10.1002/pbc.27369

80. Service PIC. *Paediatric Integrated Cancer Service. Family Resources, Everyday Care, Physical Activity Booklet.* (2021) Available online at: https://ed492f82-48ec-4169-8a4b-3c5f0d1cdad4.filesusr.com/ugd/3fb492_01d1ce6feefc4e63af5725f64fb3899d.pdf

81. Wurz A, McLaughlin E, Lategan C, Chamorro Viña C, Grimshaw SL, Hamari L, et al. The international pediatric oncology exercise guidelines (iPOEG). *Transl Behav Med.* (2021) 11:1915–22. doi: 10.1093/tbm/ibab028

82. Tanner LR, Hooke MC. Improving body function and minimizing activity limitations in pediatric leukemia survivors: the lasting impact of the stoplight program. *Pediatr Blood Cancer.* (2019) 66:e27596. doi: 10.1002/pbc.27596

83. McLeroy KR, Bibeau D, Steckler A, Glanz K. An ecological perspective on health promotion programs. *Health Educ Q.* (1988) 15:351–77. doi: 10.1177/109019818801500401

84. Eldridge SM, Lancaster GA, Campbell MJ, Thabane L, Hopewell S, Coleman CL, et al. Defining feasibility and pilot studies in preparation for randomised controlled trials: development of a conceptual framework. *PLoS One.* (2016) 11:e0150205. doi: 10.1371/journal.pone.0150205

85. Bowen DJ, Kreuter M, Spring B, Cofta-Woerpel L, Linnan L, Weiner D, et al. How we design feasibility studies. *Am J Prev Med.* (2009) 36:452–7. doi: 10.1016/j.amepre.2009.02.002

86. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: medical research council guidance. *BMJ.* (2015) 350:h1258. doi: 10.1136/bmj.h1258

87. Grimmett C, Foster C, Bradbury K, Lally P, May CR, Myall M, et al. Exploring maintenance of physical activity behaviour change among people living with and beyond gastrointestinal cancer: a cross-sectional qualitative study and typology. *BMJ Open.* (2020) 10:e037136. doi: 10.1136/bmjopen-2020-037136

frontiers | Frontiers in Pediatrics

TYPE Opinion
PUBLISHED 14 October 2022
DOI 10.3389/fped.2022.998337

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Oncology, a section of the journal Frontiers in Pediatrics

RECEIVED 19 July 2022
ACCEPTED 28 September 2022
PUBLISHED 14 October 2022

CITATION
Caru M and Curnier D (2022) The pediatric oncology exercise field speeds up to address important issues regarding chemotherapy-related cardiotoxicity.
Front. Pediatr. 10:998337.
doi: 10.3389/fped.2022.998337

The pediatric oncology exercise field speeds up to address important issues regarding chemotherapy-related cardiotoxicity

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KEYWORDS

physical activity, prevention, cardio-oncology, Childhood Cancer Survivors, survivorship, doxorubicin-related cardiotoxicity, healthy lifestyle, cardiovascular risk factors

Introduction

Chemotherapy-related cardiotoxicity is well understood and recognized in oncology (1, 2). Randomized controlled trials have shown that exercise has the potential to prevent chemotherapy-induced cardiotoxicity in adults diagnosed with cancer (3–6). Nevertheless, the pediatric oncology exercise field is in emergence comparatively to the adult oncology exercise field and has also the potential to adequately respond to the chemotherapy-related cardiotoxicity burden that several childhood cancer survivors face. Chemotherapy-related cardiotoxicity causes multiple late comorbidities and is the most common cause of late-onset post-treatment morbidity and mortality in childhood cancer survivors (7). In fact, childhood cancer survivors experience a 2- to 10-fold increased risk of cardiovascular diseases relative to the general population (8) and are seven times more likely to die from cardiovascular complications (e.g., high-grade ectopy, impaired left ventricular contractility, late congestive heart failure, and sudden death) (9, 10). Through the recently published international pediatric oncology exercise guidelines, clinical and research experts in pediatric oncology have highlighted that "cardiotoxicity" is a specific condition that needs to be considered in the field of pediatric oncology exercise (11). Hence, in a recent scoping review discussing the benefits of exercise at different intensities to prevent and manage cancer treatment-related cardiac dysfunction in childhood and adolescent cancer survivors, authors pointed out the necessity to do clinical research to consolidate current findings (12). This opinion paper discusses the potential of exercise for childhood cancer survivors to prevent chemotherapy-related cardiotoxicity and associated cardiovascular risk factors. It also presents the primary key challenges encountered in cardio-oncology and exercise settings.

Cardiac health and exercise capacity in childhood cancer survivors

Every year, almost 10,500 children receive a diagnosis of cancer in the United-States. Among them, approximately 85% live at least 5 years post-diagnosis. As of 2019, the National Cancer Institute has reported that there are 483,000 childhood cancer survivors in the United-States (13). Several childhood cancer survivors are facing chronic health problem related to their cancer treatments. A study combining the Childhood Cancer Survivor Study (CCSS) and the Surveillance Epidemiology and End Results (SEER) data reported that ~70% of childhood cancer survivors face mild to moderate chronic condition, and 32% of them face a severe, disabling or life-threatening chronic condition (14). The authors also showed that chronic health problems increase with age no later than 5 years post-diagnosis (14).

Although medical research and progress have allowed to reach better survival rates, children's exposure to chemotherapeutic agents causes several long-term adverse effects, such as cardiovascular diseases (15). Studies have observed that survivors exposed to anthracycline drugs may face subclinical dysfunctions and cardiac abnormalities (16–21). Indeed, some childhood cancer survivors have a reduced ejection fraction and impaired left ventricular contractility. Moreover, they are at high risk of developing cardiomyopathy and researchers have shown that some childhood cancer survivors are at an early stage of heart failure a few years after the end of their treatment (20, 22). Chemotherapy-related cardiotoxicity is a leading cause of morbidity and mortality by late congestive heart failure and sudden death (9, 10). Findings from the CCSS have shown that they are seven times more likely to die from late cardiovascular complications than their healthy peers (23).

As a result of the treatment, they received during their cancer, childhood cancer survivors have a lower exercise capacity and cardiorespiratory fitness than their healthy peers (24–26). A study performed as part of the St Jude Lifetime Cohort Study (1,041 people who had survived cancer ≥10 years) showed that exercise intolerance [defined by the authors as the inability to perform as expected on a measure of exercise capacity (<85% of predicted VO2 peak and maximal aerobic capacity <7.9 metabolic equivalents)] was associated with mortality (HR = 3.9; 95% CI = 1.09–14.14), global longitudinal strain (OR = 1.71; 95% CI = 1.11–2.63) and chronotropic incompetence (OR = 3.58; 95% CI = 1.75–7.31) (25). Global longitudinal strain is a sensitive measure to detect subclinical left ventricular dysfunction in patients at high risk for heart failure (25, 27). Chronotropic incompetence, however, is a predictor of mortality in cardiac patients and has been associated with cardiac autonomic nervous system dysfunction (28–31). Evidence from observational studies shows that these parameters can be improved by exercise in those who are physically active compared to those who are inactive (32, 33). Indeed, in 15,450 adult survivors of childhood cancer, a multicenter cohort analysis observed that exercise exposure was significantly associated with a reduction in the cumulative incidence of all-cause mortality, relapse and health-related mortality (34). A large case-control study showed that exercising less than 3 days per week was associated with an increased risk for all-cause mortality, compared to childhood cancer survivors who exercised more than 3 days per week (35).

Healthy lifestyle in childhood cancer survivors

Over the past decade, clinical and research experts in pediatric oncology have demonstrated that exercise is beneficial and safe for childhood cancer survivors. A state-of-the-art review recently highlighted the importance of exercise in childhood cancer survivors and its key role in preventing chemotherapy-related cardiotoxicity (15). Indeed, chemotherapy-related cardiotoxicity leads to cardiac dysfunctions (e.g., decline in left ventricular ejection fraction), because of mitochondrial biogenesis impairment (36), whereas exercise stimulates mitochondrial biogenesis (37). Moreover, observational studies have reported that exercise in childhood cancer survivors improves left ventricular ejection fraction (38, 39) and markers of cardiovascular health (33, 40). Several other pathways also need to be taken into consideration as potential mechanisms of chemotherapy-induced cardiotoxicity, such as inhibition of topoisomerase 2B, oxidative stress, DNA damage and Ca^{2+} release and myocardial fibrosis (41–44). Nevertheless, research on the impact of exercise on theses parameters needs to be pursued in human and animal models to strengthen the evidence (45, 46). Studies have shown, however, that chemotherapy-induced cardiotoxicity may not be reversible in animal models and observational human studies biopsies (47–49) which reinforces the importance of exercising during cancer treatments.

Nevertheless, few childhood cancer survivors are physically active. The American Association for Cancer Research (AACR) has reported that almost one in two survivors are not following the physical activity guidelines and that >70% are less likely to be physically active than their healthy peers (50). In an observational cohort study of childhood acute lymphoblastic leukemia survivors, it has been reported that survivors and healthy people had a clinically equivalent level of moderate to vigorous physical activity per week, despite a substantially lower cardiorespiratory fitness level in survivors (24). Long-term follow-up of childhood cancer survivors has shown that their physical activity level worsens significantly until they

ultimately reach a sedentary behavior state (51). These findings are worrying because a low physical activity level is associated with lower cardiac health (33, 35) and an inactive lifestyle has been associated with cardiovascular disease in childhood cancer survivors (52). To enhance cardiac health prognoses and favor health-related benefits in cancer survivors, the American College of Sports Medicine (ACSM) guidelines recommend achieving at least 30 min per day of aerobic exercise training, in addition to doing resistance training (53). Evidence has shown promising results on cardiac function, while requiring further studies to explore the preventative effects of exercise on cardiotoxicity (41, 53, 54).

Considering the current literature, it is important to note that in several childhood cancer survivors, chemotherapy-related cardiotoxicity is reinforced by their lifestyle and behavioral risk factors adopted during and after their treatment (55, 56). It has been well demonstrated that physical inactivity and sedentary behavior favor cardiovascular diseases (57). As an example, physical inactivity has been described as the fourth cardiovascular risk factor and was pointed out to be responsible for over 5 million deaths (58, 59). Cardiovascular diseases are also associated with other risk factors, such as depressive symptoms, metabolic syndrome, weight status (abdominal obesity, overweight, obesity), dyslipidemia, diabetes, hypertension and smoking (60). These cardiovascular risk factors are commonly reported in childhood cancer survivors (61, 62). Thus, addressing childhood cancer survivors' cardiovascular risk factors could be a powerful way to prevent chemotherapy-related cardiotoxicity, in addition to adopting a preventative approach initiated at cancer diagnosis (63, 64).

Primary key challenges

In a recent scoping review, Wogksch et al. described the associations between physical activity and chronic diseases and reported that childhood cancer survivors who engage in physical activity decrease their risk of cardiovascular diseases, in addition to improving markers of cardiovascular diseases and their risk of mortality, compared to childhood cancer survivors who do not engage in physical activity (33). These findings confirm those of Slater et al., who reported in a cross-sectional study that childhood cancer survivors ($n = 319$) with a high physical activity level had lower percent fat mass, abdominal subcutaneous and visceral fat, and greater lean body mass and insulin sensitivity than survivors who reported having a low physical activity level (65). Considering the current literature in cardiology, physical activity has a prophylactic effect on cardiovascular risk factors and does not require for patients to engage in several hours per day of exercise (66). Several studies share the important message that physical inactivity always needs to be avoided in childhood cancer survivors, which can be achieved by engaging in regular physical activity. This also joins the international pediatric oncology exercise guidelines global message that moving is important for all pediatric patients with cancer and survivors (11).

Exercise can be a useful approach to address chemotherapy-related cardiotoxicity in pediatric patients considering that the probability to develop a cardiovascular disease is approximately 3% in childhood cancer survivors who are 30 years old, a number that increases to about 10% at 45 years old (67). The literature highlights that exercise can be an even more powerful approach when addressing cardiovascular risk factors that may have an impact on chemotherapy-related cardiotoxicity observed in childhood cancer survivors. Managing risk factors in cardio-oncology can be challenging considering that most of childhood cancer survivors are under several cardiac parameter thresholds. It is also important to remind that the cardiac challenges they face are different than those in adult patients with cancer or cardiac patients. During the first year of their follow-up, childhood cancer survivors do not have more cardiovascular risk factors than their healthy counterparts (68). While the clinical observations could be encouraging at first glance, long-term follow-ups have shown that the prevalence of cardiovascular risk factors increases with time, as well as the risk of cardiovascular diseases (67, 69). For example, an observational study showed that the impact of chemotherapy treatment was subclinical and that childhood acute lymphoblastic leukemia survivors were in the first stage of heart failure (20). The authors hypothesized that these survivors were compensating for subclinical cardiac remodeling. These findings emphasize the importance of providing cardio-oncology follow-ups to survivors exposed to chemotherapy treatments even if they are not at risk of cardiac diseases at the time of their follow-up appointment. Therefore, ongoing studies are being conducted to enhance our understanding of the effect of exercise on cardiotoxicity in childhood cancer survivors, such as the HIMALAYAS Trial (NCT05023785). The HIMALAYAS trial aims to evaluate the impact of exercise on cardiovascular health in childhood, adolescent and young adult cancer survivors, and is a good example to understand how the research field of pediatric oncology exercise is evolving.

Another challenge is the diagnosis of cardiac dysfunction in childhood cancer survivors. There is no broad consensus on how cardiotoxicity should be measured in childhood cancer survivors, leading to heterogeneity between studies (70–74). Indeed, cardiotoxicity can be measured by a combination of different parameters, such as reduced resting systolic function, reduced resting diastolic dysfunction, impaired hemodynamics and systolic functional reserve measured during exercise or reduced exercise capacity or cardiopulmonary fitness (VO_2 peak). In this sense, clinicians and researchers need to be cautious

when interpreting the reported data and findings on the associations between exercise and cardiotoxicity.

While cardiac dysfunctions can be observed at rest, research experts and clinicians have started recommending an exercise stress test coupled with cardiac imaging techniques to unmask cardiac impairments that are not observable at rest in cancer survivors (75–77). It has been demonstrated that survivors can achieve a safe maximal cardiopulmonary exercise test without being limited by symptoms, potential overprotection, or musculoskeletal issues (78). Nevertheless, in clinical settings, performing a maximal cardiopulmonary exercise test can be a challenge since it requires human and financial resources. And although there are other exercise testing procedures that can be used (79), a maximal cardiopulmonary exercise test remains the gold standard in exercise physiology to measure the maximal oxygen consumption of childhood cancer survivors and their cardiorespiratory fitness, which is associated to their cardiac health. It is also important to note that not all exercise physiologists or healthcare providers are trained to perform a maximal cardiopulmonary exercise test and that not all countries authorize an exercise physiologist to perform this type of maximal exercise test, even under the supervision of a cardiologist.

Finally, to strengthen the pediatric oncology exercise field to address the cardiac health of children with cancer and childhood cancer survivors, exercise professionals should be trained to be experts in oncology and more specifically in cardio-oncology, as recommended (80–82). Having expertise in these two major fields can be a real challenge since a number of factors have to be taken into consideration. For example, evidence-based medicine in pediatric cardio-oncology is different than in adult cardio-oncology. In both cases, it is important to consider patients' health status, treatment trajectory and adopt a multidisciplinary approach.

Conclusion

The pediatric oncology exercise field is in its early stages and future studies are required to explore the benefits of exercise on the cardiovascular health of childhood cancer survivors. As discussed, the evidence regarding chemotherapy-related cardiotoxicity is limited and looking at the big picture by addressing cardiovascular risk factors would be a research path to follow in order to improve our knowledge. It is also important to take into consideration that childhood cancer survivors are children, adolescents and adult patients with different needs and who are at different stages of their physiological and cardiac development. Addressing chemotherapy-related cardiotoxicity is a great challenge and we hope that this paper will generate interest and ideas.

Author contributions

MC designed and wrote the manuscript, and DC revised and contributed to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

Acknowledgments

We appreciate the assistance of Ariane Levesque (Department of Psychology, University of Montreal) for her review and edit of the article in the English language.

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.

Publisher's note

References

1. Lipshultz SE, Diamond MB, Franco VI, Aggarwal S, Leger K, Santos MV, et al. Managing chemotherapy-related cardiotoxicity in survivors of childhood cancers. *Paediatr Drugs*. (2014) 16(5):373–89. doi: 10.1007/s40272-014-0085-1

2. Avila MS, Siqueira SRR, Ferreira SMA, Bocchi EA. Prevention and treatment of chemotherapy-induced cardiotoxicity. *Methodist Debakey Cardiovasc J*. (2019) 15(4):267–73. doi: 10.14797/mdcj-15-4-267

3. Tranchita E, Murri A, Grazioli E, Cerulli C, Emerenziani GP, Ceci R, et al. The beneficial role of physical exercise on anthracyclines induced cardiotoxicity in breast cancer patients. *Cancers*. (2022) 14(9):2288. doi: 10.3390/cancers14092288

4. Scott JM, Nilsen TS, Gupta D, Jones LW. Exercise therapy and cardiovascular toxicity in cancer. *Circulation*. (2018) 137(11):1176–91. doi: 10.1161/CIRCULATIONAHA.117.024671

5. Kirkham AA, Eves ND, Shave RE, Bland KA, Bovard J, Gelmon KA, et al. The effect of an aerobic exercise bout 24 h prior to each doxorubicin treatment for breast cancer on markers of cardiotoxicity and treatment symptoms: a RCT. *Breast Cancer Res Treat*. (2018) 167(3):719–29. doi: 10.1007/s10549-017-4554-4

6. Howden EJ, Bigaran A, Beaudry R, Fraser S, Selig S, Foulkes S, et al. Exercise as a diagnostic and therapeutic tool for the prevention of cardiovascular

dysfunction in breast cancer patients. *Eur J Prev Cardiol*. (2019) 26(3):305–15. doi: 10.1177/2047487318811181

7. Lipshultz SE, Adams MJ, Colan SD, Constine LS, Herman EH, Hsu DT, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions: a scientific statement from the American heart association. *Circulation*. (2013) 128(17):1927–95. doi: 10.1161/CIR.0b013e3182a88099

8. Khanna A, Pequeno P, Gupta S, Thavendiranathan P, Lee DS, Abdel-Qadir H, et al. Increased risk of all cardiovascular disease subtypes among childhood cancer survivors. *Circulation*. (2019) 140(12):1041–3. doi: 10.1161/CIRCULATIONAHA.119.041403

9. Grenier MA, Lipshultz SE. Epidemiology of anthracycline cardiotoxicity in children and adults. *Semin Oncol*. (1998) 25(4 Suppl 10):72–85. doi: 10.1053/j.seminoncol.2006.04.019

10. Kremer LC, van Dalen EC, Offringa M, Ottenkamp J, Voute PA. Anthracycline-induced clinical heart failure in a cohort of 607 children: long-term follow-up study. *J Clin Oncol*. (2001) 19(1):191–6. doi: 10.1200/JCO.2001.19.1.191

11. Wurz A, McLaughlin E, Lategan C, Chamorro Viña C, Grimshaw SL, Hamari L, et al. The international pediatric oncology exercise guidelines (iPOEG). *Transl Behav Med*. (2021) 11(10):1915–22. doi: 10.1093/tbm/ibab028

12. Kendall SJ, Langley JE, Aghdam M, Crooks BN, Giacomantonio N, Heinze-Milne S, et al. The impact of exercise on cardiotoxicity in pediatric and adolescent cancer survivors: a scoping review. *Curr Oncol*. (2022) 29(9):6350–63. doi: 10.3390/curroncol29090500

13. National cancer Institute. *Childhood cancer survivor study: An overview United-States*. Bethesda, Maryland: U.S. Department of Health and Human Services (2021). Available from: https://www.cancer.gov/types/childhood-cancers/ccss.

14. Phillips SM, Padgett LS, Leisenring WM, Stratton KK, Bishop K, Krull KR, et al. Survivors of childhood cancer in the United States: prevalence and burden of morbidity. *Cancer Epidemiol, Biomarkers Prev*. (2015) 24(4):653–63. doi: 10.1158/1055-9965.EPI-14-1418

15. Leerink JM, de Baat EC, Feijen EA, Bellersen L, van Dalen EC, Grotenhuis HB, et al. Cardiac disease in childhood cancer survivors: risk prediction, prevention, and surveillance: JACC cardiooncology state-of-the-art review. *Cardio Oncol*. (2020) 2(3):363–78. doi: 10.1016/j.jaccao.2020.08.006

16. Armstrong GT, Plana JC, Zhang N, Srivastava D, Green DM, Ness KK, et al. Screening adult survivors of childhood cancer for cardiomyopathy: comparison of echocardiography and cardiac magnetic resonance imaging. *J Clin Oncol*. (2012) 30(23):2876–84. doi: 10.1200/JCO.2011.40.3584

17. Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N Engl J Med*. (1991) 324(12):808–15. doi: 10.1056/NEJM199103213241205

18. Lipshultz SE, Lipsitz SR, Sallan SE, Dalton VM, Mone SM, Gelber RD, et al. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. *J Clin Oncol*. (2005) 23(12):2629–36. doi: 10.1200/JCO.2005.12.121

19. Ylänen K, Poutanen T, Savikurki-Heikkilä P, Rinta-Kiikka I, Eerola A, Vettenranta K. Cardiac magnetic resonance imaging in the evaluation of the late effects of anthracyclines among long-term survivors of childhood cancer. *J Am Coll Cardiol*. (2013) 61(14):1539–47. doi: 10.1016/j.jacc.2013.01.019

20. Caru M, Corbin D, Perie D, Lemay V, Delfrate J, Drouin S, et al. Doxorubicin treatments induce significant changes on the cardiac autonomic nervous system in childhood acute lymphoblastic leukemia long-term survivors. *Clin Res Cardiol*. (2019) 108(9):1000–8. doi: 10.1007/s00392-019-01427-9

21. De Caro E, Smeraldi A, Trocchio G, Calevo M, Hanau G, Pongiglione G. Subclinical cardiac dysfunction and exercise performance in childhood cancer survivors. *Pediatr Blood Cancer*. (2011) 56(1):122–6. doi: 10.1002/pbc.22606

22. Lipshultz SE, Franco VI, Miller TL, Colan SD, Sallan SE. Cardiovascular disease in adult survivors of childhood cancer. *Annu Rev Med*. (2015) 66:161–76. doi: 10.1146/annurev-med-070213-054849

23. Armstrong GT, Liu Q, Yasui Y, Neglia JP, Leisenring W, Robison LL, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the childhood cancer survivor study. *J Clin Oncol*. (2009) 27(14):2328–38. doi: 10.1200/JCO.2008.21.1425

24. Caru M, Samoilenko M, Drouin S, Lemay V, Kern L, Romo L, et al. Childhood acute lymphoblastic leukemia survivors have a substantially lower cardiorespiratory fitness level than healthy Canadians despite a clinically equivalent level of physical activity. *J Adolesc Young Adult Oncol*. (2019) 8(6):674–83. doi: 10.1089/jayao.2019.0024

25. Ness KK, Plana JC, Joshi VM, Luepker RV, Durand JB, Green DM, et al. Exercise intolerance, mortality, and organ system impairment in adult survivors of childhood cancer. *J Clin Oncol*. (2020) 38(1):29. doi: 10.1200/JCO.19.01661

26. Miller AM, Lopez-Mitnik G, Somarriba G, Lipsitz SR, Hinkle AS, Constine LS, et al. Exercise capacity in long-term survivors of pediatric cancer: an analysis from the cardiac risk factors in childhood cancer survivors study. *Pediatr Blood Cancer*. (2013) 60(4):663–8. doi: 10.1002/pbc.24410

27. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American society of echocardiography and the European association of cardiovascular imaging. *J Am Soc Echocardiogr*. (2014) 27(9):911–39. doi: 10.1016/j.echo.2014.07.012

28. Fei L, Keeling PJ, Sadoul N, Copie X, Malik M, McKenna WJ, et al. Decreased heart rate variability in patients with congestive heart failure and chronotropic incompetence. *Pacing Clin Electrophysiol*. (1996) 19(4 Pt 1):477–83. doi: 10.1111/j.1540-8159.1996.tb06519.x

29. Kawasaki T, Kaimoto S, Sakatani T, Miki S, Kamitani T, Kuribayashi T, et al. Chronotropic incompetence and autonomic dysfunction in patients without structural heart disease. *Europace*. (2010) 12(4):561–6. doi: 10.1093/europace/eup433

30. Paolillo S, Agostoni P, De Martino F, Ferrazzano F, Marsico F, Gargiulo P, et al. Heart rate during exercise: mechanisms, behavior, and therapeutic and prognostic implications in heart failure patients with reduced ejection fraction. *Heart Fail Rev*. (2018) 23(4):537–45. doi: 10.1007/s10741-018-9712-1

31. Bertrand É, Caru M, Lemay V, Andelfinger G, Laverdiere C, Krajinovic M, et al. Heart rate response and chronotropic incompetence during cardiopulmonary exercise testing in childhood acute lymphoblastic leukemia survivors. *Pediatr Hematol Oncol*. (2021) 38(6):564–80. doi: 10.1080/08880018.2021.1894279

32. Naaktgeboren WR, Groen WG, Jacobse JN, Steggink LC, Walenkamp AM, van Harten WH, et al. Physical activity and cardiac function in long-term breast cancer survivors: a cross-sectional study. *JACC CardioOncol*. (2022) 4(2):183–91. doi: 10.1016/j.jaccao.2022.02.007.

