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Determinants of physical activity level in pediatric oncological patients treated with cardiotoxic therapy – a study protocol

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Abstract

Background Childhood cancer and its therapy, especially that involving potentially cardiotoxic cancer treatment, can structurally affect muscle strength and heart function, and therefore may result in lowered physical activity (PA). This study protocol aims to find the significant determinants of PA levels in pediatric oncological patients 1–5 years after heart-toxic chemotherapy and/or radiation of the heart region.

Methods The study group will include children 1–5 years after completing cancer therapy involving cardiotoxicity risk factors. The primary outcome of interest is the PA measured with an ActiGraph GT3X Accelerometer for 14 consecutive days and the assessment of WHO pediatric age-adjusted PA norms achievement. Assessed PA levels will be evaluated according to the possible determinants of PA: disease/treatment related risk factors, treatment complications, possible complications after the treatment, cardiac function with echocardiography including 2D and 3D strain imaging, physical function and muscle strength in ALPHA (Assessing Levels of Physical Activity) health-related fitness test battery and exercise capacity in cardiopulmonary exercise testing. The self-efficacy and motivation to PA, quality of life (QoL), lifestyle, socio-demographic, and anthropogenic factors as well as knowledge about the positive impact of PA will be evaluated with original and validated questionnaires. The PA determinants of the study group will be compared to the results of the control group of children in the same follow-up period (> 1 year < 5 years) after completing cancer therapy without cardiotoxic methods.

Discussion The results may contribute to the development of future recommendations on prophylactic and therapeutic approaches, as well as proper lifestyle recommendations for children in long-term follow-up after cardiotoxic cancer therapy. The determinants will be used to develop targeted exercise prescriptions and exercise programs.

Trial registration NCT06256068.

Keywords Exercise capacity, Physical activity, Cardiotoxicity, Childhood cancer, Pediatric oncology

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Background

Cancer in childhood may impact development and everyday functioning not only because of the disease, but also due to its treatment [1, 2]. Leukemias, the most common cancers in the pediatric population, cause cancer-related malaise, malnourishment, higher risk of infections, blood coagulation alterations, anemia, and reduced blood perfusion in skeletal muscles, which can result in insufficient oxygen supply during physical effort [3–5].

Treatment protocols for childhood cancers include cardiotoxic treatment methods. Treatment of the most common childhood malignancy—acute lymphoblastic leukemia (ALL)—includes the use of anthracyclines [6, 7]. Anthracycline therapy is the most recognizable cardiotoxic cancer treatment method. Other currently recognized cardiotoxic agents include, i.a., kinase inhibitors targeting breakpoint cluster region protein-abelson (BRC-ABL), hemopoietic stem cell transplantation, and radiotherapy (total body irradiation [TBI] and mediastinum radiotherapy) [8]. The cardiac dysfunction observed after the use of cardiotoxic cancer treatment involves the reduction of contractility and abnormality in cardiac cells [9, 10]. Cancer therapy including potentially toxic methods can structurally affect the muscles (including heart muscle) resulting in cardiorespiratory fitness (CRF) deterioration [11–14]. Therefore, disease- and treatment-related complications may lead to a reduction of exercise tolerance and consequently to physical inactivity in pediatric cancer survivors [13–15].

Physical activity (PA) is a major factor in children's growth and development [16]. Most of the previous studies on PA levels in pediatric oncology patients were based on small samples of children with different diagnoses (leukemia, lymphomas, and solid tumors), time since diagnosis, and on or off treatment [17–25]. Most of the data on the topic are based on questionaries/interviews [19–25]. Some of the mentioned PA level factors include cancer-related fatigue, psychological issues and concerns, body mass, and environment – including school and peers [17–25]. Other factors like motivation and self-efficacy, which turned out to be significantly associated with PA level in other populations, were not analyzed in previous studies in groups of pediatric oncological patients.

The studies based on self-reporting methods in terms of PA measurement were at risk of social desirability and social approval bias [26–28]. Studies in which the activity trackers were used included different and short-time accelerometer measurements [17, 29–31].