33. Wogksch MD, Goodenough CG, Finch ER, Partin RE, Ness KK. Physical activity and fitness in childhood cancer survivors: a scoping review. *Aging and Cancer*. (2021) 2(4):112–28. doi: 10.1002/aac2.12042

34. Scott JM, Li N, Liu Q, Yasui Y, Leisenring W, Nathan PC, et al. Association of exercise with mortality in adult survivors of childhood cancer. *JAMA Oncol*. (2018) 4(10):1352–8. doi: 10.1001/jamaoncol.2018.2254

35. Cox CL, Nolan VG, Leisenring W, Yasui Y, Ogg SW, Mertens AC, et al. Noncancer-related mortality risks in adult survivors of pediatric malignancies: the childhood cancer survivor study. *J Cancer Surviv*. (2014) 8(3):460–71. doi: 10.1007/s11764-014-0353-7

36. Kang DW, Wilson RL, Christopher CN, Normann AJ, Barnes O, Lesansee JD, et al. Exercise cardio-oncology: exercise as a potential therapeutic modality in the management of anthracycline-induced cardiotoxicity. *Front Cardiovasc Med*. (2021) 8:805735. doi: 10.3389/fcvm.2021.805735

37. Freyssenet D, Berthon P, Denis C. Mitochondrial biogenesis in skeletal muscle in response to endurance exercises. *Arch Physiol Biochem*. (1996) 104(2):129–41. doi: 10.1076/apab.104.2.129.12878

38. Smith WA, Ness KK, Joshi V, Hudson MM, Robison LL, Green DM. Exercise training in childhood cancer survivors with subclinical cardiomyopathy who were treated with anthracyclines. *Pediatr Blood Cancer*. (2013) 61(5):942–5. doi: 10.1002/pbc.24850

39. Järvelä LS, Saraste M, Niinikoski H, Hannukainen JC, Heinonen OJ, Lähteenmäki PM, et al. Home-based exercise training improves left ventricle diastolic function in survivors of childhood ALL: a tissue Doppler and velocity vector imaging study. *Pediatr Blood Cancer*. (2016) 63(9):1629–35. doi: 10.1002/pbc.26051

40. Morales JS, Valenzuela PL, Herrera-Olivares AM, Baño-Rodrigo A, Castillo-García A, Rincón-Castanedo C, et al. Exercise interventions and cardiovascular health in childhood cancer: a meta-analysis. *Int J Sports Med*. (2020) 41(3):141–53. doi: 10.1055/a-1073-8104

41. Chen JJ, Wu PT, Middlekauff HR, Nguyen KL. Aerobic exercise in anthracycline-induced cardiotoxicity: a systematic review of current evidence and future directions. *Am J Physiol Heart Circ Physiol*. (2017) 312(2):H213–h22. doi: 10.1152/ajpheart.00646.2016

42. Carrasco R, Castillo RL, Gormaz JG, Carrillo M, Thavendiranathan P. Role of oxidative stress in the mechanisms of anthracycline-induced cardiotoxicity: effects of preventive strategies. *Oxid Med Cell Longev*. (2021) 2021:8863789. doi: 10.1155/2021/8863789

43. Bhatia S. Genetics of anthracycline cardiomyopathy in cancer survivors: JACC: cardioOncology state-of-the-art review. *JACC CardioOncol*. (2020) 2(4):539–52. doi: 10.1016/j.jaccao.2020.09.006

44. Murabito A, Hirsch E, Ghigo A. Mechanisms of anthracycline-induced cardiotoxicity: is mitochondrial dysfunction the answer? *Front Cardiovasc Med*. (2020) 7:35. doi: 10.3389/fcvm.2020.00035

45. Yen CJ, Hung CH, Tsai WM, Cheng HC, Yang HL, Lu YJ, et al. Effect of exercise training on exercise tolerance and level of oxidative stress for head and neck cancer patients following chemotherapy. *Front Oncol*. (2020) 10:1536. doi: 10.3389/fonc.2020.01536

46. Hahn VS, Lenihan DJ, Ky B. Cancer therapy–induced cardiotoxicity: basic mechanisms and potential cardioprotective therapies. *J Am Heart Assoc*. (2014) 3(2):e000665. doi: 10.1161/JAHA.113.000665

47. Mackay B, Ewer MS, Carrasco CH, Benjamin RS. Assessment of anthracycline cardiomyopathy by endomyocardial biopsy. *Ultrastruct Pathol*. (1994) 18(1-2):203–11. doi: 10.3109/01913129409016291

48. Jensen BV, Skovsgaard T, Nielsen SL. Functional monitoring of anthracycline cardiotoxicity: a prospective, blinded, long-term observational study of outcome in 120 patients. *Ann Oncol*. (2002) 13(5):699–709. doi: 10.1093/annonc/mdf132

49. Timm KN, Perera C, Ball V, Henry JA, Miller JJ, Kerr M, et al. Early detection of doxorubicin-induced cardiotoxicity in rats by its cardiac metabolic signature assessed with hyperpolarized MRI. *Commun Biol*. (2020) 3(1):1–10. doi: 10.1038/s42003-019-0734-6

50. Florin TA, Fryer GE, Miyoshi T, Weitzman M, Mertens AC, Hudson MM, et al. Physical inactivity in adult survivors of childhood acute lymphoblastic leukemia: a report from the childhood cancer survivor study. *Cancer Epidemiol Biomarkers Prev*. (2007) 16(7):1356–63. doi: 10.1158/1055-9965.EPI-07-0048

51. Smith WA, Nolan VG, Robison LL, Hudson MM, Ness KK. Physical activity among cancer survivors and those with no history of cancer- a report from the national health and nutrition examination survey 2003–2006. *Am J Transl Res*. (2011) 3(4):342–50.

52. Shankar SM, Marina N, Hudson MM, Hodgson DC, Adams MJ, Landier W, et al. Monitoring for cardiovascular disease in survivors of childhood cancer: report from the cardiovascular disease task force of the Children's oncology group. *Pediatrics*. (2008) 121(2):e387–96. doi: 10.1542/peds.2007-0575

53. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. *Med Sci Sports Exercise*. (2019) 51(11):2375–90. doi: 10.1249/MSS.0000000000002116

54. Costello BT, Roberts TJ, Howden EJ, Bigaran A, Foulkes SJ, Beaudry RI, et al. Exercise attenuates cardiotoxicity of anthracycline chemotherapy measured by global longitudinal strain. *JACC CardioOncol*. (2019) 1(2):298–301. doi: 10.1016/j.jaccao.2019.09.002

55. Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of anthracyclines. *Front Cardiovasc Med*. (2020) 7:26. doi: 10.3389/fcvm.2020.00026

56. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC committee for practice guidelines: the task force for cancer treatments and cardiovascular toxicity of the European society of cardiology (ESC). *Eur Heart J*. (2016) 37 (36):2768–801. doi: 10.1093/eurheartj/ehw211

57. Chomistek AK, Manson JE, Stefanick ML, Lu B, Sands-Lincoln M, Going SB, et al. Relationship of sedentary behavior and physical activity to incident cardiovascular disease: results from the Women's health initiative. *J Am Coll Cardiol*. (2013) 61(23):2346–54. doi: 10.1016/j.jacc.2013.03.031

58. Wen CP, Wu X. Stressing harms of physical inactivity to promote exercise. *Lancet*. (2012) 380(9838):192–3. doi: 10.1016/S0140-6736(12)60954-4

59. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. (2004) 364 (9438):937–52. doi: 10.1016/S0140-6736(04)17018-9

60. World Health Organization. Cardiovascular diseases (CVDs): World Health Organization (2021). Available at: http://www.who.int/mediacentre/factsheets/fs317/en/.

61. Lemay V, Caru M, Samoilenko M, Drouin S, Alos N, Lefebvre G, et al. Prevention of long-term adverse health outcomes with cardiorespiratory fitness and physical activity in childhood acute lymphoblastic leukemia survivors. *J Pediatr Hematol Oncol*. (2019) 41(7):e450–e8. doi: 10.1097/MPH.0000000000001426

62. Luongo C, Randazzo E, Iughetti L, DI Iorgi N, Loche S, Maghnie M, et al. Cardiometabolic risk in childhood cancer survivors. *Minerva Pediatr*. (2021) 73 (6):588–605. doi: 10.23736/S2724-5276.21.06544-7

63. Caru M, Duhamel G, Marcil V, Sultan S, Meloche C, Bouchard I, et al. The VIE study: feasibility of a physical activity intervention in a multidisciplinary program in children with cancer. *Support Care Cancer*. (2020) 28(6):2627–36. doi: 10.1007/s00520-019-05085-5

64. Bélanger V, Delorme J, Napartuk M, Bouchard I, Meloche C, Curnier D, et al. Early nutritional intervention to promote healthy eating habits in pediatric oncology: a feasibility study. *Nutrients*. (2022) 14(5):1024–45. doi: 10.3390/nu14051024

65. Slater ME, Ross JA, Kelly AS, Dengel DR, Hodges JS, Sinaiko AR, et al. Physical activity and cardiovascular risk factors in childhood cancer survivors. *Pediatr Blood Cancer*. (2015) 62(2):305–10. doi: 10.1002/pbc.25276

66. Caru M, Kern L, Bousquet M, Curnier D. Preventive fraction of physical fitness on risk factors in cardiac patients: retrospective epidemiological study. *World J Cardiol*. (2018) 10(4):26–34. doi: 10.4330/wjc.v10.i4.26

67. Faber J, Wingerter A, Neu MA, Henninger N, Eckerle S, Münzel T, et al. Burden of cardiovascular risk factors and cardiovascular disease in childhood cancer survivors: data from the German CVSS-study. *Eur Heart J*. (2018) 39 (17):1555–62. doi: 10.1093/eurheartj/ehy026

68. Lipshultz ER, Chow EJ, Doody DR, Armenian SH, Asselin BL, Baker KS, et al. Cardiometabolic risk in childhood cancer survivors: a report from the Children's oncology group. *Cancer Epidemiol Biomarkers Prev*. (2022) 31 (3):536–42. doi: 10.1158/1055-9965.EPI-21-0360

69. Armstrong GT, Oeffinger KC, Chen Y, Kawashima T, Yasui Y, Leisenring W, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. *J Clin Oncol*. (2013) 31(29):3673–80. doi: 10.1200/JCO.2013.49.3205

70. Harake D, Franco VI, Henkel JM, Miller TL, Lipshultz SE. Cardiotoxicity in childhood cancer survivors: strategies for prevention and management. *Future Cardiol*. (2012) 8(4):647–70. doi: 10.2217/fca.12.44

71. Stone JR, Kanneganti R, Abbasi M, Akhtari M. Monitoring for chemotherapy-related cardiotoxicity in the form of left ventricular systolic dysfunction: a review of current recommendations. *JCO Oncol Prac*. (2021) 17 (5):228–36. doi: 10.1200/OP.20.00924

72. Wolf CM, Reiner B, Kühn A, Hager A, Müller J, Meierhofer C, et al. Subclinical cardiac dysfunction in childhood cancer survivors on 10-years follow-up correlates with cumulative anthracycline dose and is best detected by cardiopulmonary exercise testing, circulating serum biomarker, speckle tracking echocardiography, and tissue Doppler imaging. *Front Pediatr*. (2020) 8:123. doi: 10.3389/fped.2020.00123

73. Sofia R, Melita V, De Vita A, Ruggiero A, Romano A, Attinà G, et al. Cardiac surveillance for early detection of late subclinical cardiac dysfunction in childhood cancer survivors after anthracycline therapy. *Front Oncol*. (2021) 11:1649. doi: 10.3389/fonc.2021.624057

74. Ryerson AB, Border WL, Wasilewski-Masker K, Goodman M, Meacham L, Austin H, et al. Assessing anthracycline-treated childhood cancer survivors with advanced stress echocardiography. *Pediatr Blood Cancer*. (2015) 62(3):502–8. doi: 10.1002/pbc.25328

75. Kirkham AA, Virani SA, Campbell KL. The utility of cardiac stress testing for detection of cardiovascular disease in breast cancer survivors: a systematic review. *Int J Womens Health*. (2015) 7:127–40. doi: 10.2147/IJWH.S68745

76. Kearney MC, Gallop-Evans E, Cockcroft JR, Stöhr EJ, Lee E, Backx K, et al. Cardiac dysfunction in cancer survivors unmasked during exercise. *Eur J Clin Invest*. (2017) 47(3):213–20. doi: 10.1111/eci.12720

77. Foulkes S, Costello BT, Howden EJ, Janssens K, Dillon H, Toro C, et al. Exercise cardiovascular magnetic resonance reveals reduced cardiac reserve in pediatric cancer survivors with impaired cardiopulmonary fitness. *J Cardiovasc Magn Reson*. (2020) 22(1):64. doi: 10.1186/s12968-020-00658-4

78. Caru M, Laverdière C, Lemay V, Drouin S, Bertout L, Krajinovic M, et al. Maximal cardiopulmonary exercise testing in childhood acute lymphoblastic leukemia survivors exposed to chemotherapy. *Support Care Cancer*. (2021) 29 (2):987–96. doi: 10.1007/s00520-020-05582-y

79. Mizrahi D, Fardell JE, Cohn RJ, Partin RE, Howell CR, Hudson MM, et al. The 6-minute walk test is a good predictor of cardiorespiratory fitness in childhood cancer survivors when access to comprehensive testing is limited. *Int J Cancer*. (2019) 47(3):847–55. doi: 10.1002/ijc.32819

80. Gevaert SA, Halvorsen S, Sinnaeve PR, Sambola A, Gulati G, Lancellotti P, et al. Evaluation and management of cancer patients presenting with acute cardiovascular disease: a consensus document of the Acute CardioVascular Care (ACVC) association and the ESC council of cardio-oncology-part 1: acute coronary syndromes and acute pericardial diseases. *Eur Heart J Acute Cardiovasc Care*. (2021) 10(8):947–59. doi: 10.1093/ehjacc/zuab056

81. Cuomo A, Mercurio V, Varricchi G, Galdiero MR, Rossi FW, Carannante A, et al. Impact of a cardio-oncology unit on prevention of cardiovascular events in cancer patients. *ESC Heart Fail*. (2022) 9(3):1666–76. doi: 10.1002/ehf2.13879

82. Hamm LF, Sanderson BK, Ades PA, Berra K, Kaminsky LA, Roitman JL, et al. Core competencies for cardiac rehabilitation/secondary prevention professionals: 2010 update: position statement of the American association of cardiovascular and pulmonary rehabilitation. *J Cardiopulm Rehabil Prev*. (2011) 31(1):2–10. doi: 10.1097/HCR.0b013e318203999d

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 28 October 2022
DOI 10.3389/fped.2022.976012

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Oncology, a section of the journal Frontiers in Pediatrics

RECEIVED 22 June 2022
ACCEPTED 10 October 2022
PUBLISHED 28 October 2022

CITATION
Wogksch MD, Finch ER, Nolan VG, Smeltzer MP, Mzayek F, Goodenough CG, Pui C-H, Inaba H, Mulrooney DA, Kaste SC, Brinkman TM, Lanctot JQ, Srivastava DK, Jefferies JL, Armstrong GT, Robison LL, Hudson MM and Ness KK (2022) Energy cost of walking in obese survivors of acute lymphoblastic leukemia: A report from the St. Jude Lifetime Cohort. Front. Pediatr. 10:976012. doi: 10.3389/fped.2022.976012

Energy cost of walking in obese survivors of acute lymphoblastic leukemia: A report from the St. Jude Lifetime Cohort

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Purpose: Adult survivors of childhood acute lymphoblastic leukemia (ALL) have impaired adaptive physical function and poor health-related quality of life (HRQoL). Obesity may contribute to these impairments by increasing the physiological cost of walking. Due to treatment exposures during ALL therapy, survivors' cost of walking may be more impacted by obesity than the general population. Therefore, we examined associations between obesity, persistent motor neuropathy, and energy cost of walking; and examined associations between energy cost of walking, adaptive physical function, and HRQoL, in adult survivors of childhood ALL vs. community controls.

Methods: Obesity was measured *via* body mass index (BMI) and body fat percentage. The physiological cost index (PCI) was calculated from the six-minute walk test. Adaptive physical functioning was measured using two tests: the timed up and go (TUG) test and the physical performance test. Persistent motor neuropathy was measured using the modified total neuropathy score; HRQoL was measured using the Short-Form-36 questionnaire. The associations between obesity and PCI were evaluated using multivariable linear regressions in adult survivors of childhood ALL (n = 1,166) and community controls (n = 491). Then, the associations

Abbreviations
ALL, Acute lymphoblastic leukemia; 6 MWT, six-minute walk test; BMI, body mass index; HRQoL, Health-related quality of life; MCS, mental component summary score; PA, physical activity; PCI, physiological cost index; PCS, physical component summary score; SF-36, Medical Outcomes Survey Short-Form-36; PPT, physical performance test; TUG, timed up and go.

between PCI, adaptive physical functioning and peripheral neuropathy were examined using multivariable linear regressions. Finally, to determine the association between obesity, and neuropathy on PCI, while accounting for potential lifestyle and treatment confounders, a three model, sequential linear regression was used.

Results: Obese individuals (BMI > 40 kg/m^2 and excess body fat percentage [males: >25%; females: >33%]) had higher PCI compared to those with normal BMI and body fat percentage (0.56 ± 0.01 vs. 0.49 ± 0.009 beats/meter $p < .01$; and 0.51 ± 0.007 vs. 0.48 ± .0006 beats/meter $p < .01$, respectively). Treatment exposures did not attenuate this association. Increased PCI was associated with longer TUG time in survivors, but not community controls (6.14 ± 0.02 s vs. 5.19 ± 0.03 s, $p < .01$). Survivors with PCI impairment >95th percentile of community controls had lower HRQoL compared to un-impaired ALL survivors: 46.9 ± 0.56 vs. 50.4 ± 1.08, respectively ($p < .01$).

Conclusion: Obesity was associated with increased PCI. Survivors with high PCI had disproportionately worse adaptive physical function and HRQoL compared to controls. Survivors with increased energy costs of walking may benefit from weight loss interventions.

KEYWORDS

childhood cancer, fitness, obesity, quality of life, acute lymphoblastic leukemia

Introduction

Due to advances in cancer therapy and supportive care, the 5-year survival rate of childhood acute lymphoblastic leukemia (ALL) now exceeds 90%, with ALL representing 19% of all long-term childhood cancer survivors (1). Over the past six decades, therapy for ALL has not only improved survival, but has also been refined to minimize long-term morbidities and optimize health for survivors (2). Nevertheless, survivors of childhood ALL, when compared to their peers, remain at increased risk for chronic health conditions, including obesity, that interfere with activities of daily living (3).

Obesity is a prevalent public health problem associated with chronic disease, including metabolic disease, cardiovascular disease, secondary cancers, and type II diabetes (4–6). It is particularly concerning in ALL survivors, as past treatment exposures confer risk for comorbidities, including diabetes and cardiovascular disease. Obesity perpetuates these chronic health conditions. Although obesity may be a modifiable condition, it may be difficult to manage in adult survivors of childhood ALL, particularly in ALL survivors with neuromusculoskeletal problems (i.e., persistent motor neuropathy) that interfere with health optimizing behaviors, including engagement in physical activity (PA) (7). Additionally, ALL survivors have increased sedentary behavior compared to peers, which may independently increase risk for these chronic health conditions (8).

Energy cost is the relative oxygen cost required to perform an activity or to move the body through space (9). In the general population, adults with obesity have a higher energy cost of performing activities compared to those without obesity (10). Higher energy cost of activity changes the perception of exertion while moving, increases fatiguability, and reduces time spent in PA (11). This results in a reciprocal association between PA and obesity: obesity contributes to reduced PA because movement is difficult; less movement reduces overall energy expenditure and, if not countered by reduced energy intake, results in weight gain (12, 13). Excess body weight taxes the body's systems. Initially, among overweight persons, only vigorous activity may seem difficult. however, this impairment may interfere if job demands, or leisure activities, require vigorous organ system responses. Subsequently, as body weight increases, less intensive activities, e.g., walking, housework, grocery shopping, or getting out of a chair, become difficult, limiting participation in important life roles, and eventually interfering with quality of life (14).

When compared to peers, adult survivors of childhood ALL spend significantly less time in moderate to vigorous PA (15). They are also at an increased risk for difficulties with performing activities of daily living that require negotiating the environment outside of the home, and have a lower physical component summary score (PCS), a measure of physical health-related quality of life (HRQoL) (16). Peripheral neuropathy is a prevalent outcome in ALL survivors, and is related to cancer therapy (13). Associations between peripheral neuropathy, activities of daily living, and HRQoL are well known (17–20). However, the impact of obesity, and peripheral neuropathy, on the energy costs of daily activity, adaptive physical function, and HRQoL, have not been explored in this population. Understanding these associations have the potential to provide information to help tailor interventions designed to increase PA and/or promote weight loss, which have previously produced inconsistent results (21). Thus, the aims of this study were to examine

associations between obesity, persistent motor neuropathy and energy cost of walking, and to examine associations between energy cost of walking, adaptive physical function, and HRQoL in adult survivors of childhood ALL.

Materials and methods

Study population

Participants included members of the St. Jude Lifetime Cohort (22), assembled to assess health outcomes in aging survivors of childhood malignancies. For these analyses, we included any adult survivors (≥18 years of age) of childhood ALL treated at St. Jude Children's Research Hospital (since it's opening) that were at least 10 years from their original diagnosis (1962–2012). Participants also must have completed an on-campus assessment [e.g., self-reported questionnaires and a functional assessment ($n = 1{,}166$, age range 18.0–65.5 years)]. A comparison group (community controls) was also recruited from parents/relatives of current pediatric patients, and adult friends of survivors. Controls were not first-degree relatives of St. Jude Lifetime Cohort participants, had no history of childhood cancer, but did not have to be free of other chronic disease ($n = 491$, age range 18.2–70.2 years). The St. Jude Children's Research Hospital Institutional Review Board approved all procedures. Written informed consent was obtained on all participants prior to testing.

Anthropometrics

Height in centimeters (cm) and weight in kilograms (kg) were measured using a wall-mounted stadiometer and electronic scale (Model 5002, ScaleTronix, Inc., Wheaton, IL). Body mass index (BMI) was calculated and categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obese grade I (30.0–34.9 kg/m^2), obese grade II (35.0–39.9 kg/m^2), and obese grade III (≥40.0 kg/m^2). Percent body fat was measured *via* the three site technique (males: pectoral, abdominal, and thigh; females: triceps, suprailiac, and thigh) by trained exercise physiologists, using the Harpenden skinfold caliper (Baty, West Sussex, United Kingdom) (23). The three site skinfold technique is a valid alternative to dual energy x-ray absorptiometry in childhood cancer survivors (24). Survivors and controls were categorized as having normal body fat (males: <27.5%; females: <39.9%) or excess body fat (males: ≥27.5%; females: ≥39.9%) (25).

Outcomes

To measure the energy cost of walking, the physiological cost index (PCI) was calculated (maximal heart rate while walking—resting heart rate)/(meters walked) (beats per meter) from the six-minute walk test (6 MWT). While the PCI calculation from the 6 MWT is not been specifically validated in adult survivors of childhood cancer, it is a valid measure of walking efficiency in children with cystic fibrosis (26), persons with traumatic brain injury (27) or stroke (28), non-disabled older adults (29), persons with amputation (30), and survivors of polio (31). Before the test, participants were asked to sit quietly for five minutes to acquire resting heart rate. Participants were then instructed to walk as fast as they could around a 41-meter track. Heart rate (measured using the Masimo Rad-5 handheld pulse oximeter, Irvine, CA) was taken at two-, four-, and six-minutes. To meet the assumption that the participants' heart rate was in steady state, maximal heart rate was defined as the highest heart rate at the four-minute or six-minute measurement.

To assess HRQoL, participants completed the Medical Outcomes Survey Short-Form-36 (SF-36), which has been previously validated in adult survivors of childhood cancer (32). The SF-36 contains eight subscales: physical function, role physical, vitality, bodily pain, general health, social functioning, role emotional and mental health; and two summary scores: PCS and mental component summary (MCS). For these analyses, we included subscale scores and summary scores. Raw scores were calculated and converted into T-scores: with the general population mean 50 and standard deviation 10. Higher scores indicated better HRQoL.

Adaptive physical functioning was assessed using a 7-item physical performance test (PPT) and a timed up-and-go (TUG) test. The PPT is an examination of fine and gross motor skills designed to simulate activities of daily living. More specifically, the examiner evaluates the participant on how fast they can write a sentence, simulate eating by moving five beans into an empty bowl with a spoon, lift an object onto a shelf, put on and remove a jacket, pick up a coin from the floor, and turn 360 degrees and walk 50 feet. The PPT is more sensitive than traditional self-reports in detecting loss of function (33). The TUG test evaluates balance and mobility, measured as the time required to stand up from a seated position, walk three meters, turn around, walk back three meters, and sit down again. The TUG has excellent reliability (intraclass correlation coefficient: 0.93) and good discriminate validity (area under the curve: 0.65) (34).

Other measures

Diagnosis and treatment information were obtained from medical records by trained abstractors and included type of individual chemotherapeutic agents and if survivors received cranial radiation therapy. Demographic information such as smoking status and educational attainment were obtained

from questionnaires that the participants complete during their St. Jude Lifetime Cohort evaluation.

Physical activity levels were determined using six self-report items from the National Health and Nutrition Examination Survey (35). The questions asked if the participant spent at least ten minutes doing vigorous PA, on how many days per week they did these activities, and for how many total minutes per day; identical questions were asked for moderate physical activities. Weekly minutes of vigorous activity were multiplied by six; weekly minutes of moderate activities were multiplied by three and summed to get metabolic equivalent minutes per week. For analysis, PA was dichotomized into meeting (≥450 metabolic equivalent minutes per week) or not meeting the 2018 Centers for Disease Control and Prevention (CDC) guidelines (36).

Peripheral nervous system integrity was evaluated with the modified Total Neuropathy Scale (37) consisting of self-reported sensory and motor symptoms, and quantitative testing. Protective sensation was evaluated with a 4.17 log force Semmes Weinstein Monofilament. Vibration was measured using a Bioesthesiometer with a threshold of 9.0 volts (Bio-Medical Instrument Company, Newbury, OH). Manual muscle testing was performed on the fingers, ankles, and wrists (37). Reflex testing was performed in the ankles, knees, brachioradialis, biceps, and triceps tendons. A total score of 24 was possible: having fewer or no symptoms or measured deficits equated to having lower scores (37).

Statistical analysis

Descriptive statistics of participants vs. non-participants characteristics and survivors vs. community controls were calculated and compared using chi-squared tests or Fischer's exact test for categorical variables, and two sample t-tests for continuous variables. Multivariable linear regressions were used to examine the associations of BMI and percent body fat with PCI in survivors and community controls. The models were adjusted for potential confounders (age, sex, race, and smoking status) that changed the beta estimate for the association between BMI or body fat percentage and PCI by more than ten percent. Initial models included interaction terms (BMI × group and percent body fat × group) which were not significant. Due to the changing trends in PA over the decades, as well as the marked increase in 5-year survival starting in the 1980s for ALL, a supplemental analysis limited survivors to those treated after 1980 to see if results differed when those treated in the 1960s and 1970s were not included (38, 39). To determine the effects of neuropathy and obesity on the energy cost of walking among survivors, while accounting for potential confounders of these associations, three sequential regression models were used (40). The first model regressed past treatment exposures and prevalent neuropathy on PCI; the second regressed past treatment exposures, BMI, and prevalent neuropathy on PCI, and the third model regressed treatment exposures, BMI, prevalent neuropathy, and lifestyle factors on PCI (40). Multivariable linear models, adjusted for potential confounders (age, sex, race, smoking status, and PA), and that included a PCI by group (survivor vs. control) interaction term were used to determine associations between PCI (as both a continuous measure and as two separate dichotomies (>90th percentile (impaired) vs. ≤90th percentile (not impaired); >95th percentile (severely impaired) vs. ≤95th percentile (not severely impaired), adaptive physical functioning and HRQoL. Variables that modified associations between PCI and either adaptive physical functioning or HRQoL were retained (41). Data were analyzed with SAS version 9.4 (SAS Institute, Cary, NC).

Results

Characteristics of participants

Among 1,521 adult ALL survivors potentially eligible for analysis, 1,166 (76.7%) participants completed an on campus visit and a functional assessment that included the 6 WMT, while the remaining 355 eligible survivors refused to participate, could not be contacted, completed a survey only, or did not complete the 6 MWT (**Supplementary Figure S1**). Compared to non-participants, participants were older, more likely to have received glucocorticoids, 6-mercaptopurine, cytarabine, doxorubicin, daunorubicin, and etoposide, but less likely to have received cranial irradiation (**Supplementary Table S1**).

Compared to community controls, survivors were older and more likely to be male, more likely to report current smoking, and less likely to report adequate PA, and had lower educational attainment. Survivors were also more likely to be categorized as obese grade I, obese grade II, and were more likely to have excess body fat vs. community controls (**Table 1**).

Physiological cost index

Means (±SE) of the PCI in survivors and community controls, categorized by BMI and body fat percentage, are shown in **Table 2**. After removing nine survivors and seven community controls who could not complete the 6 MWT (see **Table 2** footnote for reasons), the PCI was significantly higher in individuals classified by BMI with grade III obesity compared to those with normal weight; and those with excess body fat percentage, compared to those who were normal. The PCI was also significantly higher in survivors compared to community controls in the model with BMI as an

TABLE 1 Demographic characteristics of acute lymphoblastic leukemia survivors and the community controls.

	Survivors (n = 1,166)	Controls (n = 491)	p
Age at evaluation in years, mean (SD)	37.3 (9.9)	34.8 (10.1)	0.001
Age at diagnosis in years, mean (SD)	6.8 (4.5)	N/A N/A	N/A
Sex, n (%)			
Male	607 (52.0)	221 (44.5)	0.001
Female	559 (48.0)	275 (55.4)	
Race,[a] n (%)			
White	1,036 (88.8)	432 (88.0)	0.15
Black	104 (8.9)	40 (8.1)	
Other	26 (2.2)	19 (3.9)	
Body mass index, n (%)			
Normal weight	292 (25.1)	174 (35.4)	0.001
Overweight	323 (27.7)	133 (27.1)	
Obese grade I	266 (22.8)	77 (15.7)	
Obese grade II	153 (13.1)	52 (13.1)	
Obese grade III	111 (9.5)	43 (8.8)	
Underweight	21 (1.8)	12 (2.4)	
Body fat percentage, n (%)			
Normal	518 (44.4)	336 (67.7)	0.001
Excess	648 (55.6)	160 (32.3)	
Smoking status, n (%)			
Past	130 (11.2)	73 (14.7)	0.04
Current	229 (19.6)	79 (15.9)	
Never	807 (69.3)	344 (69.3)	
Met physical activity guidelines, n (%)			
Yes	571 (49.0)	297 (60.0)	0.001
No	595 (51.0)	199 (40.0)	
College degree, n (%)			
Yes	417 (35.8)	271 (54.6)	0.001
No	733 (62.9)	217 (43.8)	
Not reported	16 (1.3)	8 (1.6)	

Body mass index (BMI) classifications: normal weight (BMI 18.5–24.9 kg/m^2); overweight (BMI 25.0–29.9 kg/m^2); obese grade I (BMI 30.0–34.9 kg/m^2); obese II (BMI 35.0–39.9 kg/m^2); obese III (BMI ≥ 40.0 kg/m^2); underweight (BMI < 18.5 kg/m^2).
Normal body fat percentage (males: <27.5%; females: <39.9%); excess body fat percentage (males: ≥27.5%; females: ≥39.9%).
Physical activity guidelines based on the 2018 CDC recommendations of 450 metabolic equivalent minutes per week.
BMI, body mass index; CDC, Centers for Disease Control and Prevention; kg/m^2, kilogram per square meter; <, less than; ≥, more than or equal to; n, number; %, percent; p, probability; SD, standard deviation; N/A, not applicable.
[a]Fisher exact test used for analysis.

independent predictor of PCI, but not in the model when body fat percentage was used as the independent variable. There was no interaction between survivor status and either BMI or body fat percentage; interaction terms were not included in final models. Limiting the models to survivors treated after 1980 did not significantly change the results (**Supplementary Table S2**).

TABLE 2 Associations between physiological cost index and body mass index or body fat percentage in adult survivors of childhood acute lymphoblastic leukemia vs. community controls.

	n	Physiological cost index (BMI model)			Physiological cost index (Body fat percentage model)		
		mean	SE	p	mean	SE	p
Group							
Community control	484	0.49	0.009	REF	0.50	0.008	REF
ALL survivors	1,157	0.51	0.008	0.03	0.51	0.006	0.06
Body mass index							
Normal weight	462	0.49	0.008	REF	N/A	N/A	N/A
Overweight	454	0.49	0.008	0.62	N/A	N/A	N/A
Obese grade I	340	0.49	0.009	0.43	N/A	N/A	N/A
Obese grade II	203	0.50	0.01	0.28	N/A	N/A	N/A
Obese grade III	150	0.55	0.01	<0.01	N/A	N/A	N/a
Underweight	32	0.45	0.03	0.32	N/A	N/A	N/A
Body fat percentage							
Normal	843	N/A	N/A	N/A	0.48	0.006	REF
Excess	798	N/A	N/A	N/A	0.51	0.007	<0.01

Body mass index (BMI) classifications: normal weight (BMI 18.5–24.9 kg/m^2); overweight (BMI 25.0–29.9 kg/m^2); obese grade I (BMI 30.0–34.9 kg/m^2); obese II (BMI 35.0–39.9 kg/m^2); obese III (BMI ≥ 40.0 kg/m^2); underweight (BMI < 18.5 kg/m^2).
Normal body fat percentage (males: <27.5%; females: <39.9%); excess body fat percentage (males: ≥27.5%; females: ≥39.9%).
Models were adjusted for sex, age at evaluation, physical activity, height, and smoking status.
Nine survivors did not complete the six-minute walk and were removed from analysis due to uncontrolled asthma (1), paralysis (2), painful swelling in legs (2), acute neurological symptoms (1), chronic low back pain (2), and a recent triple bypass surgery (1).
Seven community controls were removed from analysis due to a recently placed pacemaker (1), acute angina (1), technical error (2), severe COPD (1), unable to ambulate without assistance (1), and severe shortness of breath (1).
BMI, body mass index; <, less than; n, number; N/A, not applicable; %, percent; p, probability; SE, standard error; REF, reference.

Treatment exposures, persistent motor neuropathy, body composition, and physiological cost index

Table 3 summarizes associations between persistent motor neuropathy, and PCI in three sequential multivariable models (A, B, and C) in survivors. After adjustment for treatment exposures age at analysis, age at diagnosis, and sex, survivors with persistent motor neuropathy had a higher energy cost of walking than those without persistent motor neuropathy (0.57 ± 0.04 vs. 0.52 ± 0.03 beats/meter) (Model A). With additional adjustment for the BMI categories, the association between persistent motor neuropathy and PCI was attenuated

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TABLE 3 Sequential linear regressions examining associations between treatment exposures, BMI, prevalent neuropathy, and lifestyle factors on physiological cost index in adult survivors of childhood acute lymphoblastic leukemia.

	n	Physiological cost index								
		Model A ($R^2 = 0.08$)			Model B ($R^2 = 0.10$)			Model C ($R^2 = 0.11$)[a]		
		mean	SE	*p*	mean	SE	*p*	mean	SE	*p*
Cranial Radiation										
Yes	549	0.54	0.04	0.73	0.53	0.04	0.19	0.53	0.03	0.21
No	608	0.55	0.03	REF	0.54	0.03	REF	0.51	0.04	REF
Anthracyclines										
Yes	890	0.56	0.03	0.08	0.55	0.03	0.05	0.53	0.04	0.07
No	267	0.53	0.03	REF	0.52	0.03	REF	0.51	0.04	REF
Corticosteroids										
Yes	1,150	0.53	0.01	0.64	0.52	0.01	0.64	0.51	0.01	0.78
No	7	0.55	0.06	REF	0.55	0.07	REF	0.53	0.06	REF
Neuropathy										
Yes	89	0.57	0.04	0.03	0.55	0.04	0.07	0.54	0.04	0.05
No	1,068	0.52	0.03	REF	0.52	0.03	REF	0.50	0.03	REF
Body mass index										
Normal weight	289	N/A	N/A	N/A	0.53	0.03	REF	0.52	0.04	REF
Overweight	322	N/A	N/A	N/A	0.54	0.04	0.69	0.53	0.04	0.68
Obese grade I	235	N/A	N/A	N/A	0.54	0.04	0.48	0.52	0.03	0.74
Obese grade II	151	N/A	N/A	N/A	0.54	0.03	0.56	0.53	0.04	0.72
Obese grade III	109	N/A	N/A	N/A	0.61	0.04	<0.01	0.59	0.03	<0.01
Underweight	21	N/A	N/A	N/A	0.46	0.05	0.05	0.44	0.05	0.05

BMI classifications: normal weight (BMI 18.5–24.9 kg/m^2); overweight (BMI 25.0–29.9 kg/m^2); obese grade I (BMI 30.0–34.9 kg/m^2); obese II (BMI 35.0–39.9 kg/m^2); obese III (BMI ≥ 40.0 kg/m^2); underweight (BMI < 18.5 kg/m^2).
All models were adjusted for sex, age at assessment, and age at diagnosis.
Nine survivors did not complete the six-minute walk and were removed from analysis due to uncontrolled asthma (1), paralysis (2), painful swelling in legs (2), acute neurological symptoms (1), chronic low back pain (2), and a recent triple bypass surgery (1).
Seven community controls were removed from analysis due to a recently placed pacemaker (1), acute angina (1), technical error (2), severe COPD (1), unable to ambulate without assistance (1), severe shortness of breath (1).
BMI, body mass index; <, less than; n, number; N/A, not applicable; R^2, Coefficient of determination; REF, reference.
[a]Additionally adjusted for smoking status and physical activity status.

(Model B). After adjustment for all variables in models A and B and for lifestyle factors (smoking, PA), both grade III obesity and neuropathy were associated with the PCI (Model C).

Quality of life and adaptive physical function

Table 4 shows associations between the PCI, group (survivors or community controls), PA status, and the PCS and MCS of the SF-36. Survivors had significantly lower MCS and PCS scores than community controls. However, scores were not impacted by the energy cost of walking, in models with or without interaction terms (PCI by group status). Participants who met CDC PA guidelines had higher scores on the MCS and PCS. Results were similar for the other SF-36 subscales. Adaptive physical function was measured with PPT and TUG time (Table 4). Compared to community controls, survivors scored lower on the PPT. There was no association between the PCI, PPT, or SF-36 scores. Survivors with higher PCI scores had significantly longer TUG times compared to community controls with higher PCI scores.

Associations between PCI, quality of life, and adaptive physical function

To further assess HRQoL, participants were categorized by PCI as impaired (>90th percentile) and not impaired (<90th percentile), as well as severely impaired (>95th percentile) and not severely impaired (<95th percentile). Impairment was associated with lower PCS scores in survivors but not community controls (Figure 1A). Severe impairment was also associated with lower PCS in survivors but not community controls (Figure 1B).

10.3389/fped.2022.976012

TABLE 4 Associations between the physiological cost index, SF-36 component summaries, and adaptive physical function in adult survivors of acute lymphoblastic leukemia vs. community controls.

	SF-36						Adaptive physical function					
	PCS[a]			MCS[b]			PPT[c]			Timed up and go[a]		
	mean	SE	*p*	mean	SE	*p*	mean	SE	*p*	mean	SE	*p*
PCI	51.70	0.09	0.26	48.41	0.07	0.94	26.91	0.11	0.78	5.86	0.02	0.11
Group												
Community controls	53.47	0.43	REF	48.83	0.53	REF	27.46	0.06	REF	5.36	0.12	REF
Survivors	50.20	0.31	<0.01	46.80	0.38	<0.01	26.59	0.09	<0.01	6.26	0.14	0.82
PA												
Inactive	50.29	0.35	REF	46.78	0.46	REF	26.68	0.07	REF	6.18	0.13	REF
Active	53.43	0.34	<0.01	48.86	0.43	<0.01	27.37	0.08	<0.01	5.43	0.13	<0.01
PCI*group, control	54.71	0.14	REF	49.94	0.12	REF	27.60	0.02	REF	5.19	0.03	REF
PCI*group, survivor	50.46	0.09	0.18	47.62	0.08	0.39	26.63	0.01	0.19	6.14	0.02	<0.01

Physical activity guidelines based on the 2018 CDC recommendations of 450 metabolic equivalent minutes per week.
Interaction term was removed from the model when not significant.
Nine survivors did not complete the six-minute walk and were removed from analysis due to uncontrolled asthma (1), paralysis (2), painful swelling in legs (2), acute neurological symptoms (1), chronic low back pain (2), and a recent triple bypass surgery (1).
Seven community controls were removed from analysis due to a recently placed pacemaker (1), acute angina (1), technical error (2), severe COPD (1), unable to ambulate without assistance (1), severe shortness of breath (1).
42 (sixteen community controls, 26 survivors) did not complete their SF-36 questionnaire.
One survivor did not complete their physical performance test due to cognitive limitations.
Three survivors did not complete timed up and go due to patient refusal (1) and tester error (2).
SF-36, Medical Outcomes Survey Short-Form-36; MCS, mental component summary; PCI, physiological cost index; PCS, physical component summary; PPT, physical performance test.
[a]Model additionally adjusted for age, sex, physical activity, smoking status, and race.
[b]Model additionally adjusted for age, sex, physical activity, and smoking status.
[c]Model additionally adjusted for physical activity, sex, and smoking status.

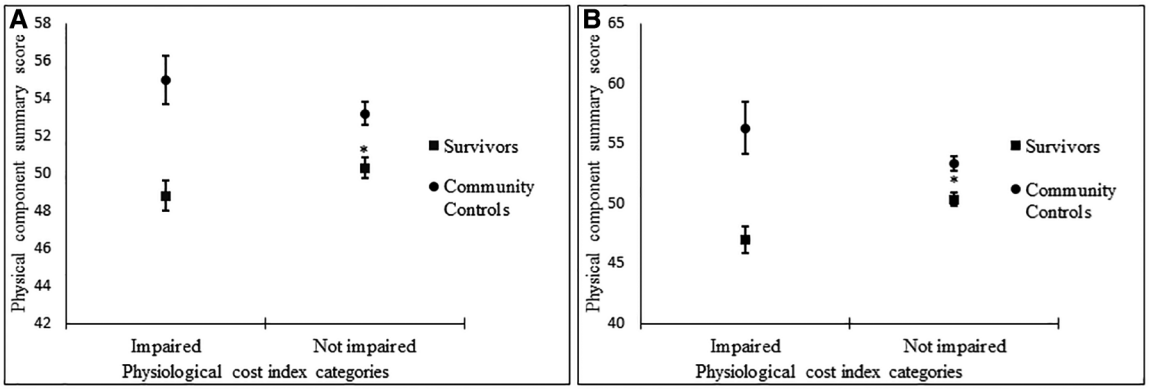

FIGURE 1
Associations between impaired vs. not impaired physiological cost index and physical component summary score (A), severely impaired vs. not impaired physiological cost index, physical component summary score (B).

Discussion

Adult survivors of childhood ALL who are morbidly obese (BMI ≥ 40 kg/m^2) have an increased energy cost of walking. This association persists after accounting for treatment exposures and other host factors, including persistent symptoms of motor neuropathy. Moreover, impaired waking efficiency impacts activities of daily life, as survivors who have increased energy cost of walking take longer to complete the TUG, an indicator of general mobility and future functional decline (42). Decreased walking efficiency also impacts perceived well-being among survivors as evident by the lower physical HRQoL reported by survivors with the most impaired energy cost of walking (>90th percentile and >95th

percentile) compared to survivors not impaired. Community controls whose energy cost of walking is the most impaired do not report impaired HRQoL, suggesting that survivors, compared to persons without a history of childhood ALL, have more difficulty compensating for obesity during day-to-day activities. Because obesity is potentially modifiable, these data support the need for tailored weight loss interventions that consider the specific energy costs of adult survivors of childhood ALL.

Our finding of increased energy cost of walking among young adult survivors of childhood ALL, compared to community controls, is supported by a study that examined energy cost of walking in younger ALL survivors, but that did not consider obesity or neuropathy as risk factors. Warner et al. compared differences in heart rate at rest and during a treadmill walking test [set speed of 2 kilometers/hour (km/h)] in children and adolescents after treatment for ALL (median age 12.3 years; range 7.2–18.2 years) and sibling controls (43). In their study, heart rate differences were greater among ALL survivors [mean: 112 beats per min (bpm) range: 85–134 bpm] than siblings (mean: 101 bpm; range 75–128 bpm, $p < 0.01$). As stated, the impact of obesity on this association was not examined, however, survivors had higher BMI values [1.27 standard deviation score (SDS)] than siblings (0.62 SDS). Our additional findings that both obesity and peripheral neuropathy are independently associated with energy cost of walking are supported by studies in populations with neuromuscular disease, that identified associations between gait patterns and energy cost of walking, and by studies in the general population, that observed independent effects of obesity and gait kinematics, on energy cost of walking.

Abnormal gait mechanics, predicted by degree of neuromuscular impairment, are associated with the energy cost of walking in studies that include persons with multiple sclerosis ($n = 33$, mean age 41 ± 1.7 years) and those with Charcot Marie Tooth Disease ($n = 8$, median age 34 ± 9.7 years; 37.5% male) (44, 45). Obesity was not included as a risk factor in either of these studies. In studies of the general population, obesity increases the energy cost of walking by 10%–33% (10, 46), independent of abnormal gait biomechanics (47). Adult survivors of childhood ALL are at an increased risk for obesity (3), which confers increased demand, and peripheral motor neuropathy (48, 49), which appears to limit their ability to respond to increased demand (48, 49). Thus, to promote PA in adult survivors of childhood ALL, those who are obese, or have peripheral neuropathy, will need an intervention that addresses both impairments.

In our analysis, when obesity is measured by body fat percentage, rather than BMI, the impact of excess mass on the energy cost of walking is similar between adult ALL survivors and community controls. This suggests that BMI is a measure that does not adequately characterize obesity in adult ALL survivors. As we have previously shown, BMI misclassifies a large proportion of childhood cancer survivors (47% males; 53% females) as obese, when compared to the gold standard (body fat percentage) (24). Alternatively, it may be that body composition is less impactful on energy costs of walking than actual body size among survivors, whose muscle quality may be impaired (50), resulting in altered gait dynamics and reduced gait efficiency. The latter hypothesis is supported by Browning et al. who examined the effects of both excess weight measured by BMI and body composition, measured by dual energy x-ray absorptiometry, on the energy cost of walking at set speeds (0.5, 0.75, 1.00, 1.25, 1.50, or 1.75 m/s) in 39 otherwise healthy persons, some of whom who were obese (mean age 24.5 ± 5.1 years; 48.7% obese; 51.2% male) (51). Participants with obesity (BMI > 30 kg/m^2) had 10% higher energy cost of walking, whereas body composition only explained a small part of the increase ($r^2 = 0.15$). In another study, Griffin et al. evaluated the impact of adding lead weights to a waist band (0, 10, 20, or 30% of body weight) on energy cost of walking in eight healthy individuals (mean weight 68.7 ± 12.5 kg; mean age 26.0 ± 5.0 years; 50% male) (52). Adding 30% of body weight increased cost of walking by 47 ± 17%. Survivors of childhood ALL also have impaired lower body strength compared to their peers (50), which could further limit their capacity to compensate for excess weight. Hunter et al. reported a significant association between isometric quadriceps strength and energy cost of walking in 66 overweight premenopausal women (mean age 34.6 ± 6.2 years). They showed an increase of 36 newtons of quadriceps force was associated with a lower peak oxygen uptake requirement [VO_2 (mL/kg/min) β −0.37; $p < 0.01$] at a set walking speed of 4.84 km/h (53). Thus, in addition to addressing obesity and neuropathy to increase ease of movement and promote PA in adult survivors of childhood ALL, increasing muscle strength should be further researched as another component to raise walking efficiency.

Although our study is not the first to report lower adaptive physical function (slower TUG time) or lower scores on measures of HRQoL among ALL survivors compared to community controls (50, 54), our data adds to existing literature by documenting that deficits in adaptive physical function and HRQoL are associated with the energy cost of movement in this vulnerable population. Deficits in adaptive physical function and HRQoL are problematic and relevant. In the general adult population ($n = 200$, age range 20–50 years, 44.5% male), slower TUG time is associated with higher scores on the cumulative illness rating scale and with lower scores on the PCS SF-36 Summary Scale (55). Among older adults, increasing time on the TUG is associated with risk of future falls, hospitalizations, and functional decline (56–58). When dichotomized, a decline below 50 on the PCS SF-36 Summary Scale is associated with a 58% (95% CI, 30%–91%) increased risk of mortality in women; (59) and when evaluated as a continuous measure, every three point

decrement on the PCS increased risk for mortality by 27% (60). Thus, because increased energy cost of walking from obesity is associated both adaptive physical function and HRQoL, early weight management strategies in survivors of childhood ALL, if successful, are likely to have a significant impact on long term health.

Our study has some important strengths. First, we have a large, well characterized study population with not only detailed clinical data, but also detailed disease, treatment, and lifestyle information. This allows for robust analysis and control of confounders of our estimates. Second, our study has a control group, which allows for direct comparisons to a representative sample of the general population, as well as relevant categorizations of impaired energy cost using control percentile scores. Third, objective measures of predictors (BMI and body fat percentage) and outcomes (adaptive physical functioning) limit measurement bias associated with non-objective measures and self-report.

Our study is, however, not without limitations. These data are cross-sectional: temporal associations between obesity, energy cost of walking, adaptive physical function and HRQoL cannot be definitively determined. For example, in an older population, poor physical function is associated with increasing energy costs performing submaximal activities, and survivors can develop functional deficits during treatment that persist through their childhood. More research should be done to exam the temporality between function and energy costs. In addition, our sample was treated at one institution (St. Jude Children's Research Hospital) between 1962 and 2012; our data may not be generalizable to adult survivors of ALL treated more recently, or at other institutions with different treatment regimens. Furthermore, not every eligible participant agreed to take part in the study. This may bias our estimates of the association between obesity and energy cost of walking. For example, if non-participants were healthier, and less obese, the direction of the association between obesity and the energy cost of walking would be away from the null. Conversely, if the non-participants were less healthy and more obese, the direction of the association would be towards the null. In our study, while we used a self-report questionnaire widely used in population cohorts to characterize PA (35), these data are prone to error when compared to data collected by doubly labelled water or accelerometry (61, 62). Additionally, using calipers to ascertain body fat percentage increases measurement error, thus increase the risk of misclassification bias. Finally, our study looked at the associations between obesity, neuropathy, and energy costs of walking, however, other factors could be impacting energy costs of walking in our survivors. Some examples include muscle weakness, balance, and compensation for chronic pain (63, 64). Future studies should examine these exposures impact on energy costs of walking.

However, using calipers for body fat percentage is valid replacement for the dual energy x-ray absorptiometry in both the general population and childhood cancer survivors (24, 65). Finally, while the PCI is a valid measure of the energy cost of walking, and easy to do across clinical settings, it is not the gold standard, which would include evaluating energy consumption during walking using a portable metabolic cart.

Nevertheless, this study provides important information about the impact of obesity on daily function in adult survivors of childhood ALL. Among survivors, but not among community controls, obesity increased the energy cost of walking, suggesting that the survivors have difficulty compensating for excess weight. Unfortunately, due to their increased energy cost of walking, survivors have disproportionally worse adaptive physical function and HRQoL, compared to community controls. Tailored interventions, accessible to those with increased energy cost of walking, with a focus on weight loss and decreasing the burden of peripheral neuropathy, are needed for this vulnerable population. Providing adaptive equipment or exercise modifications to help manage neuropathy, accompanied by behavioral strategies that promote weight loss and encourage physical activity, should be considered.

Data availability statement

The data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by St. Jude Children's Research Hospital Human Research Protection Program (HRPP) and the Institutional Review board (IRB). The patients/participants provided their written informed consent to participate in this study.

Author contributions

KKN conceived the study; MDW and KKN provided the study design and manuscript draft; MDW and KKN provided statistical analysis; MDW and KKN acquired data; MMH and LLR designed and conducted the SJLIFE cohort study; MDW and KKN interpreted data; all authors contributed to manuscript revision.

Funding

This study was supported by research funding by the St. Jude Lifetime Cohort Study [NIH U01 CA195547 (MMH

and KKN)], Cancer Center Support (CORE) (NIH CA 21765) (CR), and American Lebanese Syrian Associated Charities.

Acknowledgments

The authors acknowledge Tracie Gatewood for her assistance preparing the manuscript.

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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.976012/full#supplementary-material.

References

1. SEER Cancer Statistics Review, 1975–2014 (2017). Available from: https://seer.cancer.gov/csr/1975_2014/ (Accessed January 1, 2022).

2. Mulrooney DA, Hyun G, Ness KK, Bhakta N, Pui CH, Ehrhardt MJ, et al. The changing burden of long-term health outcomes in survivors of childhood acute lymphoblastic leukaemia: a retrospective analysis of the St Jude Lifetime Cohort Study. *Lancet*. (2019) 6:e306–e16. doi: 10.1016/S2352-3026(19)30050-X

3. Oeffinger KC, Mertens AC, Sklar CA, Yasui Y, Fears T, Stovall M, et al. Obesity in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *J Clin Oncol*. (2003) 21:1359–65. doi: 10.1200/JCO.2003.06.131

4. Gurney JG, Ness KK, Sibley SD, O'Leary M, Dengel DR, Lee JM, et al. Metabolic syndrome and growth hormone deficiency in adult survivors of childhood acute lymphoblastic leukemia. *Cancer*. (2006) 107:1303–12. doi: 10.1002/cncr.22120

5. Archives of Physical Medicine and Rehabilitation, Oeffinger KC, Buchanan GR, Eshelman DA, Denke MA, Andrews TC, et al. Cardiovascular risk factors in young adult survivors of childhood acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*. (2001) 23:424–30. doi: 10.1097/00043426-200110000-00007

6. Mody R, Li S, Dover DC, Sallan S, Leisenring W, Oeffinger KC, et al. Twenty-five–year follow-up among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Blood*. (2008) 111:5515–23. doi: 10.1182/blood-2007-10-117150

7. Ness KK, DeLany JP, Kaste SC, Mulrooney DA, Pui CH, Chemaitilly W, et al. Energy balance and fitness in adult survivors of childhood acute lymphoblastic leukemia. *Blood*. (2015) 125:3411–9. doi: 10.1182/blood-2015-01-621680

8. Lemay V, Caru M, Samoilenko M, Drouin S, Mathieu M-E, Bertout L, et al. Physical activity and sedentary behaviors in childhood acute lymphoblastic leukemia survivors. *J Pediatr Hematol Oncol*. (2020) 42:53–60. doi: 10.1097/MPH.0000000000001594

9. Bernardi M, Macaluso A, Sproviero E, Castellano V, Coratella D, Felici F, et al. Cost of walking and locomotor impairment. *J Electromyogr Kinesiol*. (1999) 9:149–57. doi: 10.1016/s1050-6411(98)00046-7

10. Browning RC, Kram R. Energetic cost and preferred speed of walking in obese vs. normal weight women. *Obes Res*. (2005) 13:891–9. doi: 10.1038/oby.2005.103

11. Wert DM, Brach JS, Perera S, VanSwearingen J. The association between energy cost of walking and physical function in older adults. *Arch Gerontol Geriat*. (2013) 57:198–203. doi: 10.1016/j.archger.2013.04.007

12. Brown DW, Balluz LS, Heath GW, Moriarty DG, Ford ES, Giles WH, et al. Associations between recommended levels of physical activity and health-related quality of life - findings from the 2001 Behavioral Risk Factor Surveillance System (BRFSS) survey. *Prev Med*. (2003) 37:520–28. doi: 10.1016/S0091-7435(03)00179-8

13. Brach JS, Simonsick EM, Kritchevsky S, Yaffe K, Newman AB, Health A, et al. The association between physical function and lifestyle activity and exercise in the health, aging and body composition study. *J Am Geriatr Soc*. (2004) 52:502–9. doi: 10.1111/j.1532-5415.2004.52154.x

14. Monteiro F, Ponce DAN, Silva H, Pitta F, Carrilho AJF. Physical function, quality of life, and energy expenditure during activities of daily living in obese, post-bariatric surgery, and healthy subjects. *Obes Surg*. (2017) 27:2138–44. doi: 10.1007/s11695-017-2619-4

15. Howell CR, Wilson CL, Ehrhardt MJ, Partin RE, Kaste SC, Lanctot JQ, et al. Clinical impact of sedentary behaviors in adult survivors of acute lymphoblastic leukemia: a report from the St. Jude Lifetime Cohort study. *Cancer*. (2018) 124:1036–43. doi: 10.1002/cncr.31162

16. Zeltzer LK, Lu Q, Leisenring W, Tsao JC, Recklitis C, Armstrong G, et al. Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: a report from the childhood cancer survivor study. *Cancer Epidemiol Biomarkers Prev*. (2008) 17:435–46. doi: 10.1158/1055-9965.EPI-07-2541

17. Bjornard KL, Gilchrist LS, Inaba H, Diouf B, Hockenberry MJ, Kadan-Lottick NS, et al. Peripheral neuropathy in children and adolescents treated for cancer. *Lancet Child Adolesc Health*. (2018) 2:744–54. doi: 10.1016/S2352-4642(18)30236-0

18. Varedi M, Lu L, Howell C, Partin R, Hudson M, Pui C-H, et al. Peripheral neuropathy, function and quality of life in adult survivors of childhood acute lymphoblastic leukemia. *Arch Phys Med Rehabil*. (2017) 98:e91–2. doi: 10.1016/j.apmr.2017.08.293

19. Mols F, Beijers T, Vreugdenhil G, van de Poll-Franse L. Chemotherapy-induced peripheral neuropathy and its association with quality of life: a systematic review. *Support Care Cancer*. (2014) 22:2261–69. doi: 10.1007/s00520-014-2255-7

20. Kandula T, Farrar MA, Cohn RJ, Mizrahi D, Carey K, Johnston K, et al. Chemotherapy-induced peripheral neuropathy in long-term survivors of childhood cancer: clinical, neurophysiological, functional, and patient-reported outcomes. *JAMA Neurol*. (2018) 75:980–88. doi: 10.1001/jamaneurol.2018.0963

21. Cohen JE, Wakefield CE, Cohn RJ. Nutritional interventions for survivors of childhood cancer. *Cochrane Database Syst Rev*. (2016) 2016:CD009678. doi: 10.1002/14651858.CD009678.pub2

22. Hudson MM, Ness KK, Nolan VG, Armstrong GT, Green DM, Morris EB, et al. Prospective medical assessment of adults surviving childhood cancer: study design, cohort characteristics, and feasibility of the St. Jude Lifetime Cohort study. *Pediatr Blood Cancer*. (2011) 56:825–36. doi: 10.1002/pbc.22875

23. Jackson AS, Pollock ML. Practical assessment of body composition. *Phys Sportsmed*. (1985) 13:76–90. doi: 10.1080/00913847.1985.11708790

24. Karlage RE, Wilson CL, Zhang N, Kaste S, Green DM, Armstrong GT, et al. Validity of anthropometric measurements for characterizing obesity among adult survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study. *Cancer*. (2015) 121:2036–43. doi: 10.1002/cncr.29300

25. Heo M, Faith MS, Pietrobelli A, Heymsfield SB. Percentage of body fat cutoffs by sex, age, and race-ethnicity in the US adult population from

NHANES 1999–2004. *Am J Clin Nutr*. (2012) 95:594–602. doi: 10.3945/ajcn.111.025171

26. Okuro RT, de Oliveira Ribeiro MAG, Ribeiro JD, Minsky RC, Schivinski CIS. Alternative indexes to estimate the functional capacity from the 6-minute walk test in children and adolescents with cystic fibrosis. *Respir Care*. (2017) 62:324–32. doi: 10.4187/respcare.04625

27. Merritta C, Cherian B, Macaden AS, John JA. Measurement of physical performance and objective fatigability in people with mild-to-moderate traumatic brain injury. *Int J Rehabil Res*. (2010) 33:109–14. doi: 10.1097/MRR.0b013e32832e6b37

28. Delussu AS, Morone G, Iosa M, Bragoni M, Paolucci S, Traballesi M. Concurrent validity of physiological cost Index in walking over ground and during robotic training in subacute stroke patients. *Biomed Res Int*. (2014) 20146. doi: 10.1155/2014/384896

29. Peebles KC, Woodman-Aldridge AD, Skinner MA. The physiological cost index in elderly subjects during treadmill and floor walking. *N Z J Physiother*. (2003) 31:11–7.

30. Hagberg K, Tranberg R, Zügner R, Danielsson A. Reproducibility of the physiological cost index among individuals with a lower-limb amputation and healthy adults. *Physiother Res Int*. (2011) 16:92–100. doi: 10.1002/pri.477

31. Hachisuka K, Makino K, Wada F, Saeki S, Yoshimoto N. Oxygen consumption, oxygen cost and physiological cost index in polio survivors: a comparison of walking without orthosis, with an ordinary or a carbon-fibre reinforced plastic knee-ankle-foot orthosis. *J Rehabil Med*. (2007) 39:646–50. doi: 10.2340/16501977-0105

32. Reulen RC, Zeegers MP, Jenkinson C, Lancashire ER, Winter DL, Jenney ME, et al. The use of the SF-36 questionnaire in adult survivors of childhood cancer: evaluation of data quality, score reliability, and scaling assumptions. *Health Qual Life out*. (2006) 4:77. doi: 10.1186/1477-7525-4-77

33. Rozzini R, Frisoni GB, Bianchetti A, Zanetti O, Trabucchi M. Physical Performance Test and Activities of Daily Living scales in the assessment of health status in elderly people. *J Am Geriatr Soc*. (1993) 41:1109–13. doi: 10.1111/j.1532-5415.1993.tb06460.x

34. Lin MR, Hwang HF, Hu MH, Wu HD, Wang YW, Huang FC. Psychometric comparisons of the timed up and go, one-leg stand, functional reach, and Tinetti balance measures in community-dwelling older people. *J Am Geriatr Soc*. (2004) 52:1343–8. doi: 10.1111/j.1532-5415.2004.52366.x

35. Chen T, Clark J, Riddles MK, Mohadjer LK, Fakhouri THI. National health and nutrition examination survey, 2015–2018: sample design and estimation procedures. National center for health statistics. *Vital Health Stat*. (2020) 2:1–35.

36. Ojha RP, Oancea SC, Ness KK, Lanctot JQ, Srivastava DK, Robison LL, et al. Assessment of potential bias from non-participation in a dynamic clinical cohort of long-term childhood cancer survivors: results from the St. Jude Lifetime Cohort Study. *Pediatr Blood Cancer*. (2013) 60:856–64. doi: 10.1002/pbc.24348

37. Wampler MA, Miaskowski C, Hamel K, Byl N, Rugo H, Topp K. The Modified Total Neuropathy Score: a clinically feasible and valid measure of taxane-induced peripheral neuropathy in women with breast cancer. *J Support Oncol*. (2006) 4:9–16.

38. Harber MP, Metz M, Peterman JE, Whaley MH, Fleenor BS, Kaminsky LA. Trends in cardiorespiratory fitness among apparently healthy adults from the Ball State Adult Fitness Longitudinal Lifestyle STudy (BALL ST) cohort from 1970 to 2019. *PLoS One*. (2020) 15:e0242995. doi: 10.1371/journal.pone.0242995

39. Pui CH, Evans WE. A 50-year journey to cure childhood acute lymphoblastic leukemia. *Semin Hematol*. (2013) 50:185–96. doi: 10.1053/j.seminhematol.2013.06.007

40. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. (1986) 51:1173–82. doi: 10.1037//0022-3514.51.6.1173

41. Steyerberg EW, Eijkemans MJ, Harrell Jr. FE, Habbema JD. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. *Stat Med*. (2000) 19:1059–79. doi: 10.1002/(sici)1097-0258(20000430)19:8<1059::aid-sim412>3.0.co;2-0

42. Wennie Huang WN, Perera S, VanSwearingen J, Studenski S. Performance measures predict onset of activity of daily living difficulty in community-dwelling older adults. *J Am Geriatr Soc*. (2010) 58:844–52. doi: 10.1111/j.1532-5415.2010.02820.x

43. Warner JT, Bell W, Webb DK, Gregory JW. Daily energy expenditure and physical activity in survivors of childhood malignancy. *Pediatr Res*. (1998) 43:607–13. doi: 10.1203/00006450-199805000-00008

44. Olgiati R, Burgunder JM, Mumenthaler M. Increased energy cost of walking in multiple sclerosis: effect of spasticity, ataxia, and weakness. *Arch Phys Med Rehabil*. (1988) 69:846–9.

45. Menotti F, Felici F, Damiani A, Mangiola F, Vannicelli R, Macaluso A. Charcot-Marie-Tooth 1A patients with low level of impairment have a higher energy cost of walking than healthy individuals. *Neuromuscular Disord*. (2011) 21:52–7. doi: 10.1016/j.nmd.2010.09.008

46. Freyschuss U, Melcher A. Exercise energy expenditure in extreme obesity: influence of ergometry type and weight loss. *Scand J Clin Lab Invest*. (1978) 38:753–9. doi: 10.1080/00365517809104883

47. Browning RC, McGowan CP, Kram R. Obesity does not increase external mechanical work per kilogram body mass during walking. *J Biomech*. (2009) 42:2273–78. doi: 10.1016/j.jacc.2008.12.068

48. Gilchrist L, Tanner L. Gait patterns in children with cancer and vincristine neuropathy. *Pediatr Phys Ther*. (2016) 28:16–22. doi: 10.1097/PEP.0000000000000208

49. Tay CG, Lee VWM, Ong LC, Goh KJ, Ariffin H, Fong CY. Vincristine-induced peripheral neuropathy in survivors of childhood acute lymphoblastic leukaemia. *Pediatr Blood Cancer*. (2017) 64:e26471. doi: 10.1002/pbc.26471

50. Ness KK, Baker KS, Dengel DR, Youngren N, Sibley S, Mertens AC, et al. Body composition, muscle strength deficits and mobility limitations in adult survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer*. (2007) 49:975–81. doi: 10.1002/pbc.21091

51. Browning RC, Baker EA, Herron JA, Kram R. Effects of obesity and sex on the energetic cost and preferred speed of walking. *J Appl Physiol*. (2006) 100:390–8. doi: 10.1152/japplphysiol.00767.2005

52. Griffin TM, Roberts TJ, Kram R. Metabolic cost of generating muscular force in human walking: insights from load-carrying and speed experiments. *J Appl Physiol*. (2003) 95:172–83. doi: 10.1152/japplphysiol.00944.2002

53. Hunter GR, McCarthy JP, Bryan DR, Zuckerman PA, Bamman MM, Byrne NM. Increased strength and decreased flexibility are related to reduced oxygen cost of walking. *Eur J Appl Physiol*. (2008) 104:895–901. doi: 10.1007/s00421-008-0846-z

54. Khan RB, Hudson MM, Ledet DS, Morris EB, Pui CH, Howard SC, et al. Neurologic morbidity and quality of life in survivors of childhood acute lymphoblastic leukemia: a prospective cross-sectional study. *J Cancer Surviv*. (2014) 8:688–96. doi: 10.1007/s11764-014-0375-1

55. Kear BM, Guck TP, McGaha AL. Timed up and go (TUG) test: normative reference values for ages 20 to 59 years and relationships with physical and mental health risk factors. *J Prim Care Community Health*. (2017) 8:9–13. doi: 10.1177/2150131916659282

56. Eagles D, Perry JJ, Sirois MJ, Lang E, Daoust R, Lee J, et al. Timed up and go predicts functional decline in older patients presenting to the emergency department following minor traumadagger. *Age Ageing*. (2017) 46:214–18. doi: 10.1093/ageing/afw184

57. Viccaro LJ, Perera S, Studenski SA. Is timed up and go better than gait speed in predicting health, function, and falls in older adults? *J Am Geriatr Soc*. (2011) 59:887–92. doi: 10.1111/j.1532-5415.2011.03336.x

58. Russell MA, Hill KD, Blackberry I, Day LL, Dharmage SC. Falls risk and functional decline in older fallers discharged directly from emergency departments. *J Gerontol A Biol Sci Med Sci*. (2006) 61:1090–5. doi: 10.1093/gerona/61.10.1090

59. Kroenke CH, Kubzansky LD, Adler N, Kawachi I. Prospective change in health-related quality of life and subsequent mortality among middle-aged and older women. *Am J Public Health*. (2008) 98:2085–91. doi: 10.2105/AJPH.2007.114041

60. Bjorner JB, Lyng Wolden M, Gundgaard J, Miller KA. Benchmarks for interpretation of score differences on the SF-36 health survey for patients with diabetes. *Value Health*. (2013) 16:993–1000. doi: 10.1016/j.jval.2013.06.022

61. Shephard RJ. Limits to the measurement of habitual physical activity by questionnaires. *Br J Sports Med*. (2003) 37:197–206; discussion 06. doi: 10.1136/bjsm.37.3.197

62. Rikli RE. Reliability, validity, and methodological issues in assessing physical activity in older adults. *Res Q Exercise Sport*. (2000) 71(Suppl 2):89–96. doi: 10.1080/02701367.2000.11082791

63. Marques NR, LaRoche DP, Hallal CZ, Crozara LF, Morcelli MH, Karuka AH, et al. Association between energy cost of walking, muscle activation, and biomechanical parameters in older female fallers and non-fallers. *Clin Biomech (Bristol, Avon)*. (2013) 28:330–36. doi: 10.1016/j.clinbiomech.2013.01.004

64. IJmker T, Houdijk H, Lamoth CJ, Jarbandhan AV, Rijntjes D, Beek PJ, et al. Effect of balance support on the energy cost of walking after stroke. *Arch Phys Med Rehabil*. (2013) 94:2255–61. doi: 10.1016/j.apmr.2013.04.022

65. Duz S, Kocak M, Korkusuz F. Evaluation of body composition using three different methods compared to dual-energy x-ray absorptiometry. *Eur J Sport Sci*. (2009) 9:181–90. doi: 10.1002/sim.9441

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 08 November 2022
DOI 10.3389/fped.2022.982996

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Oncology, a section of the journal Frontiers in Pediatrics

RECEIVED 30 June 2022
ACCEPTED 18 October 2022
PUBLISHED 08 November 2022

CITATION
Gaser D, Peters C, Oberhoffer-Fritz R, Götte M, Feuchtinger T, Schmid I, Haller B, von Luettichau I and Kesting S (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.
Front. Pediatr. 10:982996.
doi: 10.3389/fped.2022.982996

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

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Objectives: Pediatric patients with cancer experience impairments in muscle strength and physical activity (PA) that may reduce autonomy during hospitalization. To determine the effects of strength exercise interventions on the accomplishment of activities of daily living (ADLs), motor performance, and PA in children with leukemia or non-Hodgkin lymphoma, we randomly allocated patients (4–18 years) immediately after diagnosis into two exercise groups.

Methods: The intervention group (IG; $n = 21$) received a specific strength training combined with a standard care exercise program, whereas the control group (CG; $n = 20$) was provided standard care exercise program without any targeted muscle strengthening. After the baseline visit, participants were followed-up three times until intensive treatment cessation. We assessed physical function limitations using the Activities Scale for Kids© (ASK) and Functional ADL Screen. Secondary outcomes were PA levels using accelerometer and motor performance as measured by MOON-test (motor performance in pediatric oncology-test).

Abbreviations

ADLs, activities of daily living; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ASK, Activities Scale for Kids©; ASKp, Activities Scale for Kids© performance version; BMI, body mass index; HSCT, hematopoietic stem cell transplantation; MET, metabolic equivalents; MOON-test, motor performance in pediatric oncology-test; MVPA, moderate-to-vigorous physical activity; NHL, non-Hodgkin lymphoma; PA, physical activity; V, visit; WHO, World Health Organization

Results: In both groups, ADL accomplishment had significantly increased ($p < 0.05$). However, no significant between-group differences for ASK outcome were noted. Motor performance was reduced in all motor abilities.

Conclusions: Both exercise interventions were effective to maintain ADLs and motor performance during intensive treatment. In comparison, regular strength exercise interventions in the course of therapy tended to be more beneficial with regards to muscular explosive and endurance strength.

KEYWORDS

supervised exercise program, strength training, physical function, motor skills, accelerometry, childhood cancer, intensive treatment

Introduction

Regular exercise for children with cancer is strongly recommended by international guidelines (1, 2). However, professional exercise programs are not implemented nationwide in pediatric oncology departments so far in Germany (3) and are rarely distributed worldwide (4). Disease- and treatment-related implications throughout intensive treatment can cause restrictions in the patients' activity level (5), which can be further associated with decline in cardiorespiratory fitness (6) and motor performance (7). Patients with leukemia reduce their daily step counts by 70% compared with healthy peers during inpatient stays (8). As a consequence, the amount of physical activity (PA) is reduced through treatment by up to 91% (9). In a large number of patients, impairments persist well beyond therapy cessation and into adulthood (10–12). Recently, the number of published studies increased regarding exercise intervention among pediatric patients with cancer and consequently provided growing evidence concerning PA during intensive treatment (13). Thus, positive effects of exercise interventions on exercise capacity (14), cardiorespiratory fitness (15), fatigue (16), muscle strength (17), and PA levels (18) have been shown in pediatric cohorts with mixed cancer entities. Furthermore, data increasingly identified the potential of PA and exercise during follow-up care to reduce disease- and therapy-related late effects, including fatigue (19), obesity (20), or cardiovascular diseases (21), as well as all-cause mortality among childhood cancer survivors (22).

Strength ability assumes a central role in general locomotion and the execution of everyday tasks. Muscle strength is needed for all levels of physical activity. In older adults, low muscle mass and reduced muscle strength are associated with activities of daily living (ADLs) dependency (23). Reduced strength ability is evident in children with acute lymphoblastic leukemia (ALL) during acute therapy (24). As previously described, patients with other pediatric diseases showed reduced muscle strength, which may have an impact on their autonomous coping with ADLs (25, 26). However, little is known about the functional impairments affecting ADLs induced by cancer and the therapy duration, or about potential benefits of strength training for ADL accomplishment throughout the intensive treatment period. From a clinical perspective, ADL impairments typically become obvious as an additional burden upon the disease for these patients, especially for adolescents, considering the need for assistance and dependency on parents or caregivers. Therefore, even essential human needs (e.g., getting up, putting on clothes, using the toilet) can become insurmountable hurdles in clinical routine and may affect children's autonomy and mobility. In our recent publication, patients have shown multifunctional impairments in self-reported ADLs immediately after the diagnosis of leukemia or non-Hodgkin lymphoma (NHL) (27). Furthermore, long-term childhood cancer survivors experienced limitations in physical function (28) and ADL accomplishment, including personal care, routine activities, or attending work, compared with their siblings (29). Accordingly, tailored exercise interventions during intensive treatment could promote children's autonomy and strengthen both physical and mental well-being.

This randomized controlled trial (RCT) aimed to determine the effects of regular supervised strength exercise interventions on self-reported ADLs, motor performance, and PA among pediatric patients with cancer with ALL or acute myeloid leukemia (AML) or NHL during acute treatment. We hypothesized that a specific strength training would be a more appropriate method than our standard care exercise program without targeted strengthening interventions to improve the primary outcome of ADL accomplishment until intensive treatment cessation. Secondary outcomes were exercise effects on motor performance (including functional strength, speed, coordination, flexibility) and PA levels in the course of treatment.

Materials and methods

Participants and study design

The exploratory bicentric ActiveADL Study (ClinicalTrials.gov: NCT03934060) followed a randomized

controlled design in adherence to the ethical guidelines of the Declaration of Helsinki. This study was approved by the Ethics Committees of TUM School of Medicine, Technical University of Munich (TUM; 25/17 S) and University of Munich (18-323). The study content was communicated orally and in written form to the eligible patients. The children's legal guardians and all participants aged ≥16 years provided written informed consent to participate in this study. The ActiveADL Study was conducted at the Children's Hospital Schwabing and Dr. von Hauner Children's Hospital in Munich between September 2017 and February 2021 (last patient-in: June 2020). Eligibility criteria included those aged 4–18 years, with primary or secondary diagnosis (5 years post-primary tumor) of ALL, AML, or NHL. The exclusion criteria were as follows: patients with medical contraindications for PA post-diagnosis (i.e., thrombosis, high risk of bleedings, or fractures), those with the absence of German or English language abilities, and those who communicated a change of hospital during the first weeks of treatment. The lower age limit was selected to realize the exercise methods, particularly strength training for children, and allow the comparison of outcome measures with normative data, respectively. Allocation to the control (CG) and intervention group (IG) was based on a predefined block randomization schedule (with a block size of four).

Sample size

Prior to the ActiveADL Study, power analysis to estimate the intervention effect was not feasible due to the lack of reliable data from previous studies. All patients who met the inclusion criteria were asked to participate since the case numbers are small *per se* owing to the low incidences in pediatric oncology. Considering the potential initial diagnosis at both study sites, the case number estimation over a 2-year recruitment period resulted in a total number of 20 participants in the IG and CG, respectively. A possible 10% dropout (participation decline or death) was considered.

Exercise interventions

All participants followed an in-hospital tailored exercise program that occurred during the entire acute treatment period. The program included 2–3 exercise sessions per week. All exercise sessions were supervised and documented by exercise physiologists; the training load was oriented toward the participants' physical capacity, current health status, and age. Participants individually performed the exercise sessions inside their rooms, on the corridor, or outdoor in the hospital area. Despite isolation and contact reduction during the COVID-19 pandemic (05/2020–01/2021), exercise intervention continuation was constantly ensured. To ensure the amount of training during this period, supervised web-based exercise sessions were additionally offered using the video conferencing platform Zoom (Zoom Video Communications, Inc., San Jose, CA, United States), if necessary. Before each session, the physiologists screened the participants' general health condition together with physicians. The following were the potential contraindications for exercise: fever combined with fatigue or vertigo, vomiting, diarrhea, lumbar puncture procedure, pneumonia, sepsis, severe pain, and intensive care periods. The IG received a specific strength training combined with a standard care exercise program, whereas the CG was provided standard care without any targeted muscle strengthening to the same extent. Standard care exercise program included sportive games, aerobic or coordination exercises. Group-specific contents of exercise interventions are outlined in **Table 1**. Due to the heterogeneous cohort according to common age distribution in pediatric oncology, two strength training modules were developed and adapted to the age of the participants (4–8 and 9–18 years). Both modules contained four identical exercise emphases with 40–45 child-friendly and playful exercises on core stability, complex full-body strengthening, and upper and lower body strengthening. Each specific strength training consisted of four exercises and included one exercise from each emphasis. For each exercise, 2–3 sets were performed with a 60 s rest period between sets and a 90 s break between exercises. With the selection of exercises, all body regions and large muscle groups were explicitly trained. Additional warm-up and cool-down exercises aimed to achieve the 30-min training duration. Exercise intensity was not defined on the basis of physiological parameters—for example, one-repetition maximum for resistance exercise or heart rate peak for aerobic exercise—although was determined and increased individually depending on the physiologists' discretion. The IG focused on strength endurance exercise. According to hygiene standards, solely disinfectable and mobile training devices—including kettlebells/dumbbells, swinging bars, resistance bands, balance pads/boards, bicycle ergometers, or aerobic steppers—were used. Additionally, the IG exercised against the resistance of their body weight. Exercise interventions of both groups started after baseline visit immediately after diagnosis. All participants had access to standard care physiotherapy during the intensive treatment. Particularly, participants with severe functional limitations received regular physiotherapy. Physiotherapeutic measures did not provide targeted exercise interventions; however, the measures included were as follows: respiratory therapy, massages for pain relief, mobilization after catheter surgery or intensive care treatment, muscle stretching, medical brace fitting, lymphatic drainage, and fall prevention.

TABLE 1 Contents of exercise interventions by group.

	Intervention group	Control group
Training method	Specific strength training combined with standard care exercise program	Standard care exercise program
Training emphases	Strength AND Endurance/coordination Sportive games Flexibility/relaxation	Endurance/ coordination Sportive games Flexibility/relaxation
Exercise session example		
Warm-up (5 min)	Bicycle ergometer, joint mobilization	Walking
Main part (20 min)	Elbow planks, squats combined with shoulder press, biceps curls, sidewalks with resistance band	Coordination with juggling balls, table tennis
Cool-down (5 min)	Muscle relaxation	Fantasy relaxation

Min, minutes.
The amount of training for both groups was identical with 30 min per exercise session and 2–3 sessions per week.

Data collection and assessments

All participants were assessed at four inpatient visits: at baseline (V0), after the induction phase (V1), after the consolidation phase (V2), and at intensive treatment cessation before the transition to maintenance therapy or follow-up care (V3). A combination of participation/activity-based and impairment-based measures was used to evaluate functional limitations of ADL accomplishment and individual motor skills: ADL accomplishment was investigated using the Activities Scale for Kids© (ASK), performance version (ASKp), a self-report measure of childhood physical function (30). Furthermore, the self-developed Functional ADL Screen was used to objectively verify functional limitations in ADL performance (27). Motor performance (including functional strength, speed, coordination, flexibility) was assessed using the MOON-test (motor performance in pediatric oncology), a standardized motor performance diagnostic tool in clinical routine among pediatric patients with cancer (31). Functional motor performance measures are feasible in pediatric oncology (32, 33). Compared to isolated strength testing, functional measures provide immediate conclusions regarding the ability to perform everyday tasks. Based on the testing results, the exercise interventions were controlled and adjusted. PA was measured using the accelerometer Move 3 (movisens GmbH, Karlsruhe, Germany) at outpatient periods for seven consecutive days. While the primary outcome—ADL accomplishment based on the ASK and Functional ADL Screen—was collected at all visits, secondary outcomes—MOON-test and PA—were conducted at V0 and V2. Medical data were collected from patients' records. Anthropometric data were measured using the scale seca 701 and stadiometer seca 216 (seca GmbH & Co., Hamburg, Germany). We calculated the PA level, step count, and wear time using the DataAnalyser software (version 1.13.16). The exercise physiologists documented participants' adherence to the exercise sessions. Adverse events concerning exercise interventions or assessments were recorded with regard to the study of Gauß et al. (34). For a detailed description of the measurement methods, we refer to the publication of the baseline data (27).

Statistical analysis

Participants with valid recordings of at least 8 h/day for 4 days were included in the analysis. For all outcomes, between-group differences were assessed using two-sample t tests (normally distributed data) or Mann–Whitney U tests for non-normally distributed data. Longitudinal within-group differences between visits were assessed using paired t tests or the Wilcoxon signed-rank tests. For the MOON-test, comparisons with a healthy population were made using age- and gender-matched reference values. Differences from these reference values were analyzed using one-sample t test or the Wilcoxon signed-rank test as a non-parametric alternative. Statistical analysis was performed using SPSS version 25. Graphs were created using GraphPad Prism version 9. Data analyses were performed following the intention-to-treat principle; for one participant who did not complete the study data, prior elimination was included. Data are presented as mean ± standard deviation for continuous variables and as absolute and relative frequencies for categorical variables. For continuous data, median and range are also presented to assess the skewness of the distribution. Due to the exploratory nature of the study, a level of significance of $\alpha = 0.10$ was used and 90% confidence intervals were estimated. All statistical tests were performed two-sided.

Results

Participant recruitment and visits

A flow diagram of the study participants is shown in Figure 1. From September 2017, a total of 70 children were screened eligible. Of them, 41 met all inclusion criteria and entered the study until June 2020. They were randomized in the IG ($n = 21$) or CG ($n = 20$). All participants completed the baseline assessment at V0. To achieve the recruitment goal, a 41st participant was included because one participant of the IG died after V0 3.3 months after recruitment without completing the follow-up visits. Thirty-six patients performed the assessments at V1 and V2 due to the different treatment protocols and individual capacity during the course of

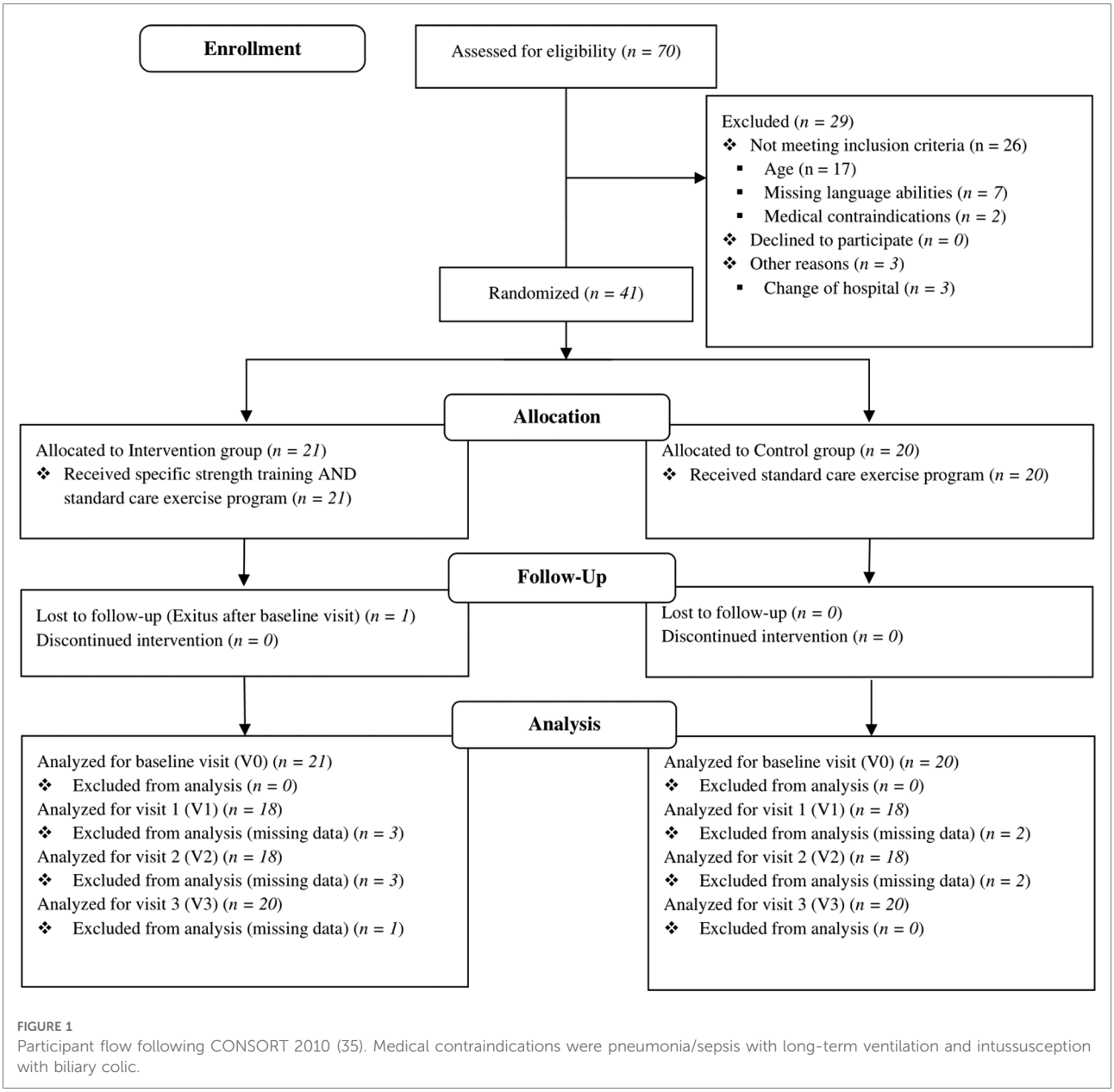

FIGURE 1
Participant flow following CONSORT 2010 (35). Medical contraindications were pneumonia/sepsis with long-term ventilation and intussusception with biliary colic.

treatment. The final assessment (V3) was completed by 40 participants.

Participants' characteristics, including disease- and treatment-related information divided by group, are shown in Table 2. Male participants were in the majority in both groups. The age distribution was nearly balanced. Overall, participants with ALL ($n = 25$) were the predominant number. One participant in the IG underwent allogeneic stem cell transplantation 104 days after V1. Four participants were fitted with a brace owing to vertebral compression fractures. The brace was worn during the exercise interventions and assessments.

Intervals between study inclusion and each visit are presented in Table 3. Assessments of the two groups were performed at similar measurement points during treatment.

Exercise interventions, adverse events, and adherence

Exercise characteristics are shown in Table 4. Over a mean exercise intervention period of 7.1 ± 3.1 months, the IG completed 33.0 ± 20.0 exercise sessions (range, 10–84 sessions). In comparison, the CG performed 40.9 ± 20.6 sessions (range, 15–79 sessions) over a period of 7.7 ± 1.5 months. The IG rejected an average of 18.1 ± 12.8 exercise sessions over the intervention period compared with 18.9 ± 9.4 sessions in the CG. Adherence to the exercise sessions throughout the intervention period in relation to all exercise sessions offered was 65% and 68% in the IG and CG, respectively. Among all participants, the average exercise

TABLE 2 Participants' anthropometric and clinical baseline characteristics by group.

Characteristics	Intervention group ($n = 21$)				Control group ($n = 20$)			
	N (%)	M ± SD	Median	Range	*N* (%)	M ± SD	Median	Range
Recruitment								
Age at recruitment (years)	21 (100)	10.2 ± 4.2	10.1	4.4–17.1	20 (100)	9.7 ± 3.9	9.2	4.3–17.5
Days post-diagnosis	21 (100)	14.7 ± 9.1	13.0	3–49	20 (100)	15.6 ± 11.4	11.5	4–52
Gender and age (years)								
Male	15 (71)	10.4 ± 4.0	10.8	4.4–16.1	12 (60)	9.6 ± 3.8	9.2	5.2–17.5
Female	6 (29)	9.6 ± 5.0	7.2	4.4–17.1	8 (40)	9.9 ± 4.2	9.7	4.3–15.7
BMI (kg/m^2)	21 (100)	17.2 ± 3.3	15.8	13.3–23.9	20 (100)	17.0 ± 4.8	16.0	12.1–35.1
BMI z-score[a]	21 (100)	−0.3 ± 0.9	−0.3	−2.2 to 1.4	20 (100)	0.5 ± 1.5	−0.4	−3.5 to 3.1
Tumor type and age (years)								
ALL	11 (52)	9.5 ± 4.6	8.5	4.4–17.1	14 (70)	8.5 ± 3.3	8.0	4.3–15.7
AML	1 (5)	16.1	16.1	16.1	3 (15)	12.4 ± 2.5	11.1	10.8–15.3
NHL	9 (43)	10.3 ± 3.5	12.0	6.1–15.4	3 (15)	13.1 ± 5.2	14.5	7.3–17.5
Second primary cancer[b]	1 (5)				1 (5)			
Treatment[c]								
Chemotherapy	21 (100)				20 (100)			
Radiation therapy	1 (5)				2 (10)			
Allogeneic HSCT	1 (5)				0 (0)			
Medical brace[d]	0 (0)				4 (20)			

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation; NHL, non-Hodgkin lymphoma; M, mean; SD, standard deviation; N, number; BMI, body mass index; kg, kilogram; m^2, square meter; mg, milligram. Gender-, age-, and disease-related information were determined from hospital records.

[a]BMI z-score was calculated using gender- and age-adjusted reference values (36).

[b]Participants who were diagnosed with a second primary cancer >5 years after the first treatment: $n = 1$ ALL → NHL after 15 years; $n = 1$ NHL → different NHL type after 8 years. The participants had completely recovered and had no limitations or long-term effects of the primary tumor.

[c]Characteristics on treatment methods refer to the entire study course.

[d]Medical brace in the course of treatment was necessary in cases of osteoporotic vertebral compression fractures in four participants. This limited the upper body mobility during the assessment. The exercise intervention implementation was not restricted.

TABLE 3 Intervals between study recruitment and follow-up visits by group.

Characteristics	Intervention group				Control group			
	N	M ± SD	Median	Range	*N*	M ± SD	Median	Range
From recruitment to V0 (days)	21	4.9 ± 9.0	1.0	0–36	20	3.2 ± 3.8	1.5	0–14
From recruitment to V1 (days)	18	65.7 ± 25.3	62.0	26–106	18	60.2 ± 15.6	60.0	38–98
From recruitment to V2 (days)	18	141.7 ± 47.0	141.0	53–216	18	143.3 ± 35.9	142.5	57–190
From recruitment to V3 (days)	20	223.7 ± 92.4	224.5	76–449	20	235.0 ± 44.9	247.5	120–322

M, mean; N, number; SD, standard deviation; V, visit.

session duration was 29.7 ± 4.7 (range, 22–44) min. No serious adverse events (grades 2–5) or injuries associated with 1,539 exercise interventions, including 29 supervised web-based sessions (distributed among five participants of the IG) and 153 assessments, were recorded. One minor treatment-related event (vomiting) led to exercise session termination. One participant stumbled during balance training without any consequences and was able to continue the exercise session. For another participant, the MOON-test was discontinued due to treatment-related nausea and vertigo and continued the following day. No participants were lost to follow-up due to personal or exercise-related reasons.

Activities of daily living

The analysis of self-reported ADLs (**Table 5**) revealed no between-group differences at V3. The CG significantly

TABLE 4 Exercise characteristics by group.

Characteristics	Intervention group ($n = 21$)			Control group ($n = 20$)		
	M ± SD	Median	Range	M ± SD	Median	Range
Total exercise intervention duration (months)	7.1 ± 3.1	7.3	2.5–14.7	7.7 ± 1.5	8.1	3.9–10.6
Exercise sessions	33.0 ± 20.0	28.0	10–84	40.9 ± 20.6	37.5	15.0–79.0
Exercise sessions rejected	18.1 ± 12.8	13.0	2–57	18.9 ± 9.4	16.5	5.0–39.0
Mean number of exercise sessions/week	1.0 ± 0.4	1.1	0.4–2.1	1.2 ± 0.5	1.2	0.5–2.2
Mean number of potential exercise sessions/week[a]	1.6 ± 0.6	1.6	0.6–2.7	1.8 ± 0.6	2.0	1.0–2.8
Mean exercise session duration (min)	30.6 ± 4.2	30.0	23.5–42.0	28.9 ± 5.2	27.5	22.2–43.6

M, mean; min, minutes; *N*, number; SD, standard deviation.
[a]The quotient of the number of completed exercise sessions and the total number of potential exercise sessions, considering the rejected sessions.

TABLE 5 Effects of exercise interventions on activities of daily living by group and visits.

Outcome	Group	M ± SD (90% CI); *N* at V0	Δ from V0 to V1 (90% CI); *N*	Δ from V0 to V2 (90% CI); *N*	M ± SD (90% CI); *N* at V3	*P* within groups (V0–V3)	*P* between groups at V3
Self-reported ADL							
ASKp score[a,b] (range, 0–100)	CG	69.4 ± 19.8 (60–79); 14	8.7 (−2 to 20); 12	13.2 (3–23); 12	86.7 ± 12.2 (74–86); 19	0.005	0.822
	IG	62.6 ± 18.8 (52–73); 11	8.0 (−6 to 22); 9	17.8 (10–31); 10	84.7 ± 12.5 (80–90); 20	0.010	
ASK total score[b] (range, 0–100)	CG	66.8 ± 17.7 (60–74); 20	9.1 (0–18); 18	14.7 (6–23); 18	84.8 ± 14.4 (79–90); 20	<0.001	0.978
	IG	60.1 ± 19.5 (53–67); 21	20.1 (10–30); 18	23.2 (16–30); 18	84.7 ± 12.5 (80–90); 20	<0.001	
Functional ADL Screen							
Total score[c] (range, 0–28)	CG	27.0 ± 3.7 (25–28); 19	0 (−2 to 2); 17	−0.6 (−3 to 2); 17	26.9 ± 3.8 (25–28); 20	0.916	0.043
	IG	26.1 ± 4.2 (25–28); 21	0.8 (−1 to 3); 18	1.0 (0–2); 17	28.0 ± 0.2 (28); 19	0.034	

ASK/ASKp, Activities Scale for Kids©/Activities Scale for Kids© performance version; CI, confidence interval of differences; CG, control group; IG, intervention group; M, mean; *N*, number; *P*, *p*-value; SD, standard deviation; V, visit.
Score changes (mean) from the baseline (V0) to V3 within the groups were assessed using paired *t* tests (ASKp/ASK total score in the IG; ASK total score in the CG), and Wilcoxon singed-rank tests for all other longitudinal comparisons, respectively. Between-group differences were assessed using two-sample *t* tests for ASK total score or Mann–Whitney *U* tests for ASKp score and Functional ADL Screen. Positive Δ-values represent score improvements.
[a]Case number differences between ASKp score and ASK total score based on the different calculation methods. The prerequisite to calculate the ASKp score was 23 out of 30 valid responses (30).
[b]A total score of 100 indicates no functional limitations.
[c]A total score of 28 indicates no functional limitations.

increased the ASK total score (18.0 ± 20.5; $p < 0.001$) in the course of treatment (V0–V3). Within-group analysis of the IG revealed a significant ASK total score improvement (24.7 ± 20.3; $p < 0.001$) between V0 and V3 (**Figure 2**). The analysis of the Functional ADL Screen showed an improvement of the total score from V0 to V3 in the IG compared with the CG (1.9 ± 4.4; $p = 0.034$ vs. −0.1 ± 5.4; $p = 0.916$). In the IG, seven participants required locomotion support indoor and/or outdoor in the study course, compared with eight participants in the CG. Reported aids for locomotion were wheelchairs, crutches, hands and knees, and carried by parents.

Motor performance

The MOON-test results are presented in **Table 6**. The number of tested participants varies within test items due to published age-specific reference values and limited individual capacity. Except for muscular explosive strength at V2 (IG: −20.3 ± 8.0 vs. CG: −34.5 ± 12.8; $p = 0.012$), no significant between-group differences were noted. In the IG, we observed improved mean values for eye-hand coordination ($p = 0.177$), static balance ($p = 0.325$), speed ($p = 0.016$), muscular explosive strength ($p = 0.214$), and muscular endurance for

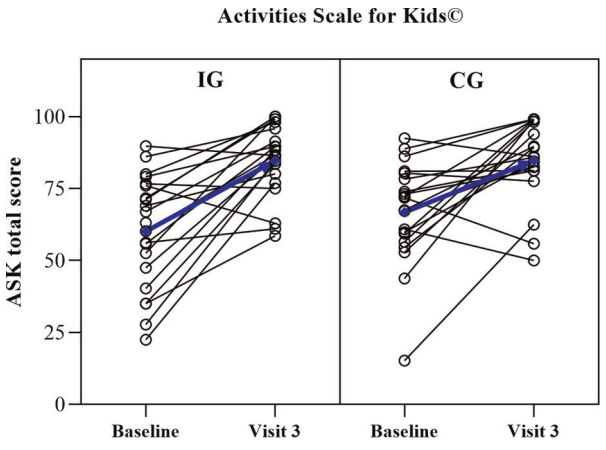

FIGURE 2
Within-participant development from the baseline (Visit 0) to Visit 3 for the activities scale for Kids© total score in the intervention (IG, $n = 20$) and control group (CG, $n = 20$). Blue lines represent within-group mean development.

the legs ($p = 0.011$) at V2 than at V0. Moreover, in the CG, mean value changes in eye-hand coordination ($p = 0.983$), static balance ($p = 0.221$), speed ($p = 0.158$), upper extremity coordination ($p = 0.465$), and muscular endurance for the legs ($p = 0.407$) were observed between V0 and V2. The intergroup comparison of means provided results that were below the age- and gender-matched reference values in almost all eight motor abilities.

Physical activity

Overall, 72 accelerometer measurements were conducted across both groups, including 61 valid recordings at V0 and V2. The mean wear time of valid recordings was 5.9 ± 1.0 days (maximum of 7 days). Reasons for invalid measurements were the lack of compliance and unscheduled inpatient hospitalizations. Both the CG (V0: 17 ± 21 min, range 0–102 min, $n = 13$; V2: 25 ± 29 min, range 2–103 min, $n = 11$) and IG (V0: 18 ± 18 min, range 2–60 min, $n = 13$; V2: 49 ± 51 min, range 5–186 min, $n = 11$) increased their level of moderate-to-vigorous PA (MVPA, ≥3 METs) in the course of therapy (**Figure 3**). The mean number of steps per day increased between V0 and V2 within CG (+37%) and IG (+44%). At V2, five participants from the IG achieved a step count of >10,000 steps on individual days throughout the investigated week, whereas two participants from the control group achieved >10,000 steps. In the IG, the accelerometer acceptability, presented as mean relative off-ratio, was 56% at V0, and 52% at V2, respectively, compared with the CG (49% at V0; 52% at V2). No significant between-group differences were observed.

Discussion

To our knowledge, the ActiveADL Study is the first randomized controlled clinical trial investigating the effects of a specific strength training on the ADL accomplishment in a pediatric cancer cohort during intensive treatment. Only a few studies among pediatric patients with cancer included regular tailored in-hospital exercise interventions throughout the entire acute therapy period (21, 39). Thus, our study provides further insights into the effects of supervised exercise interventions, which are still limited according to published literature due to moderate evidence, study bias or small sample sizes (40, 41). Nevertheless, the potential benefits of exercise on psychosocial and physical parameters have been shown in various intervention studies among children with cancer in recent years (13, 39, 42). Positive effects of exercise interventions during pediatric cancer treatment have been demonstrated regarding increased functional mobility (40), muscle strength (16), health-related quality of life (43), and decreased cancer-related fatigue level (44). Childhood cancer survivors and their parents also reported the importance of being physically active during hospitalization through a combined intervention of physical and social activities and with the motivation of peers (45). However, it is not clearly investigated from which training content patients benefit the most to ensure functionality and autonomy in everyday acute therapy. In particular, for the intensive treatment phase, advantages of supervised exercise interventions over non-supervised independently conducted training protocols became apparent (46). As a minimum level of strength is the basic requirement for locomotion, infantile play and the accomplishment of everyday tasks, the IG received a specific training to maintain their strength abilities. To present differences between both groups as transparently as possible, the CG did not receive any specific exercises to target strength abilities. To answer the research question regarding ADL accomplishment, participants experienced changes in daily living skills and functional impairments were intentionally assessed both, subjectively with the Functional ADL Screen and objectively with the ASK.

The longitudinal analysis has shown that the ASK total score of both groups increased during the course of therapy and only slightly differed from healthy children (mean age, 11.0 ± 2.9 years; $n = 209$; IG: −4.4%; CG: −2.4%) at the end of the intensive treatment (47). Compared with a cohort of patients with bone tumors ($n = 21$, mean 14.9 years of age, mean 2.1 years after tumor surgery), our intervention groups achieved similar ASKp scores at the intensive treatment cessation (48). The data suggest that a specific strength training does not consistently increase the ability to perform better ADL accomplishment. The results of a study in a population of elderly people showed that sarcopenia, defined

TABLE 6 Effects of exercise interventions on motor performance by group and visits.

Motor ability	Test item		Visit	Intervention group					Control group					*P* between groups
				N	*Differences to reference values (%)*			Scoring below reference (%)	*N*	*Differences to reference values (%)*			Scoring below reference (%)	
					M ± SD	Median	90% CI			M ± SD	Median	90% CI		
Eye-hand coordination	Inserting pins (time in s)		V0	21	−15.3 ± 32.3	−6.9	(−27 to −3)	71	20	−13.7 ± 30.6	−10.4	(−26 to −2)	70	0.896
			V2	17	−5.1 ± 32.9	−1.6	(−19 to 9)	53	18	−12.2 ± 34.0	−2.2	(−26 to 2)	50	0.947
Static balance	Static stand (*n* of contacts)[b,c]		V0	19	15.4 ± 65.3	−2.0	(−11 to 41)	42	15	1.3 ± 6.7	0.3	(−2 to 4)	60	0.835
			V2	17	0.4 ± 6.9	−3.7	(−2 to 3)	41	14	0 ± 6.7	−2.8	(−3 to 3)	29	0.736
Speed	Reaction test (time in s)		V0	20	−12.9 ± 14.9	−13.9	(−19 to −7)	80	19	−15.4 ± 31.8	−8.3	(−28 to −3)	68	0.536
			V2	17	−4.1 ± 16.2	0	(−11 to 3)	47	18	−10.5 ± 22.1	−5.7	(−20 to −1)	56	0.498
Upper extremity coordination	Throwing at a target (hits)[a]		V0	8	−16.3 ± 76.2	−43.6	(−67 to 35)	63	8	−16.8 ± 30.1	−23.8	(−37 to 3)	63	0.505
			V2	6	−35.6 ± 17.6	−35.8	(−50 to −21)	100	5	−9.6 ± 35.1	0	(−43 to 24)	40	0.329
Flexibility	Stand-and-reach (difference in cm)[b]		V0	19	−9.2 ± 11.4	−6.0	(−14 to −5)	79	20	−9.2 ± 12.0	−6.8	(−14 to −5)	65	0.736
			V2	17	−9.8 ± 11.3	−10.4	(−14 to −5)	82	18	−10.2 ± 10.3	−11.8	(−14 to −6)	83	0.717
Muscular explosive strength	Medicine ball shot (distance in m)[a]		V0	14	−23.4 ± 16.0	−19.5	(−31 to −16)	100	11	−27.2 ± 18.2	−29.5	(−37 to −17)	91	0.647
			V2	14	−20.3 ± 8.0	−17.3	(−29 to −12)	86	13	−34.5 ± 12.8	−35.7	(−41 to −28)	100	0.012
Muscular endurance for the legs	Sit-to-stand (time in s)		V0	20	−46.1 ± 100.0	−25.1	(−82 to −10)	90	20	−24.9 ± 37.0	−16.7	(−39 to −11)	65	0.607
			V2	17	−18.0 ± 66.6	5.2	(−46 to 10)	35	17	−11.4 ± 26.1	−1.3	(−22 to 0)	59	0.547
Hand grip strength	Hand-held dynamometry (strength in kg)[a]	Right	V0	17	−20.3 ± 24.6	−23.2	(−31 to −10)	82	16	−29.5 ± 16.2	−27.3	(−37 to −22)	94	0.296
			V2	15	−22.7 ± 31.5	−27.3	(−37 to −8)	80	13	−32.4 ± 24.8	−32.1	(−39 to −26)	92	0.650
		Left	V0	17	−19.3 ± 26.9	−23.2	(−31 to −8)	77	16	−26.4 ± 18.1	−23.3	(−34 to −18)	100	0.601
			V2	15	−21.3 ± 29.8	−26.4	(−35 to −8)	80	14	−30.4 ± 15.8	−30.7	(−38 to −23)	93	0.652

CI, confidence interval; cm, centimeter; kg, kilogram; m, meter; M, mean; *N*, number; *P*, *p*-value; s, seconds; SD, standard deviation; V, visit.

sit-to-stand results were compared with unpublished age- and gender-specific pupils reference values ($n = 289$) in Munich (37). All other results were compared with the reference values of each single test items (31, 38). Single test items could not be assessed or analyzed due to missing reference values or restricted health status.

[a]Because of published reference values, throwing at a target is limited to participants between 6 and 11 years of age, the test items medicine ball shot and hand-held dynamometry are limited between 6 and 18 years of age.

[b]Absolute differences to reference values were calculated, because values around zero lead to exaggerated percentage values.

[c]A positive difference in static stand represents a result below the reference values, because it means a higher number of ground contacts of the free leg.

10.3389/fped.2022.982996

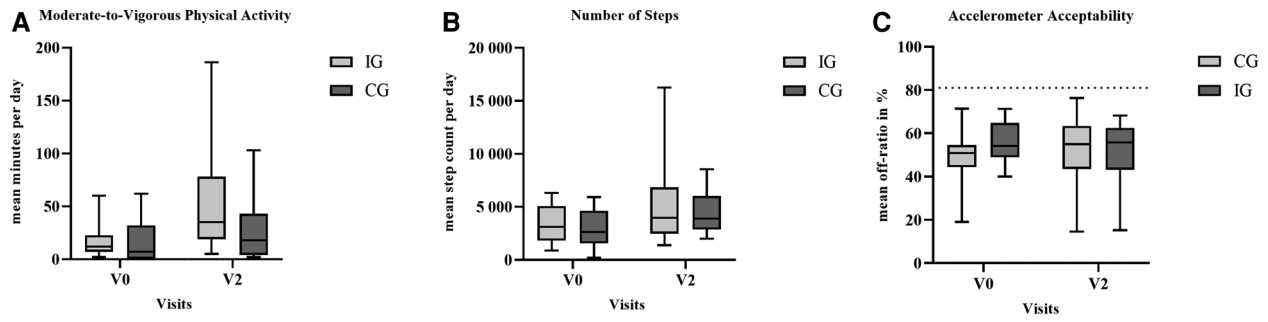

FIGURE 3
Between-group differences at the baseline (V0) and Visit 2 regarding the outcome (A) moderate-to-vigorous physical activity; (B) physical activity amplitude, and (C) accelerometer acceptability. The dashed line at 81% off-ratio represents the minimum accelerometer wearing time of 4 days with 8 h/day. Note: Whiskers represent the minimum and maximum of the cases.

by physical performance, muscle mass and muscle strength, is associated with impairment of higher-level functional capacity in daily living (49). In a cohort of adult cancer patients, a combined in-hospital physical therapy with resistance, aerobic, and stretching exercises improved muscle strength and functional independence regarding ADLs (50). Also a retrospective analysis among pediatric cancer patients identified that functional limitations in ADLs could be reduced through an inpatient rehabilitation program, including strength training during treatment (51).

Both immediately after diagnosis and after the consolidation phase, our cohort shows impairments in all dimensions of motor performance compared with healthy children and adolescents. These results confirm the findings of a pediatric study population with different cancer entities at the end of acute therapy (7) and those of a cohort of patients with leukemia and lymphoma in the maintenance therapy and follow-up care, respectively (52). The MOON-test results suggest motor skills preservation in both groups in the course of treatment. In comparison, the strength training intervention seems to be slightly superior with regards to muscular explosive and endurance strength.

The accelerometer data show limited PA during outpatient treatment periods in almost all participants. The WHO PA recommendations for children and adolescents of at least 60 min of daily MVPA are only met by a few participants (53). However, our cohort was similarly physically active compared with their healthy peers (54). Both groups increased the amount of PA over the course of the study.

The data on adherence illustrate that, in principle, both—sessions of general exercise promotion and specific strength training interventions—can be implemented throughout the acute therapy period. Based on published exercise studies in pediatric oncology, exercise content, frequency, duration, and adverse events were standardized documented in the ActiveADL Study. Regarding study enrollment, none of the screened 70 patients had to be excluded due to the absence of personal/parental consent. The most common reason for exclusion was the patients' age. This mainly includes children with ALL aged <4 years old. None of the participants prematurely terminated the intervention on their personal initiative, underlining the fact that potentially occurring physical limitations in the course of treatment are manageable by training adjustment.

Our interventions proofed safe and feasible in all age groups (55). No adverse events with consequences that occurred during supervised exercise sessions have been reported. Three Grade 1 adverse events among our participants represent a 0.002% relative frequency. In Germany, fewer adverse events occurred in our cohort than those with other acute cancer clinics with an exercise program (34). After consultation with physicians and based on published literature, one participant continued to exercise after stem cell transplantation and successfully completed the intervention (56, 57).

Due to the lack of practicability, exercise control *via* physiological parameters was dispensed with. Accordingly, following the recommendation of Coombs et al. (39), the training content, dose, and intensity were adapted to the individual's state of health and adjusted to the therapy phase (i.e., outpatient or inpatient) and the children's interests. Furthermore, therapy-related performance changes could be considered, making it possible to provide training stimuli even for participants with low exercise capacity (i.e., sitting or lying in bed). With weekly 1.7 ± 0.6 (range, 0.6–2.8) training opportunities in the cohort, not all participants achieved the intended number of 2–3 exercise sessions per week. Deviations in exercise frequency or duration in relation to the defined training parameters have also been described in other RCTs with shorter intervention periods (17, 56). During the mean intergroup intervention period of 7.4 ± 2.4 (range, 2.5–14.7) months, several factors—for example, therapy-related side effects, limited physical capacity, or outpatient treatment

phases—have influenced the exercise frequency. Reasons for exercise session rejections included sobriety prior to invasive procedures, time constraints in clinical routine, and, in rare cases, a lack of motivation. The higher number of exercise sessions in the CG compared with the IG (40.9 ± 20.6 vs. 33.0 ± 20.0 sessions) could be related to the intervention period that was on average 3.5 weeks longer. Variations in treatment regimen led to individual variability in the number of exercise sessions. In conclusion, 2–3 weekly exercise sessions during the intensive treatment are a realistic goal, which should be re-evaluated and, if necessary, adjusted weekly due to the different courses of the disease and individual activity levels.

Considering the findings of our baseline analysis that children and adolescents revealed multifunctional impairments in ADLs, PA and motor performance immediately after diagnosis of ALL, AML or NHL, patients may benefit from early exercise interventions immediately after diagnosis to reduce ADL impairments and maintain motor performance and activity levels until treatment cessation (27). Consequently, the exercise behavior of patients could be positively influenced in the long term to improve coping skills for everyday tasks even in the follow-up care in order to decrease the risk of physical performance limitations among childhood cancer survivors (58).

It is worth mentioning that the COVID-19 pandemic had no serious consequences for exercise interventions and data collection. Exercise interventions could continue while adhering to strict hygiene measures. In particular, at the beginning of the pandemic, which is equivalent to the last third of the study, contact times at outpatient follow-up visits were reduced to a minimum. Following a COVID-19 diagnosis, one participant of the CG was isolated over 14 days. The disease was asymptomatic, and the interventions could be continued after isolation period without any restrictions.

Our hypothesis of the superiority of strength training as the more appropriate exercise method compared with standard care for accomplishing daily tasks was not confirmed in the ActiveADL study. In our cohort, it became clear that the training content may play a subordinate role. Instead, regular exercise sessions to maintain the PA during treatment, as well as individual adaptation of low-to-moderate exercise intensity to the patient's performance and health status, could be essential to support the ability to continue ADL accomplishment. Our results demonstrate that a population of patients with ALL, AML, and NHL can benefit from supervised exercise interventions in the course of acute therapy in general.

With regard to recruitment- and assessment-related limitations, we refer to the publication of the baseline data (27). In the following, we present exercise-specific limitations. Due to the small number of initial diagnoses of childhood, cancer at single sites and combined with the self-determination of children in the treatment process, the definition of a homogeneous study cohort for an RCT is a challenging task. Conclusions regarding intervention effects for other cancer types cannot be made. The small number of participants in each group as well as the skewed gender and age distribution limit further subgroup analysis and generalizability of the results. The findings suggest that a larger sample size is needed to clarify the exercise efficiency of specific training methods. To avoid additional burden on participants due to the number of assessments and activity measurements during the intensive treatment, secondary outcomes were collected at only two visits. To provide stronger conclusions about the effects of exercise on motor performance and PA, the MOON-test and accelerometer should have been used at V3. Strict adherence to visits coupled with the defined therapy phases of treatment protocols could not be consistently maintained. Individual measurement time points were adjusted to ensure the participants' regeneration episodes. Associated with a high total score at V0 and the low possibility of improvement in the course of treatment, Functional ADL Screen results suggest a ceiling effect. According to the three exercise physiologists distributed over two study sites, a standardized training over a 3.5-year study duration was possible only to a limited extent. However, clear documentation, predefinition of a strength training manual and regular agreements, contributed to interventions as standardized as possible during the long study period.

Conclusion

Our results indicate the relevance of a regular, supervised exercise program throughout the acute anticancer treatment to maintain the children's autonomy and participation in clinical routine and potentially counteract physical inactivity and motor performance impairments. In this context, a specific strength training could not be shown to be the method of first choice, as the outcome parameters of the CG with standard care exercise program have also been stabilized in the course of therapy. However, the ActiveADL Study illustrates that patients should have access to a structured and holistic exercise program early after diagnosis. Considering the complex interplay of neuromotor, musculoskeletal, and cognitive mechanisms involved in locomotion and performance of everyday tasks, patients could potentially benefit from a combination of exercise interventions and skilled physical therapy to address the individual needs. For example, physical therapists could provide supporting intervention sessions that cover neuromotor reeducation and mobility training for vincristine peripheral neuropathy or pain due to osteonecrosis. The present findings may be useful for

future multicenter studies in defining standardized training content, duration, and intensity of exercise interventions within a homogeneous pediatric cancer cohort. To verify the suspected exercise effects, we are investigating a control cohort at a study site without an implemented exercise program, who did not receive any exercise interventions, at the cessation of intensive.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committees of TUM School of Medicine, Technical University of Munich, Germany (TUM; 25/17 S) and University of Munich, Germany (18-323). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

SK and MG were responsible for conceptualization of the study. DG and SK were responsible for the interventions, examinations, and data collection. DG and SK performed data curation and analysis. BH gave important input for statistical analysis. IS and IvL contributed to medical supervision. IvL, RO-F and TF proofread the study concept. CP was involved in an advisory capacity with the study administration. DG and SK wrote the first draft of the manuscript. SK was responsible for project administration and funding acquisition. All authors contributed to the article and approved the submitted version.

Funding

This research was funded by German José Carreras Leukemia Foundation, grant number DJCLS 15R/2016.

Acknowledgments

The authors gratefully acknowledge all the children and adolescents and their parents for their participation. Furthermore, the authors thank the supporting staff of the Department of Pediatric Hematology and Oncology at the Department of Pediatrics and Children's Cancer Research Center, Kinderklinik München Schwabing, TUM School of Medicine, Technical University of Munich and also the Dr. von Hauner Children's Hospital, Pediatric Hematology and Oncology, Ludwig-Maximilians-University Munich. We thank Joachim Boos for supporting the study idea and grant writing. We thank TUM Graduate School for proofreading this article.

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.

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References

1. Wurz A, McLaughlin E, Lategan C, Chamorro Vina C, Grimshaw SL, Hamari L, et al. The international pediatric oncology exercise guidelines (Ipoeg). *Transl Behav Med*. (2021) 11(10):1915–22. doi: 10.1093/tbm/ibab028

2. Gauß G, Kesting S, Creutzig U, Baumann F, Boos J, Dirksen U, et al. Neue Awmf-S2k-Leitlinie bewegungsförderung und bewegungstherapie in der pädiatrischen onkologie. *Monatsschr Kinderheilkd*. (2022) 170(6):548–50. doi: 10.1007/s00112-022-01474-z

3. Gotte M, Sontgerath R, Gauss G, Wiskemann J, Buzdon M, Kesting S. A national implementation approach for exercise as usual care in pediatric and adolescent oncology: network activeoncokids. *Pediatr Exerc Sci*. (2022):1–8. doi: 10.1123/pes.2021-0218

4. Wurz A, Daeggelmann J, Albinati N, Kronlund L, Chamorro-Vina C, Culos-Reed SN. Physical activity programs for children diagnosed with cancer: an international environmental scan. *Support Care Cancer*. (2019) 27(4):1153–62. doi: 10.1007/s00520-019-04669-5

5. Braam KI, van Dijk-Lokkart EM, Kaspers GJL, Takken T, Huisman J, Bierings MB, et al. Cardiorespiratory fitness and physical activity in children with cancer. *Support Care Cancer*. (2016) 24(5):2259–68. doi: 10.1007/s00520-015-2993-1

6. Thorsteinsson T, Larsen HB, Schmiegelow K, Thing LF, Krustrup P, Pedersen MT, et al. Cardiorespiratory fitness and physical function in children with cancer from diagnosis throughout treatment. *BMJ Open Sport Exerc Med*. (2017) 3(1): e000179. doi: 10.1136/bmjsem-2016-000179

7. Gotte M, Kesting SV, Winter CC, Rosenbaum D, Boos J. Motor performance in children and adolescents with cancer at the End of acute treatment phase. *Eur J Pediatr*. (2015) 174(6):791–9. doi: 10.1007/s00431-014-2460-x

8. Winter C, Muller C, Brandes M, Brinkmann A, Hoffmann C, Hardes J, et al. Level of activity in children undergoing cancer treatment. *Pediatr Blood Cancer*. (2009) 53(3):438–43. doi: 10.1002/pbc.22055

9. Götte M, Kesting S, Winter C, Rosenbaum D, Boos J. Comparison of self-reported physical activity in children and adolescents before and during cancer treatment. *Pediatr Blood Cancer*. (2014) 61(6):1023–8. doi: 10.1002/pbc.24898

10. Antwi GO, Jayawardene W, Lohrmann DK, Mueller EL. Physical activity and fitness among pediatric cancer survivors: a meta-analysis of observational studies. *Support Care Cancer*. (2019) 27(9):3183–94. doi: 10.1007/s00520-019-04788-z

11. Wilson CL, Gawade PL, Ness KK. Impairments that influence physical function among survivors of childhood cancer. *Children*. (2015) 2(1):1–36. doi: 10.3390/children2010001

12. Yildiz Kabak V, Calders P, Duger T, Mohammed J, van Breda E. Short and long-term impairments of cardiopulmonary fitness level in previous childhood cancer cases: a systematic review. *Support Care Cancer*. (2019) 27(1):69–86. doi: 10.1007/s00520-018-4483-8

13. Morales JS, Valenzuela PL, Velazquez-Diaz D, Castillo-Garcia A, Jimenez-Pavon D, Lucia A, et al. Exercise and childhood cancer-a historical review. *Cancers (Basel)*. (2021) 14(1):82. doi: 10.3390/cancers14010082

14. Saultier P, Vallet C, Sotteau F, Hamidou Z, Gentet J-C, Barlogis V, et al. A randomized trial of physical activity in children and adolescents with cancer. *Cancers (Basel)*. (2021) 13(1):121. doi: 10.3390/cancers13010121

15. Nielsen MKF, Christensen JF, Frandsen TL, Thorsteinsson T, Andersen LB, Christensen KB, 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*. (2020) 18(1):175. doi: 10.1186/s12916-020-01634-6

16. Stössel S, Neu MA, Wingerter A, Bloch W, Zimmer P, Paret C, et al. Benefits of exercise training for children and adolescents undergoing cancer treatment: results from the randomized controlled mucki trial. *Front Pediatr*. (2020) 8:243 (243). doi: 10.3389/fped.2020.00243

17. Fiuza-Luces C, Padilla JR, Soares-Miranda L, Santana-Sosa E, Quiroga JV, Santos-Lozano A, et al. Exercise intervention in pediatric patients with solid tumors: the physical activity in pediatric cancer trial. *Med Sci Sports Exercise*. (2017) 49(2):223–30. doi: 10.1249/MSS.0000000000001094

18. Winter CC, Müller C, Hardes J, Gosheger G, Boos J, Rosenbaum D. The effect of individualized exercise interventions during treatment in pediatric patients with a malignant bone tumor. *Support Care Cancer*. (2013) 21 (6):1629–36. doi: 10.1007/s00520-012-1707-1

19. Malysse C, Romero-Galisteo RP, Merchan-Baeza JA, Duran-Millan JI, Gonzalez-Sanchez M, Galan-Mercant A. Physical activity promotion programmes in childhood cancer patients and their impact on fatigue and pain: a systematic review. *Children (Basel)*. (2021) 8(12):1119. doi: 10.3390/children8121119

20. Zhang FF, Kelly MJ, Must A. Early nutrition and physical activity interventions in childhood cancer survivors. *Curr Obes Rep*. (2017) 6(2):168–77. doi: 10.1007/s13679-017-0260-0

21. Morales JS, Valenzuela PL, Herrera-Olivares AM, Bano-Rodrigo A, Castillo-Garcia A, Rincon-Castanedo C, et al. Exercise interventions and cardiovascular health in childhood cancer: a meta-analysis. *Int J Sports Med*. (2020) 41 (3):141–53. doi: 10.1055/a-1073-8104

22. Scott JM, Li N, Liu Q, Yasui Y, Leisenring W, Nathan PC, et al. Association of exercise with mortality in adult survivors of childhood cancer. *JAMA Oncol*. (2018) 4(10):1352–8. doi: 10.1001/jamaoncol.2018.2254

23. Wang DXM, Yao J, Zirek Y, Reijnierse EM, Maier AB. Muscle mass, strength, and physical performance predicting activities of daily living: a meta-analysis. *J Cachexia Sarcopenia Muscle*. (2020) 11(1):3–25. doi: 10.1002/jcsm.12502

24. Gocha Marchese V, Chiarello LA, Lange BJ. Strength and functional mobility in children with acute lymphoblastic leukemia. *Med Pediatr Oncol*. (2003) 40(4):230–2. doi: 10.1002/mpo.10266

25. Arikan H, Yatar İ, Calik-Kutukcu E, Aribas Z, Saglam M, Vardar-Yagli N, et al. A comparison of respiratory and peripheral muscle strength, functional exercise capacity, activities of daily living and physical fitness in patients with cystic fibrosis and healthy subjects. *Res Dev Disabil*. (2015):45–6. doi: 10.1016/j.ridd.2015.07.020

26. Bendixen RM, Lott DJ, Senesac C, Mathur S, Vandenborne K. Participation in daily life activities and its relationship to strength and functional measures in boys with duchenne muscular dystrophy. *Disabil Rehabil*. (2014) 36 (22):1918–23. doi: 10.3109/09638288.2014.883444

27. Gaser D, Peters C, Götte M, Oberhoffer-Fritz R, Feuchtinger T, Schmid I, et al. Analysis of self-reported activities of daily living, motor performance and physical activity among children and adolescents with cancer: baseline data from a randomised controlled trial assessed shortly after diagnosis of leukaemia or non-hodgkin lymphoma. *Eur J Cancer Care (Engl)*. (2022) 31(2):e13559. doi: 10.1111/ecc.13559

28. DeFeo BM, Kaste SC, Li Z, Brinkman TM, Neel MD, Srivastava DK, et al. Long-term functional outcomes among childhood survivors of cancer who have a history of osteonecrosis. *Phys Ther*. (2020) 100(3):509–22. doi: 10.1093/ptj/pzz176

29. Ness KK, Mertens AC, Hudson MM, Wall MM, Leisenring WM, Oeffinger KC, et al. Limitations on physical performance and daily activities among long-term survivors of childhood cancer. *Ann Intern Med*. (2005) 143(9):639–47. doi: 10.7326/0003-4819-143-9-200511010-00007

30. Young NL, Williams JI, Yoshida KK, Wright JG. Measurement properties of the activities scale for kids. *J Clin Epidemiol*. (2000) 53(2):125–37. doi: 10.1016/s0895-4356(99)00113-4

31. Götte M, Kesting S, Albrecht C, Worth A, Bos K, Boos J. Moon-test - determination of motor performance in the pediatric oncology. *Klin Padiatr*. (2013) 225(3):133–7. doi: 10.1055/s-0033-1343411

32. Hartman A, te Winkel ML, van Beek RD, de Muinck Keizer-Schrama SMPF, Kemper HCG, Hop WCJ, et al. 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) 53(1):64–71. doi: 10.1002/pbc.21942

33. Yildiz Kabak V, Ekinci Y, Atasavun Uysal S, Cetin M, Duger T. Motor and basic cognitive functions in children with acute lymphoblastic leukemia undergoing induction or consolidation chemotherapy. *Percept Mot Skills*. (2021) 128(3):1091–106. doi: 10.1177/00315125211002065

34. Gauß G, Beller R, Boos J, Daggelmann J, Stalf H, Wiskemann J, et al. Adverse events during supervised exercise interventions in pediatric oncology-a nationwide survey. *Front Pediatr*. (2021) 9:682496. doi: 10.3389/fped.2021.682496

35. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. Consort 2010 statement: extension to randomised pilot and feasibility trials. *BMJ*. (2016) 355:15239. doi: 10.1136/bmj.i5239

36. Kromeyer-Hauschild K, Wabitsch M, Kunze D, Geller F, Geiß HC, Hesse V, et al. Percentiles of body mass Index in children and adolescents evaluated from different regional German studies. *Monatsschr Kinderheilkd*. (2001) 149 (8):807–18. doi: 10.1007/s001120170107

37. Metzinger C. *Generation of standard values for the sit-to-stand test with children and adolescents at the age of 4–17 years*. [*Unpublished master's thesis*]. Munich: Technical University of Munich (2017).

38. McQuiddy VA, Scheerer CR, Lavalley R, McGrath T, Lin L. Normative values for grip and pinch strength for 6- to 19-year-olds. *Arch Phys Med Rehabil*. (2015) 96(9):1627–33. doi: 10.1016/j.apmr.2015.03.018

39. Coombs A, Schilperoort H, Sargent B. The effect of exercise and motor interventions on physical activity and motor outcomes during and after medical intervention for children and adolescents with acute lymphoblastic leukemia: a systematic review. *Crit Rev Oncol Hematol*. (2020) 152:103004. doi: 10.1016/j.critrevonc.2020.103004

40. Morales JS, Valenzuela PL, Rincón-Castanedo C, Takken T, Fiuza-Luces C, Santos-Lozano A, et al. Exercise training in childhood cancer: a systematic review and meta-analysis of randomized controlled trials. *Cancer Treat Rev*. (2018) 70:154–67. doi: 10.1016/j.ctrv.2018.08.012

41. Braam KI, van der Torre P, Takken T, Veening MA, van Dulmen-den Broeder E, Kaspers GJ. Physical exercise training interventions for children and young adults during and after treatment for childhood cancer. *Cochrane Database Syst Rev*. (2016) 3:CD008796. doi: 10.1002/14651858.CD008796.pub3

42. Grimshaw SL, Taylor NF, Shields N. The feasibility of physical activity interventions during the intense treatment phase for children and adolescents with cancer: a systematic review. *Pediatr Blood Cancer*. (2016) 63(9):1586–93. doi: 10.1002/pbc.26010

43. Speyer E, Herbinet A, Vuillemin A, Briancon S, Chastagner P. Effect of adapted physical activity sessions in the hospital on health-related quality of life for children with cancer: a cross-over randomized trial. *Pediatr Blood Cancer*. (2010) 55(6):1160–6. doi: 10.1002/pbc.22698

44. Lam KKW, Li WHC, Chung OK, Ho KY, Chiu SY, Lam HS, et al. 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) 101(11):1947–56. doi: 10.1016/j.pec.2018.07.008

45. Petersen NN, Larsen HB, Pouplier A, Schmidt-Andersen P, Thorsteinsson T, Schmiegelow K, et al. Childhood cancer Survivors' and their Parents' experiences with participation in a physical and social intervention during cancer treatment: a respect study. *J Adv Nurs*. (2022) 78(11):3806–16. doi: 10.1111/jan.15381

46. Götte M, Kesting S, Winter C, Rosenbaum D, Boos J. Experience of barriers and motivations for physical activities and exercise during treatment of pediatric patients with cancer. *Pediatr Blood Cancer*. (2014) 61(9):1632–7. doi: 10.1002/pbc.25071

47. Costi S, Bressi B, Cavuto S, Braglia L, Ferrari A, Pelosin E. Cross-cultural validation of activities scale for kids: the performance of healthy Italian children. *J Sports Med Phys Fitness*. (2020) 60(7):1014–9. doi: 10.23736/S0022-4707.20.10466-3

48. Piscione PJ, Davis AM, Young NL. An examination of adolescent bone tumor patient responses on the activities scale for kids (ask). *Phys Occup Ther Pediatr*. (2014) 34(2):213–28. doi: 10.3109/01942638.2013.784719

49. Tanimoto Y, Watanabe M, Sun W, Sugiura Y, Tsuda Y, Kimura M, et al. Association between sarcopenia and higher-level functional capacity in daily living in community-dwelling elderly subjects in Japan. *Arch Gerontol Geriatr*. (2012) 55(2):e9–13. doi: 10.1016/j.archger.2012.06.015

50. Narao H, Hirota K, Koya S, Tomita M, Manako Y, Ogawa S, et al. Effects of in-hospital physical therapy on activities of daily living in patients with hepatocellular carcinoma. *Int J Environ Res Public Health*. (2020) 17(23):9098. doi: 10.3390/ijerph17239098

51. Taguchi K, Ueno T, Shimizu Y, Ishimoto R, Hada Y. Effect of inpatient rehabilitation on activities of daily living in pediatric cancer patients in Japan. *Int J Rehabil Res*. (2018) 41(2):146–51. doi: 10.1097/MRR.0000000000000280

52. Keiser T, Gaser D, Peters C, Oberhoffer-Fritz R, Kesting S, von Luettichau I. Short-Term consequences of pediatric anti-cancer treatment regarding blood pressure, motor performance, physical activity and reintegration into sports structures. *Front Pediatr*. (2020) 8:463. doi: 10.3389/fped.2020.00463

53. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World health organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. (2020) 54(24):1451–62. doi: 10.1136/bjsports-2020-102955

54. Finger JD, Varnaccia G, Borrmann A, Lange C, Mensink G. Körperliche Aktivität von Kindern und Jugendlichen in Deutschland - Querschnittergebnisse aus KiGGS Welle 2 und Trends. *Journal of Health Monitoring*. (2018) 3(1). doi: 10.17886/RKI-GBE-2018-006.2

55. Rustler V, Hagerty M, Daeggelmann J, Marjerrison S, Bloch W, Baumann FT. Exercise interventions for patients with pediatric cancer during inpatient acute care: a systematic review of literature. *Pediatr Blood Cancer*. (2017) 64 (11):e26567. doi: 10.1002/pbc.26567

56. Wallek S, Senn-Malashonak A, Vogt L, Schmidt K, Bader P, Banzer W. Impact of the initial fitness level on the effects of a structured exercise therapy during pediatric stem cell transplantation. *Pediatr Blood Cancer*. (2018) 65(2): e26851. doi: 10.1002/pbc.26851

57. Chamorro-Viña C, Valentín J, Fernández L, González-Vicent M, Pérez-Ruiz M, Lucía A, et al. Influence of a moderate-intensity exercise program on early nk cell immune recovery in pediatric patients after reduced-intensity hematopoietic stem cell transplantation. *Integr Cancer Ther*. (2017) 16(4):464–72. doi: 10.1177/1534735416679515

58. Ness KK, Hudson MM, Ginsberg JP, Nagarajan R, Kaste SC, Marina N, et al. Physical performance limitations in the childhood cancer survivor study cohort. *J Clin Oncol*. (2009) 27(14):2382–9. doi: 10.1200/JCO.2008.21.1482

frontiers | Frontiers in Oncology

TYPE Original Research
PUBLISHED 08 November 2022
DOI 10.3389/fonc.2022.1014661

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Pediatric Oncology, a section of the journal Frontiers in Oncology

RECEIVED 08 August 2022
ACCEPTED 13 October 2022
PUBLISHED 08 November 2022

CITATION
Goodenough CG, Wogksch MD, Kundu M, Lear M, Thomas PG, Srivastava DK, Wang Z, Armstrong GT, Hudson MM, Robison LL and Ness KK (2022) Associations between exercise capacity, p16^{INK4a} expression and inflammation among adult survivors of childhood cancer.
Front. Oncol. 12:1014661.
doi: 10.3389/fonc.2022.1014661

Associations between exercise capacity, p16^{INK4a} expression and inflammation among adult survivors of childhood cancer

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Background: Over 50% of childhood cancer survivors are exercise intolerant, with maximal aerobic capacities comparable to individuals decades older, suggesting early physiologic ageing. In addition, 36% of survivors are obese. Optimal exercise capacity provides a foundation to support daily function and healthy body habitus and is associated with benefits to cognition, cardiovascular health, and longevity. Cellular senescence and inflammation are key mechanisms that drive age-related disease, quantifiable as biomarkers in peripheral blood.

Aims: This study aimed to evaluate associations between p16^{INKa}, a biomarker of cellular senescence, and inflammation and exercise capacity among adult survivors of childhood cancer.

Materials and methods: Eligible survivors were recruited from the St. Jude Lifetime (SJLIFE) Cohort Study. Exercise capacity was assessed by maximal oxygen uptake (VO_2, ml/kg/min) obtained *via* cardiopulmonary exercise testing using a modified Bruce protocol. Body fat (%) was determined from dual energy x-ray absorptiometry (DEXA). Peripheral blood samples were used to evaluate log_2 p16^{INK4a} mRNA expression, a biomarker of cellular senescence, and inflammation with high sensitivity C-reactive protein (hs-CRP) levels. Multivariable regression evaluated associations between p16^{INK4a}, hs-CRP, body fat, and exercise capacity.

Results: Participants included 185 five-year childhood cancer survivors (mean age 36.6 [range 20.1 - 55.7] years, 44% male, 77% non-Hispanic white, 53% leukemia/lymphoma). Compared to males, females had lower peak VO_2 (mean ± SD, 22.5 ± 8.2 vs. 28.8 ± 7.7 ml/kg/min, p<0.01), higher p16^{INK4a} expression (9.6 ± 1.2 vs. 9.2 ± 1.2 fold, p=0.02), and hs-CRP concentration (5.9 ± 8.4 vs. 3.3 ± 3.9 mg/L, p=0.01). Among females (n=103), hs-CRP concentration (β -0.2,

95% CI -0.34 to -0.05, p=0.01) and $p16^{INK4a}$ expression (β-5.32, 95% CI 10.42 to -0.22, p=0.04) were inversely associated and statistically significant with peak exercise capacity, with a significant interaction between $p16^{INK4a}$ expression and body fat (β 0.15, 95% CI 0.02 to 0.28, p=0.03). Among males (n=82), $p16^{INK4a}$ expression (β -1.01, 95% CI -2.14 to 0.12, p=0.08), and body fat (β -0.54, 95% CI -0.70 to -0.38, p<0.01) were inversely associated with peak exercise capacity.

Conclusion: Inflammation and $p16^{INK4a}$ expression, a biomarker of cellular senescence, are associated with lower exercise capacity in childhood cancer survivors, suggesting potential targets or outcome measures for interventions designed to prevent or remediate accelerated physiologic ageing in this population.

KEYWORDS

cellular senescence, p16, inflammation, childhood cancer surivor, exercise capacity

Introduction

Significant advances in treatment of childhood cancers have contributed to five-year survival exceeding 85% (1, 2). However, childhood cancer survivors are at risk for adverse health outcomes associated with cancer treatment, including exercise intolerance. Exercise intolerance is the result of impairment of or poor integration of cardiovascular, autonomic, pulmonary, muscular, and neurosensory system function. Over 56% of survivors are exercise intolerant (VO_2 peak <85% predicted) (3), with exercise capacities comparable to individuals' decades older (4). Young adult survivors of childhood cancer with exercise intolerance have a 3.9-fold increased risk of mortality (3). Within this population, risk for exercise intolerance is highest among those exposed to cardiotoxic therapy such as anthracyclines and chest radiation (3). However, survivors not exposed are also at risk, suggesting that either the disease process or other systemic alteration such as inflammation or cellular damage also contribute to decline in exercise capacity.

Cellular senescence is the functional consequence of serious DNA damage (5), resulting in accumulation of cells unresponsive to growth stimuli. Although these cells appear to remain in a stable state of proliferation arrest, they are not benign. Senescent cells accumulate with age (6–10), secrete high levels of inflammatory cytokines, immune modulators, growth factors, and proteases, and are associated with an increased prevalence of age-related health conditions, including both subclinical inflammation and high fat and/or low lean body mass (11). Although senescent cells are largely undetectable in younger populations, $p16^{INK4a}$ expression (mRNA), a biomarker of biologic ageing and indicator of senescent cells in older adults, is elevated in skin biopsies of young survivors of childhood cancer exposed to radiation (12).

$p16^{INK4a}$ is an important tumor suppressor gene that prevents cells with damaged DNA from growing and dividing too rapidly (13). When expressed, $p16^{INK4a}$ binds to and inactivates cyclin-dependent kinases (CDK4, CDK6), preventing the phosphorylation of retinoblastoma protein (pRB), halting cell cycle progression and initiating cellular senescence (14–16). Expression of $p16^{INK4a}$ occurs in response to stress, such as DNA damaging radiation and chemotherapy, and is highly expressed in senescent cells (15). Thus, it is an excellent biomarker for cellular senescence (17). Given that children with cancer are exposed to cancer therapies capable of inducing DNA damage, and that accelerated physiologic ageing is evident in this population (18–20), it is possible that senescent cells, with their secretory properties, may contribute to the pathobiology of exercise intolerance.

Further, cellular senescence is also associated with abnormal body composition; senescent cells accumulate in white adipose tissue (21), increasing the release and circulation of senescence-associated secretory phenotype (SASP) (10, 22, 23). Unfortunately, children with cancer experience significant changes in body composition during treatment (24–28), with increased risk for both obesity and underweight that can persist into survivorship (28–30). Childhood cancer survivors also have poor dietary habits (31, 32), which may further influence adipose tissue senescence (33). Early accumulation of adipose tissue may be a reservoir for senescent cells and a source of inflammation (34), underlining the pathobiology of early onset of age-related chronic conditions in this population. Recent evidence from murine and human studies suggest that interventions resulting in clearance of cells expressing the $p16^{INK4a}$ gene are capable of delaying the onset of, and attenuate existing, metabolic abnormalities (33) and age-related conditions (11, 35), perhaps defining a potential targets for intervention among survivors.

In this study, we measured $p16^{INK4a}$ expression, a biomarker of biologic age and cellular senescence, and high sensitivity C-reactive protein (hs-CRP), a biomarker of inflammation, in young adult survivors of childhood cancer and evaluated the cross-sectional associations with body fat percent and exercise capacity. We hypothesized that $p16^{INK4a}$ expression and hs-CRP levels would be higher among survivors with high body fat and low exercise capacity.

Materials and methods

Study population

Participants for this study were St. Jude Lifetime Cohort (SJLIFE) members, a retrospective cohort with prospective follow-up designed to evaluate childhood cancer survivors as they age. The study design and characteristics of the study population have been previously described (36–38). Briefly, cohort members were diagnosed with childhood cancer between 1962 and 2012 and treated at St. Jude Children's Research Hospital. For these analyses, participants were at least 18 years old, 10 years from their primary diagnosis, had no evidence of cancer recurrence, and had previous chemotherapy exposure. Potentially eligible participants returning for a second clinical visit to evaluate frail health (including measures of exercise intolerance and body composition) were randomly recruited to provide a blood sample until we reached a powered sample size of 196 participants. Pregnant women or those with a current cancer diagnosis were excluded. Medical records were abstracted by trained personnel to collect demographic information, including age at assessment, sex, height (m), and weight (kg).

Biomarkers

Cellular Senescence Expression of $p16^{INK4a}$ mRNA was determined from CD3 T-lymphocytes processed from peripheral blood samples. Cells were isolated and enriched to >90% purity using RosetteSep™ Human T Cell Enrichment Cocktail (STEMCELL Technologies, Cambridge, MA). Total RNA was isolated from T-lymphocytes (ZR-96 Quick-RNA kit, Zymo Research, Irvine, CA), and reverse transcribed into cDNA using ImProm-II reverse transcription system (Promega Corp., Madison, WI). cDNA was reversed transcribed using Taqman® quantitative reverse-transcription PCR (ThermoFisher Scientific, Waltham, MA) to determine $p16^{INK4a}$ mRNA expression levels. Expression of $p16^{INK4a}$ mRNA transcript was normalized to 18s ribosomal RNA (HS03003631, Applied Biosystems, ThermoFisher Scientific - US, Waltham, MA) as previously described (39, 40). Data were log transformed for analysis (log_2).

Inflammation High sensitivity C-reactive protein (hs-CRP) concentration (mg/L) was determined from serum samples isolated from peripheral blood. Blood samples of 2ml were collected in serum preparation tubes and allowed to clot completely at room temperature. Samples were centrifuged at 1,000-2,000 x g for 10 minutes in a refrigerated centrifuge. Serum supernatant was separated from samples in 1ml aliquots into ARUP standard Transport Tubes and refrigerated until processed on a Quantitative Immunoturbidimetry assay (reference value ≤3.0 mg/L) (41).

Outcomes

Exercise capacity

Exercise capacity was determined *via* cardiopulmonary exercise testing (CPET) on a treadmill using a modified Bruce protocol (42). A leg (n=4) or arm (n=7) cycle ergometer was substituted using a ramp protocol if a participant was unable to walk on a treadmill (lower extremity paralysis, amputations without prostheses, or poor balance). Continuous breath by breath analysis, using a metabolic cart (Ultima CardioO2; MCG Diagnostics, St. Paul, MN), was used to estimate attainment of VO_2 peak. Blood pressure was measured during each stage of the protocol, and a continuous 12-lead electrocardiogram (ECG) monitored cardiac symptoms (43). Cardiopulmonary exercise testing (CPET) was terminated for safety before maximal exertion for signs of ischemia (>2 mm ST depression), frequent arrhythmias (bigeminy and trigeminy), hypertensive blood pressure (BP) response (250/115 mm Hg), symptoms (e.g. angina, shortness of breath, wheezing), or failure of heart rate (HR) to increase with increased exercise intensity. Immediately at test termination, participants were asked for peak rating of perceived exertion (44).

Body fat

Body fat (percent [%]) was determined with dual x-ray absorptiometry (DEXA) using a total body scanning mode (QDR 4500, software version 13.3:3; Hologic, Bedford, MA) (45, 46).

Covariates

Smoking history

Participants self-reported their smoking history, and were classified as current, former, or never smokers.

Statistical analyses

Descriptive statistics characterized demographic and diagnosis related variables (Table 1). Given that exercise

capacity and body composition are influenced by sex, we stratified analysis by sex. Comparisons between male and female participants were made using $\chi 2$ statistics or two sample t tests as appropriate. Associations between smoking history, hs-CRP concentration, and $p16^{INK4a}$ expression were evaluated using linear regression models. Smoking history was not associated with either hs-CRP concentration or $p16^{INK4a}$ expression, and was not retained in final multivariate models. Separate multivariable linear regression models were used to evaluate associations between $p16^{INK4a}$ expression or hs-CRP concentration, and exercise capacity (ml/kg/min). Smoking status was evaluated as a potential covariate. Models were stratified by sex and adjusted for body fat % and age at assessment. Two-way interactions between either $p16^{INK4a}$ expression or hs-CRP concentration and body fat % were evaluated in each model. All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC).

Results

Characteristics of study population

Among 2,823 potentially eligible survivors, 234 were contacted to provide a blood sample. Among these, 30 (12.8%) declined participation. Of 204 samples collected, 15 (7.4%) did not pass quality control (low RNA yield), and 4 (2.0%) samples were not shipped, resulting in 185 participants with complete phenotype and biomarker data (Figure 1). Demographics of study participants are displayed in Table 1. On average,

TABLE 1 Demographic and primary cancer characteristics of survivors of childhood cancer.

Characteristic	All Participants (n=185)	Males (n=82)	Females (n=103)
Race/Ethnicity, N (%)			
Black	39 (21.1)	13 (15.6)	26 (25.2)
Hispanic	3 (1.6)	2 (2.4)	1 (1.0)
White	143 (77.3)	67 (81.7)	76 (73.8)
Mean Diagnosis Age, years (SD)	8.0 (5.8)	7.5 (5.3)	8.4 (6.1)
Mean Age at Evaluation, years (SD)	36.9 (8.0)	34.9 (8.4)	37.9 (7.7)
Mean Survival Time, years (SD)	28.7 (9.0)	27.8 (8.6)	29.9 (9.2)
Smoking Status, N (%)			
Current	21 (11.3)	9 (11.0)	12 (11.7)
Former	25 (13.5)	12 (14.6)	13 (12.6)
Never	139 (75.1)	61 (74.4)	78 (75.7)
Primary Cancer Diagnosis, N (%)			
Leukemia	80 (43.2)	49 (49.0)	31 (37.8)
Lymphoma	34 (18.4)	17 (17.0)	17 (20.7)
Sarcoma	18 (9.7)	10 (10.0)	8 (9.8)
Neuroblastoma	15 (8.1)	10 (10.0)	5 (6.1)
Wilms Tumor	13 (7.0)	8 (8.0)	5 (6.1)
Central Nervous System	10 (5.4)	4 (4.0)	6 (7.3)
Retinoblastoma	5 (2.7)	1 (1.0)	4 (4.9)
Other	10 (5.4)	4 (4.0)	6 (7.3)
Treatment Type, N (%)			
Chemotherapy only	89 (48.1)	36 (43.9)	53 (51.5)
Chemotherapy + Radiation	96 (51.9)	46 (56.1)	50 (48.5)
Treatment Duration, mean (SD)			
Chemotherapy (years)	1.6 (1.3)	1.5 (1.1)	1.7 (1.4)
Radiation (days)	14.5 (18.1)	16.4 (19.1)	13.0 (17.1)
Chemotherapy Agent, N (%)			
Vinca Alkaloids	141 (76.2)	66 (80.5)	75 (72.8)
Anthracyclines	136 (73.5)	61 (73.4)	75 (72.8)
Alkylating Agents	131 (70.8)	62 (75.6)	69 (67.0)
Corticosteroids	101 (54.6)	44 (53.7)	57 (55.3)
Methotrexate	96 (51.9)	41 (50.0)	55 (53.4)
Epipodophyllotoxins	91 (49.2)	42 (51.2)	49 (47.6)
Platinum Agents	39 (21.1)	19 (23.2)	20 (19.4)

survivors were 36.6 years old (range 20.1 to 55.7 years) and 28.7 (± 9.01) years from diagnosis. Forty-four percent were male, 77% were non-Hispanic white, and 44% had a primary diagnosis of Acute Lymphoblastic or Myeloid Leukemia. Females were older than males at time of assessment (p<0.01).

Exercise capacity and body fat

Female survivors had lower peak VO_2 (mean (SD), 22.5 (8.2) vs. 28.8 (7.7) ml/kg/min, p<0.01) and higher body fat (39.2 (7.9) vs. 27.2 (8.2) %, p<0.01) compared to males (Supplemental Figure 1).

Association between inflammation and exercise capacity

Female survivors had higher hs-CRP concentrations (5.9 (8.4) vs. 3.3 (3.9) mg/L, p=0.01) than males (Figure 2A). The results of multivariable linear regression, stratified by sex, and adjusted for age (years), and body fat (%) are shown in Figure 3. Among the 103 female survivors, hs-CRP concentration (β -0.2, 95% CI -0.34 to -0.05, p=0.01), body fat (β -0.54, 95% CI -0.70 to -0.37, p<0.01), and age (β -0.25, 95% CI -0.41 to -0.10, p<0.01) were inversely associated with peak VO_2 (ml/kg/min). Among the 82 male survivors, hs-CRP concentration (β -0.31, 95% CI -0.65 to 0.03, p=0.07), body fat (β -0.55, 95% CI -0.71 to -0.39, p<0.01), and age (β -0.32, 95% CI -0.39 to -0.07, p<0.01), were inversely associated with peak VO_2 (ml/kg/min), though hs-CRP concentration did not achieve statistical significance.

Association between $p16^{INK4a}$ expression and exercise capacity

Female survivors had higher $p16^{INK4a}$ expression (9.6 (1.2) vs. 9.2 (1.2) fold, p=0.02) compared to male survivors (Figure 2B). Multivariable linear regression models, stratified by sex, were used to evaluate the association between $p16^{INK4a}$ expression and peak VO_2 (ml/kg/min), adjusted for age (years) and body fat (%) (Figure 3). Among the 103 female survivors, $p16^{INK4a}$ expression (β -5.32, 95% CI -10.42 to -0.22, p=0.04), body fat (β -2.02, 95% CI -3.26 to -0.78, p<0.01), age (β -0.28, 95% CI -0.43 to -0.11, p<0.01), and the interaction between $p16^{INK4a}$ expression and body fat (β 0.15, 95% CI 0.02 to 0.28, p=0.03), were associated with peak VO_2 (ml/kg/min). Among the 82 male survivors, $p16^{INK4a}$ expression (β -1.01, 95% CI -2.14 to 0.12, p=0.08), body fat (β -0.54, 95% CI -0.70 to -0.38, p<0.01), and age (β -0.22, 95% CI -0.38 to -0.06, p=0.01) were inversely associated with peak VO_2 (ml/kg/min), though $p16^{INK4a}$ expression concentration did not achieve statistical significance.

To explore the interaction effect of $p16^{INK4a}$ expression and body fat on exercise capacity in females, data were sliced by

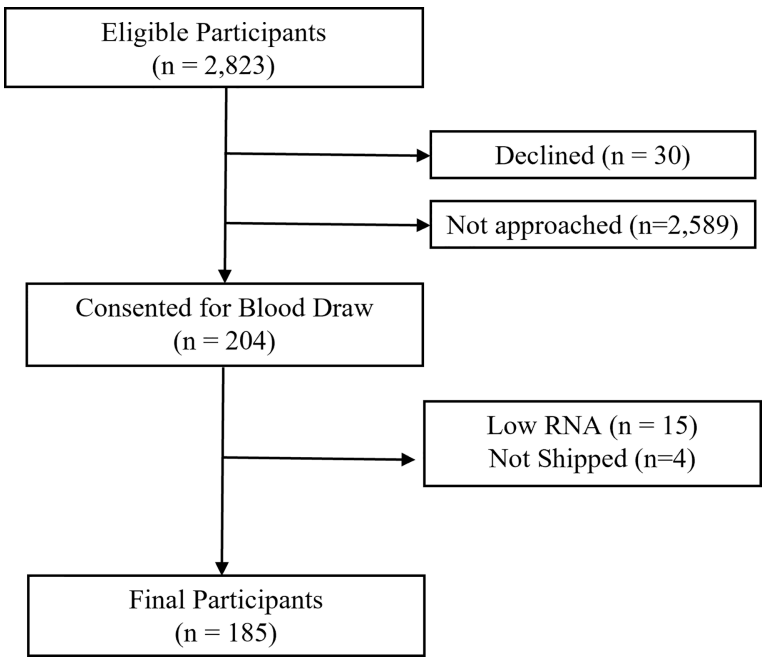


FIGURE 1
Participant flow.

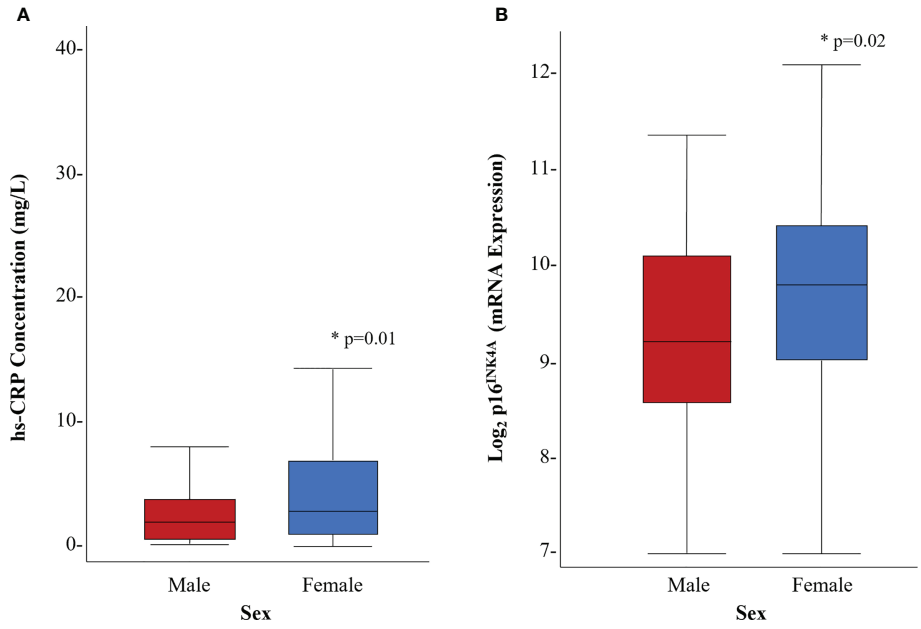


FIGURE 2
Distribution of biomarkers of inflammation and cellular senescence by sex. **(A)** hs-CRP concentration (mg/L) **(B)** p16 ^{INK4A} expression. * denotes statistical significance at p<0.05

progressing levels of body fat percent (Figure 4). Expression of $p16^{INK4a}$ was inversely associated with exercise capacity at body fat percentages less than 35%.

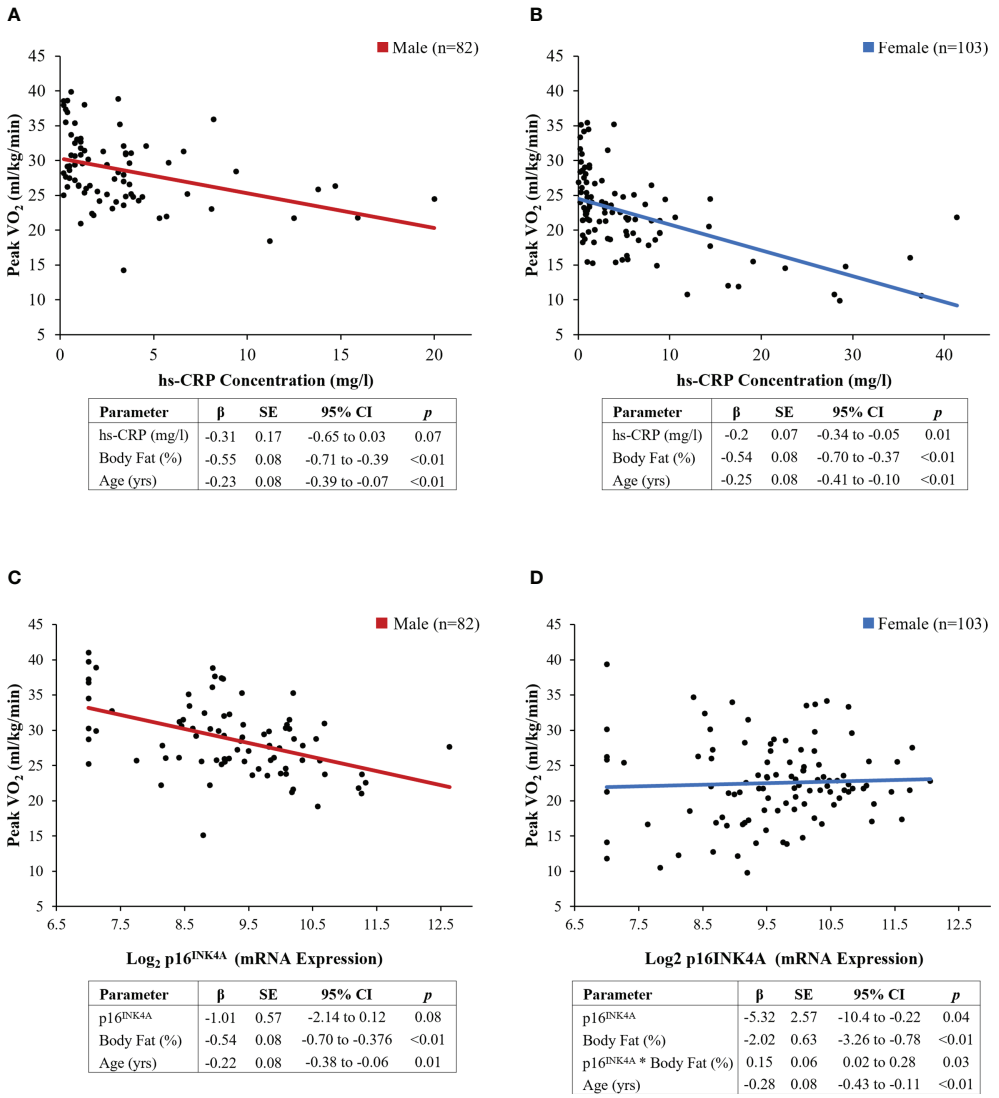
Discussion

Adult survivors of childhood cancer are at risk for exercise intolerance, a predictor of all-cause mortality (3). In this study, we found increased $p16^{INK4a}$ and low-grade inflammation was associated with reduced exercise capacity. Among females, this association was only present among survivors with body fat percentages less than 35%. To our knowledge, this is the first study to demonstrate an association between a biomarker of cellular senescence, low-grade inflammation, and exercise capacity in childhood cancer survivors.

Expression of $p16^{INK4a}$ is generally undetectable in children and younger adults (39). However, it is detectable in peripheral blood T-lymphocytes among older adults and among young survivors of childhood cancer exposed to radiation (12). More recently, Smitherman et al (47) showed evidence of $p16^{INK4a}$ expression in young survivors of childhood, adolescent, and young adult cancers. They found elevated levels of $p16^{INK4a}$ to be associated with frailty, an age-associated phenotype indicating reduced physiological reserve. These data and our findings support the hypothesis that $p16^{INK4a}$ expression is present in other tissues (i.e. organs), and thus cellular senescence is potential mediator of physiologic deregulation in childhood cancer survivors.

Further, not only was elevated $p16^{INK4a}$ expression and hs-CRP concentration associated with lower peak VO_2 and exercise intolerance, but the mean VO_2 peak among our survivors was similar to values in persons several decades their senior (4). This is concerning as poor exercise capacity is associated with early mortality (48, 49), future cardiovascular events (50), and reduced cognitive reserve (51). Early impairments in exercise capacity concomitant with a hallmarks of ageing suggest that VO_2 may be a new biomarker capable of identifying survivors at greatest risk of early onset of chronic conditions and mortality.

The detection of these ageing biomarkers is not surprising given recent work that identified other hallmarks of ageing, including reduced physiologic reserve (19, 52), telomere attrition (53), altered DNA methylation patterns (54), and mitochondrial dysfunction (55). Cellular senescence is an important biological mechanism, and is a part of normal ageing. Inherently designed to guard against proliferation of damaged cells, senescent cells lose the capacity to replicate. As a result of cell cycle arrest, senescent cells secrete proteins, including growth factors and proteases that alter tissue structure and function, and cytokines and chemokines with pro-inflammatory properties. The SASP promote a state of subclinical inflammation, which results in tissue fibrosis and deterioration (56). A similar mechanism may be responsible for the early onset of reduced exercise capacity seen among young adult survivors of childhood cancer. Early



Parameter	β	SE	95% CI	*p*
hs-CRP (mg/l)	-0.31	0.17	-0.65 to 0.03	0.07
Body Fat (%)	-0.55	0.08	-0.71 to -0.39	<0.01
Age (yrs)	-0.23	0.08	-0.39 to -0.07	<0.01

Parameter	β	SE	95% CI	*p*
hs-CRP (mg/l)	-0.2	0.07	-0.34 to -0.05	0.01
Body Fat (%)	-0.54	0.08	-0.70 to -0.37	<0.01
Age (yrs)	-0.25	0.08	-0.41 to -0.10	<0.01

Parameter	β	SE	95% CI	*p*
$p16^{INK4A}$	-1.01	0.57	-2.14 to 0.12	0.08
Body Fat (%)	-0.54	0.08	-0.70 to -0.376	<0.01
Age (yrs)	-0.22	0.08	-0.38 to -0.06	0.01

Parameter	β	SE	95% CI	*p*
$p16^{INK4A}$	-5.32	2.57	-10.4 to -0.22	0.04
Body Fat (%)	-2.02	0.63	-3.26 to -0.78	<0.01
$p16^{INK4A}$ * Body Fat (%)	0.15	0.06	0.02 to 0.28	0.03
Age (yrs)	-0.28	0.08	-0.43 to -0.11	<0.01

FIGURE 3
Results of sex-stratified multivariable models. **(A, B)** hs-CRP concentration (mg/L), **(C, D)** p16 ^{INK4A} expression. Regression lines represent the linear associations between individual biomarkers and exercise capacity, adjusted for covariates

exposure to DNA damaging agents may trigger early accumulation of senescent cells that is not completely reversible.

Senescent cells also accumulate dysfunctional mitochondria, capable of influencing SASP production (57). Our recent work found association between decreased mitochondrial copy number (mtDNAcn) and increased odds for sarcopenia (55). Impaired skeletal muscle oxidative phosphorylation is implicated in exercise intolerance among induvial with mitochondrial myopathies (58). It is possible that mitochondrial dysfunction is the pathobiological mediator between elevated $p16^{INK4a}$ and hs-CRP levels in survivors with low exercise capacity.

Our data demonstrating elevated $p16^{INK4a}$ expression and hs-CRP concentration in survivors with impaired exercise capacity indicates a potential intervention target, given evidence that $p16^{INK4a}$ levels are modifiable, potentially with exercise (59, 60). In an animal model, Schafer et al (59) demonstrated an improvement in exercise capacity and a concomitant reduction in diet-induced $p16^{INK4a}$ mRNA expression in rodents who exercised. Resistance training, although primarily associated with muscle mass and strength gains, also has the potential to clear accumulated senescent cells. Yang et al. noted significant gains in muscle mass and an associated rapid clearance of senescent cells from skeletal muscle tissue in young men following a bout of resistance training (60). Given that childhood cancer survivors respond to both aerobic and resistance training, with improved exercise tolerance (61–63) and strength and mass gains (64), following

exercise, it is possible that either aerobic training and/or resistance training may contribute senescent cells clearance. Additional research to determine if exercise, including type, frequency, intensity, and duration of activity, can clear senescent cells and either prevent or delay the cellular ageing in survivors. Further, cellular senescence is targetable through nutraceuticals (65). Agents such as Dasatinib and flavonoids (Quercetin; Fisetin, available as nutritional supplements) interfere with the senescent pathway, with evidence of safety, tolerability, and ability to alleviate physical dysfunction in adults with chronic disease (66). Currently, we have an open-label intervention trial (NCT04733534) which aims to establish preliminary evidence of efficacy, safety, and tolerability of two senolytic regimens to reduce markers of cellular senescence and improve frailty in adult survivors of childhood cancer. Survivors with reduced exercise capacity may also benefit from senolytic agents either alone or in combination with lifestyle modifications.

In general population, overweight and obese individual have higher proinflammatory plasma profiles, specifically higher hs-CRP, than non-overweight or obese individuals (67). In our study, female survivors had significantly higher levels of body fat, concomitant with higher $p16^{INK4A}$ expression, hs-CRP concentration, and lower peak VO_2 (ml/kg/min) compared to males. Further, we noted a significant interaction between $p16^{INK4a}$ expression and body fat among female survivors, suggesting that the effect of cellular senescence on exercise capacity may be masked in females who have excess body fat. In our study, at body fat % values less than 35%, $p16^{INK4a}$ expression had a strong inverse association with exercise capacity. This association was not seen in females who had body fat % greater than 35% (68–70). Because adipose tissue is a harbor for senescent cells, is associated with reduced physical function, and is redistributed with ageing (71–73), it is possible that an evaluation of senescent cell expression in adipose tissue may have yielded different results. It is also possible that the burden of excess body fat is the primary driver of exercise capacity in females who are overweight or obese. Regardless, the influence of an interaction between body fat and biomarkers of ageing on exercise capacity are compelling and deserve further investigation.

The results of this analysis should be interpreted in the context of study limitations. Our population was small, and childhood cancer diagnoses were not evenly represented in the sample; almost half of the survivors had a history of childhood leukemia, followed by less than 20% with a history of lymphoma. While our study is limited by the use of a single biomarker of cellular senescence, our findings of detectable $p16^{INK4a}$ mRNA expression levels higher in young adult childhood cancer survivors than in persons of similar age in the general population (39), combined with the presence of low grade inflammation in our population, signifies that cellular senescence is a potential pathobiological mechanism for premature physiologic ageing in survivors of childhood cancer, contributing to exercise capacities comparable to adults decades older. Further, we did not compare $p16^{INK4a}$ and hs-CRP levels to individuals without a history of cancer. However, our mean hs-CRP value was higher than seen in a general population (41), suggesting a potential ongoing inflammatory milieu in this population. Liu et al (39) evaluated $p16^{INK4a}$ expression in peripheral blood T-cells in healthy adults, much older than our

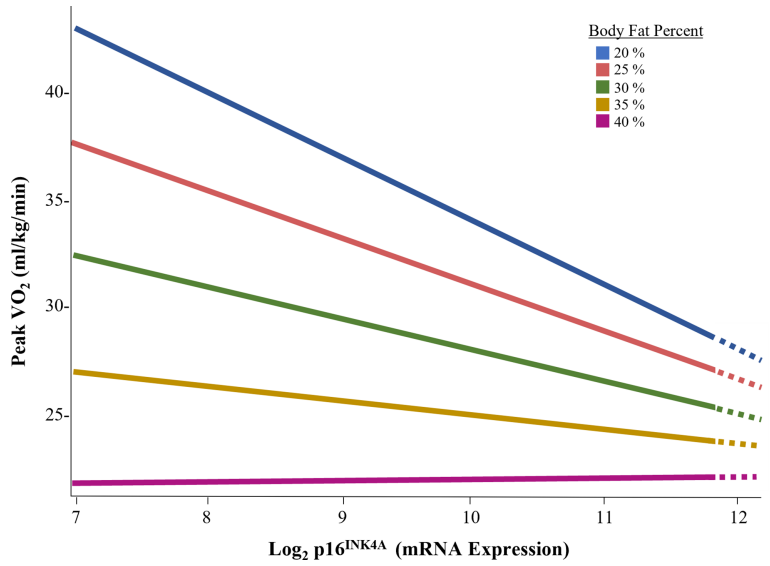


FIGURE 4
Association of $p16^{INK4A}$ expression and exercise capacity by body fat percent in female survivors.

participants (age [years], median [range], 47 [18-76] vs. 36.3 [20.1-55.7]), who were also overweight (body mass index (BMI) [kg/m^2], median [range], 26.5 [9.4-55.1] vs. 29.6 [16.5-57.4] kg/m^2). However, our participants had higher expression of p16^{INK4a} than healthy persons in the paper by Liu et al (39) (Figure 2B) (mean $\log_2$ p16^{INK4a} mRNA expression 9.4 vs. 5.5). We suscept that individuals without a history of cancer would have lower levels of both biomarkers given their lack exposure to radiation and chemotherapeutic agents capable of inducing DNA damage. Additionally, our analysis was cross-sectional, and thus we are limited in the ability to determine the direction of causality between p16^{INK4a} and exercise intolerance, and other participant characteristics, such as body composition. However, expression of p16^{INK4a} was not independently associated with BMI (p=0.08) or body fat (p=0.07), which is consistent with findings by Liu et al. (39) Further, we previously showed that over 50% of childhood cancer survivors are exercise intolerant, at BMIs comparable to healthy community controls (3), thus challenging that high adiposity is the true etiology of senescence in our survivors. More likely, adiposity and the accumulation of senescent cells in adipose tissue is additive to the pathobiology of exercise intolerance in this population. However, adiposity is a potential source of senescence etiology and further investigations into its interplay with biologic ageing, cellular senescence, and inflammation is warranted in the survivor population.

Impact statement

Cellular senescence is implicated with advancing age and the onset of chronic condition and disease. Over 50% of young childhood cancer survivors are exercise intolerant, with maximal aerobic capacities comparable to individuals decades older, suggesting early physiologic ageing. In our study, biomarkers of cellular senescence and inflammation were associated with lower exercise capacity, which was further mediated by body fat in female survivors. To our knowledge, this is the first study to demonstrate an association between p16^{INK4a} expression, low-grade inflammation, and exercise capacity in childhood cancer survivors. Our study contributes to growing body of evidence of accelerated ageing among childhood cancer survivors. Further, it highlights that interventions designed to improve exercise capacity and/or body composition have potential to remediate the accelerating ageing phenotype and early onset of chronic conditions seen among adult survivors of childhood cancer.

Data availability statement

The datasets analyzed for this study can be found in the St. Jude Cloud (https://www.stjude.cloud) (74).

Ethics statement

The studies involving human participants were reviewed and approved by St. Jude Children's Research Hospital Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

CGG, MK, DKS, and KKN contributed to the conception and design of the research, analyzed, and interpreted the data. CGG, MDW, ML, and ZW performed the data acquisition and processing. CGG drafted the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by grants provided by the National Cancer Institute (CA195547, MMH and KKN; CA174851 KKN), the Cancer Center Support Grant (CA21765, CRR), and the American Lebanese Syrian Associated Charities (ALSAC).

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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.1014661/full#supplementary-material

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* (2019) 69:7–34. doi: 10.3322/caac.21551

2. Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, et al. *SEER cancer statistics review, 1975-2015, national cancer institute*. (Bethesda, MD: National Cancer Institute, DCCPS, Surveillance Research Program) (2018). Available at: https://seer.cancer.gov/csr/1975_2015/. based on November 2017 SEER data submission, posted to the SEER web site.

3. Ness KK, Plana JC, Joshi VM, Luepker RV, Durand JB, Green DM, et al. Exercise intolerance, mortality, and organ system impairment in adult survivors of childhood cancer. *J Clin Oncol* (2020) 38:29–42. doi: 10.1200/JCO.19.01661

4. Shvartz E, Reibold RC. Aerobic fitness norms for males and females aged 6 to 75 years: a review. *Aviat Space Environ Med* (1990) 61:3–11.

5. Campisi J. Aging, cellular senescence, and cancer. *Annu Rev Physiol* (2013) 75:685–705. doi: 10.1146/annurev-physiol-030212-183653

6. Acosta JC, Banito A, Wuestefeld T, Georgilis A, Janich P, Morton JP, et al. A complex secretory program orchestrated by the inflammasome controls paracrine senescence. *Nat Cell Biol* (2013) 15:978–90. doi: 10.1038/ncb2784

7. De Cecco M, Jeyapalan J, Zhao X, Tamamori-Adachi M, Sedivy JM. Nuclear protein accumulation in cellular senescence and organismal aging revealed with a novel single-cell resolution fluorescence microscopy assay. *Aging (Albany NY)* (2011) 3:955–67. doi: 10.18632/aging.100372

8. Janzen V, Forkert R, Fleming HE, Saito Y, Waring MT, Dombkowski DM, et al. Stem-cell ageing modified by the cyclin-dependent kinase inhibitor p16INK4a. *Nature* (2006) 443:421–6. doi: 10.1038/nature05159

9. Krishnamurthy J, Ramsey MR, Ligon KL, Torrice C, Koh A, Bonner-Weir S, et al. p16INK4a induces an age-dependent decline in islet regenerative potential. *Nature* (2006) 443:453–7. doi: 10.1038/nature05092

10. Campisi J. Senescent cells, tumor suppression, and organismal aging: good citizens, bad neighbors. *Cell* (2005) 120:513–22. doi: 10.1016/j.cell.2005.02.003

11. Justice JN, Gregory H, Tchkonia T, LeBrasseur NK, Kirkland JL, Kritchevsky SB, et al. Cellular senescence biomarker p16INK4a+ cell burden in thigh adipose is associated with poor physical function in older women. *J Gerontol A Biol Sci Med Sci* (2018) 73:939–45. doi: 10.1093/gerona/glx134

12. Marcoux S, Le ON, Langlois-Pelletier C, Laverdiere C, Hatami A, Robaey P, et al. Expression of the senescence marker p16INK4a in skin biopsies of acute lymphoblastic leukemia survivors: A pilot study. *Radiat Oncol* (2013) 8:252. doi: 10.1186/1748-717X-8-252

13. LaPak KM, Burd CE. The molecular balancing act of p16(INK4a) in cancer and aging. *Mol Cancer Res* (2014) 12:167–83. doi: 10.1158/1541-7786.Mcr-13-0350

14. Vandenberk B, Brouwers B, Hatse S, Wildiers H. p16INK4a: A central player in cellular senescence and a promising aging biomarker in elderly cancer patients. *J Geriatr Oncol* (2011) 2:259–69. doi: 10.1016/j.jgo.2011.08.004

15. Ben-Porath I, Weinberg RA. The signals and pathways activating cellular senescence. *Int J Biochem Cell Biol* (2005) 37:961–76. doi: 10.1016/j.biocel.2004.10.013

16. Serrano M, Hannon GJ, Beach D. A new regulatory motif in cell-cycle control causing specific inhibition of cyclin D/CDK4. *Nature* (1993) 366:704–7. doi: 10.1038/366704a0

17. Kim WY, Sharpless NE. The regulation of INK4/ARF in cancer and aging. *Cell* (2006) 127:265–75. doi: 10.1016/j.cell.2006.10.003

18. Ness KK, Kirkland JL, Gramatges MM, Wang Z, Kundu M, McCastlain K, et al. Premature physiologic aging as a paradigm for understanding increased risk of adverse health across the lifespan of survivors of childhood cancer. *J Clin Oncol* (2018) 36:2206–15. doi: 10.1200/JCO.2017.76.7467

19. Ness KK, Krull KR, Jones KE, Mulrooney DA, Armstrong GT, Green DM, et al. Physiologic frailty as a sign of accelerated aging among adult survivors of childhood cancer: A report from the st. Jude lifetime cohort study. *J Clin Oncol* (2013) 31:4496–503. doi: 10.1200/JCO.2013.52.2268

20. Cupit-Link MC, Kirkland JL, Ness KK, Armstrong GT, Tchkonia T, LeBrasseur NK, et al. Biology of premature ageing in survivors of cancer. *ESMO Open* (2017) 2:e000250. doi: 10.1136/esmoopen-2017-000250

21. Smith U, Li Q, Ryden M, Spalding KL. Cellular senescence and its role in white adipose tissue. *Int J Obes (Lond)* (2021) 45:934–43. doi: 10.1038/s41366-021-00757-x

22. Coppé JP, Patil CK, Rodier F, Sun Y, Muñoz DP, Goldstein J, et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biol* (2008) 6:2853–68. doi: 10.1371/journal.pbio.0060301

23. Muñoz-Espín D, Serrano M. Cellular senescence: from physiology to pathology. *Nat Rev Mol Cell Biol* (2014) 15:482–96. doi: 10.1038/nrm3823

24. Browne EK, Zhou Y, Chemaitilly W, Panetta JC, Ness KK, Kaste SC, et al. Changes in body mass index, height, and weight in children during and after therapy for acute lymphoblastic leukemia. *Cancer* (2018) 124:4248–59. doi: 10.1002/cncr.31736

25. Warris LT, van den Akker ELT, Bierings MB, van den Bos C, Aarsen FK, Zwaan MC, et al. Eating behavior during dexamethasone treatment in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer* (2017) 64:e26679. doi: 10.1002/pbc.26679

26. Zhang FF, Liu S, Chung M, Kelly MJ. Growth patterns during and after treatment in patients with pediatric ALL: A meta-analysis. *Pediatr Blood Cancer* (2015) 62:1452–60. doi: 10.1002/pbc.25519

27. Zhang FF, Kelly MJ, Saltzman E, Must A, Roberts SB, Parsons SK. Obesity in pediatric ALL survivors: a meta-analysis. *Pediatrics* (2014) 133:e704–15. doi: 10.1542/peds.2013-3332

28. Murphy AJ, White M, Elliott SA, Lockwood L, Hallahan A, Davies PS. Body composition of children with cancer during treatment and in survivorship. *Am J Clin Nutr* (2015) 102:891–6. doi: 10.3945/ajcn.114.099697

29. Ness KK, Baker KS, Dengel DR, Youngren N, Sibley S, Mertens AC, et al. Body composition, muscle strength deficits and mobility limitations in adult survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer* (2007) 49:975–81. doi: 10.1002/pbc.21091

30. Ness KK, DeLany JP, Kaste SC, Mulrooney DA, Pui CH, Chemaitilly W, et al. Energy balance and fitness in adult survivors of childhood acute lymphoblastic leukemia. *Blood* (2015) 125:3411–9. doi: 10.1182/blood-2015-01-621680

31. Landy DC, Lipsitz SR, Kurtz JM, Hinkle AS, Constine LS, Adams MJ, et al. Dietary quality, caloric intake, and adiposity of childhood cancer survivors and their siblings: an analysis from the cardiac risk factors in childhood cancer survivors study. *Nutr Cancer* (2013) 65:547–55. doi: 10.1080/01635581.2013.770042

32. Zhang FF, Ojha RP, Krull KR, Gibson TM, Lu L, Lanctot J, et al. Adult survivors of childhood cancer have poor adherence to dietary guidelines. *J Nutr* (2016) 146:2497–505. doi: 10.3945/jn.116.238261

33. Pini M, Czibik G, Sawaki D, Mezdari Z, Braud L, Delmont T, et al. Adipose tissue senescence is mediated by increased ATP content after a short-term high-fat diet exposure. *Aging Cell* (2021) 20:e13421. doi: 10.1111/acel.13421

34. Tchkonia T, Morbeck DE, Von Zglinicki T, Van Deursen J, Lustgarten J, Scrable H, et al. Fat tissue, aging, and cellular senescence. *Aging Cell* (2010) 9:667–84. doi: 10.1111/j.1474-9726.2010.00608.x

35. Baker DJ, Wijshake T, Tchkonia T, LeBrasseur NK, Childs BG, van de Sluis B, et al. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. *Nature* (2011) 479:232–6. doi: 10.1038/nature10600

36. Howell CR, Bjornard KL, Ness KK, Alberts N, Armstrong GT, Bhakta N, et al. Cohort profile: The st. Jude lifetime cohort study (SJLIFE) for paediatric cancer survivors. *Int J Epidemiol* (2021) 50:39–49. doi: 10.1093/ije/dyaa203

37. Hudson MM, Ness KK, Nolan VG, Armstrong GT, Green DM, Morris EB, et al. Prospective medical assessment of adults surviving childhood cancer: study design, cohort characteristics, and feasibility of the st. Jude lifetime cohort study. *Pediatr Blood Cancer* (2011) 56:825–36. doi: 10.1002/pbc.22875

38. Ojha RP, Oancea SC, Ness KK, Lanctot JQ, Srivastava DK, Robison LL, et al. Assessment of potential bias from non-participation in a dynamic clinical cohort of long-term childhood cancer survivors: results from the st. Jude lifetime cohort study. *Pediatr Blood Cancer* (2013) 60:856–64. doi: 10.1002/pbc.24348

39. Liu Y, Sanoff HK, Cho H, Burd CE, Torrice C, Ibrahim JG, et al. Expression of p16(INK4a) in peripheral blood T-cells is a biomarker of human aging. *Aging Cell* (2009) 8:439–48. doi: 10.1111/j.1474-9726.2009.00489.x

40. Shields JM, Thomas NE, Cregger M, Berger AJ, Leslie M, Torrice C, et al. Lack of extracellular signal-regulated kinase mitogen-activated protein kinase signaling shows a new type of melanoma. *Cancer Res* (2007) 67:1502–12. doi: 10.1158/0008-5472.Can-06-3311

41. Pagana KD, Pagana TJ, Pagana TN. *Mosby's diagnostic and laboratory test reference. 14th ed.* St. Loius, MO: Elsevier Health Sciences (2019).

42. Pescatello LSAmerican College of Sports Medicine, , Riebe D, Thompson PD. *ACSM's guidelines for exercise testing and prescription. 9th ed.* Philadelphia, PA: Wolters Kluwer (2013).

43. Wang CY, Haskell WL, Farrell SW, Lamonte MJ, Blair SN, Curtin LR, et al. Cardiorespiratory fitness levels among US adults 20-49 years of age: findings from the 1999-2004 national health and nutrition examination survey. *Am J Epidemiol* (2010) 171:426–35. doi: 10.1093/aje/kwp412

44. Borg GA. *Borg's perceived exertion and pain scales*. Champaign, IL: Human Kinetics (1998).

45. Thomas SR, Kalkwarf HJ, Buckley DD, Heubi JE. Effective dose of dual-energy X-ray absorptiometry scans in children as a function of age. *J Clin Densitom* (2005) 8:415–22. doi: 10.1385/jcd:8:4:415

46. Jensen MD, Kanaley JA, Roust LR, O'Brien PC, Braun JS, Dunn WL, et al. Assessment of body composition with use of dual-energy x-ray absorptiometry: Evaluation and comparison with other methods. *Mayo Clin Proc* (1993) 68:867–73. doi: 10.1016/s0025-6196(12)60695-8

47. Smitherman AB, Wood WA, Mitin N, Ayer Miller VL, Deal AM, Davis IJ, et al. Accelerated aging among childhood, adolescent, and young adult cancer survivors is evidenced by increased expression of p16(INK4a) and frailty. *Cancer* (2020) 126:4975–83. doi: 10.1002/cncr.33112

48. Ladenvall P, Persson CU, Mandalenakis Z, Wilhelmsen L, Grimby G, Svardsudd K, et al. Low aerobic capacity in middle-aged men associated with increased mortality rates during 45 years of follow-up. *Eur J Prev Cardiol* (2016) 23:1557–64. doi: 10.1177/2047487316655466

49. Lee DC, Sui X, Artero EG, Lee IM, Church TS, McAuley PA, et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the aerobics center longitudinal study. *Circulation* (2011) 124:2483–90. doi: 10.1161/CIRCULATIONAHA.111.038422

50. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: A meta-analysis. *JAMA* (2009) 301:2024–35. doi: 10.1001/jama.2009.681

51. Hayes SM, Forman DE, Verfaellie M. Cardiorespiratory fitness is associated with cognitive performance in older but not younger adults. *J Gerontol B Psychol Sci Soc Sci* (2016) 71:474–82. doi: 10.1093/geronb/gbu167

52. Hayek S, Gibson TM, Leisenring WM, Guida JL, Gramatges MM, Lupo PJ, et al. Prevalence and predictors of frailty in childhood cancer survivors and siblings: A report from the childhood cancer survivor study. *J Clin Oncol* (2020) 38:232–47. doi: 10.1200/JCO.19.01226

53. Song N, Li Z, Qin N, Howell CR, Wilson CL, Easton J, et al. Shortened leukocyte telomere length associates with an increased prevalence of chronic health conditions among survivors of childhood cancer: A report from the st. Jude lifetime cohort. *Clin Cancer Res* (2020) 26:2362–71. doi: 10.1158/1078-0432.CCR-19-2503

54. Song N, Hsu CW, Pan H, Zheng Y, Hou L, Sim JA, et al. Persistent variations of blood DNA methylation associated with treatment exposures and risk for cardiometabolic outcomes in long-term survivors of childhood cancer in the st. Jude lifetime cohort. *Genome Med* (2021) 13:53. doi: 10.1186/s13073-021-00875-1

55. McCastlain K, Howell CR, Welsh CE, Wang Z, Wilson CL, Mulder HL, et al. The association of mitochondrial copy number with sarcopenia in adult survivors of childhood cancer. *J Natl Cancer Inst* (2021) 113:1570–80. doi: 10.1093/jnci/djab084

56. van Deursen JM. The role of senescent cells in ageing. *Nature* (2014) 509:439–46. doi: 10.1038/nature13193

57. Zlotorynski E. Defective mitochondria ignite the SASP. *Nat Rev Mol Cell Biol* (2020) 21:179. doi: 10.1038/s41580-020-0228-x

58. Taivassalo T, Jensen TD, Kennaway N, DiMauro S, Vissing J, Haller RG. The spectrum of exercise tolerance in mitochondrial myopathies: A study of 40 patients. *Brain* (2003) 126:413–23. doi: 10.1093/brain/awg028

59. Schafer MJ, White TA, Evans G, Tonne JM, Verzosa GC, Stout MB, et al. Exercise prevents diet-induced cellular senescence in adipose tissue. *Diabetes* (2016) 65:1606–15. doi: 10.2337/db15-0291

60. Yang C, Jiao Y, Wei B, Yang Z, Wu JF, Jensen J, et al. Aged cells in human skeletal muscle after resistance exercise. *Aging (Albany NY)* (2018) 10:1356–65. doi: 10.18632/aging.101472

61. Smith WA, Ness KK, Joshi V, Hudson MM, Robison LL, Green DM. Exercise training in childhood cancer survivors with subclinical cardiomyopathy who were treated with anthracyclines. *Pediatr Blood Cancer* (2013) 61(5):942–945. doi: 10.1002/pbc.24850

62. Jarvela LS, Kemppainen J, Niinikoski H, Hannukainen JC, Lahteenmaki PM, Kapanen J, et al. Effects of a home-based exercise program on metabolic risk factors and fitness in long-term survivors of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer* (2012) 59:155–60. doi: 10.1002/pbc.24049

63. Bourdon A, Grandy SA, Keats MR. Aerobic exercise and cardiopulmonary fitness in childhood cancer survivors treated with a cardiotoxic agent: a meta-analysis. *Support Care Cancer* (2018) 26:2113–23. doi: 10.1007/s00520-018-4208-z

64. Krull MR, Howell CR, Partin RE, Lanctot J, Phipps S, Klosky JL, et al. Protein supplementation and resistance training in childhood cancer survivors. *Med Sci Sports Exerc* (2020) 52:2069–77. doi: 10.1249/MSS.0000000000002345

65. Zhu Y, Tchkonia T, Pirtskhalava T, Gower AC, Ding H, Giorgadze N, et al. The achilles' heel of senescent cells: From transcriptome to senolytic drugs. *Aging Cell* (2015) 14:644–58. doi: 10.1111/acel.12344

66. Justice JN, Nambiar AM, Tchkonia T, LeBrasseur NK, Pascual R, Hashmi SK, et al. Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study. *EBioMedicine* (2019) 40:554–63. doi: 10.1016/j.ebiom.2018.12.052

67. Phillips CM, Tierney AC, Perez-Martinez P, Defoort C, Blaak EE, Gjelstad IM, et al. Obesity and body fat classification in the metabolic syndrome: impact on cardiometabolic risk metabotype. *Obes (Silver Spring)* (2013) 21:E154–61. doi: 10.1002/oby.20263

68. Okorodudu DO, Jumean MF, Montori VM, Romero-Corral A, Somers VK, Erwin PJ, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity: a systematic review and meta-analysis. *Int J Obes (Lond)* (2010) 34:791–9. doi: 10.1038/ijo.2010.5

69. Deurenberg P, Andreoli A, Borg P, Kukkonen-Harjula K, de Lorenzo A, van Marken Lichtenbelt WD, et al. The validity of predicted body fat percentage from body mass index and from impedance in samples of five European populations. *Eur J Clin Nutr* (2001) 55:973–9. doi: 10.1038/sj.ejcn.1601254

70. Bosy-Westphal A, Geisler C, Onur S, Korth O, Selberg O, Schrezenmeir J, et al. Value of body fat mass vs anthropometric obesity indices in the assessment of metabolic risk factors. *Int J Obes (Lond)* (2006) 30:475–83. doi: 10.1038/sj.ijo.0803144

71. Hagg S, Jylhava J. Sex differences in biological aging with a focus on human studies. *eLife* (2021) 10:e63425. doi: 10.7554/eLife.63425

72. Bazzocchi A, Diano D, Ponti F, Andreone A, Sassi C, Albisinni U, et al. Health and ageing: A cross-sectional study of body composition. *Clin Nutr* (2013) 32:569–78. doi: 10.1016/j.clnu.2012.10.004

73. Bazzocchi A, Ponti F, Diano D, Moio A, Albisinni U, Pasquali R, et al. Abdominal adiposity by ultrasonography: A "pocket" database for reference standard in Italian people. *Prim Care Diabetes* (2014) 8:358–64. doi: 10.1016/j.pcd.2014.02.003

74. McLeod C, Gout AM, Zhou X, Thrasher A, Rahbarinia D, Brady SW, et al. St. Jude cloud: A pediatric cancer genomic data-sharing ecosystem. *Cancer Discovery* (2021) 11:1082–99. doi: 10.1158/2159-8290.CD-20-1230

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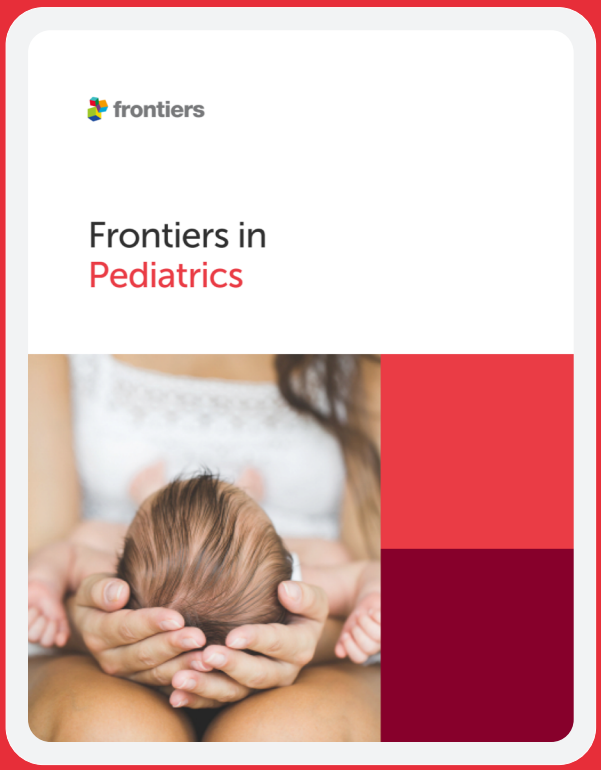

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