Treatment modalities: chemotherapy, radiotherapy, surgery, and their combinations have not been identified as factors influencing PA levels in children on and off cancer therapy [17, 19].

A risk factor with a possible effect on PA decline that has not been considered is cardiotoxic treatment. Treatment involving cardiotoxic methods may additionally affect PA levels through alteration of heart muscle contractility and the functioning of cardiac cells [8–10]. Subclinical heart failure after toxic agents may be one of the deteriorating factors of exercise capacity and therefore of PA levels.

This study will be the first aiming to find significant determinants of PA levels in pediatric oncological patients between 1 and 5 years after completing treatment involving heart-toxic chemotherapy and/or radiation of the heart region. Our hypotheses are as follows:

1) the level of PA in pediatric oncological patients is related to the cardiotoxic treatment risk factors, cardiac function with echocardiography including 2D and 3D strain imaging, and others such as physical function, exercise capacity, self-efficacy and motivation towards PA, QoL, lifestyle, socio-demographic, anthropogenic factors, as well as the knowledge about positive impact of PA,
2) children after cancer treatment involving cardiotoxic risk factors present overall daily PA limitations in comparison to children without these risk factors,

Methods/design

The aim of this study protocol is to find significant determinants of PA level in pediatric oncological patients between 1 and 5 years after completing treatment involving heart-toxic chemotherapy and/or radiation of the heart region.

The study will involve one-time evaluation of the participant with echocardiography, the cardio-pulmonary exercise test (CPET), extended ALPHA health-related fitness test battery, questionaries, and a 2-week PA assessment with an accelerometer. The data obtained and the data from the past medical records will be analyzed to assess determinants of the PA level among children treated for cancer with cardiotoxic methods. This study is funded by statutory funds of the Department of Pediatric Cardiology and General Pediatrics, Medical University of Warsaw, Poland.

Study design

For this cross-sectional study the study group will consist of 150 children > 1 year and < 5 years after completion of a cancer treatment involving cardiotoxicity risk factors, and who are currently undergoing follow-up observation at the outpatient clinic of the Pediatric Oncology, Hematology, and Transplantology Department of the Medical University of Warsaw, Poland. The cardiotoxic risk factors will be defined according to the European Society of

Cardiology guidelines as follows: use of anthracyclines, kinase inhibitors targeting BRC-ABL, hemopoietic stem cell transplantation, and radiotherapy (TBI or mediastinum irradiation) [8].

The control group will involve 150 children who are > 1 year and < 5 years after completion of a cancer treatment without cardiotoxicity risk factors, and who are currently undergoing follow-up observation at the outpatient clinic of the Pediatric Oncology, Hematology, and Transplantology Department, matched by age and gender.

Trial registration

NCT06256068 (last update 02/04/2025).

To achieve study recruitment goals the researchers take into consideration the cooperation with other in-hospital pediatric oncology outpatient clinics across the country.

Participants

The participants will be recruited to the study according to the inclusion and exclusion criteria (Table 1).

Consent

Eligible patients and their parents/caregivers will receive detailed information about the study, including its characteristics, through a patient information sheet and consent form, as well as through an oral explanation by the pediatric oncologist (member of the study team). The study participants will be approached after their routine follow-up visits at the outpatient clinic or via a telephone call from their pediatric oncology provider. According to the local and European Union legal regulations, patients over the age of 16 years and their parents/caregivers, who agree to participate in the study, will be required to sign an informed consent form. An oral consent will be required from the patients of 13 years old and above [32]. All the children and their parents/caregivers will be informed about the possibility of withdrawal from the study at any point.

Data collection

The assessment of the participants will be conducted at the enrollment and during a 14-day accelerometer observation. The assessment at the enrollment is going to

Table 1 Inclusion and exclusion criteria of the study

	Study group
Inclusion criteria	a. age 8–18 years, b. diagnosis of, and completed treatment for, cancer > 1 year and < 5 years ago, c. remission of the cancer, d. treatment involving use of anthracyclines, kinase inhibitors targeting BRC-ABL, hemopoietic stem cell transplantation, and radiotherapy (TBI or mediastinum irradiation), e. at least 6 weeks since the last signs or symptoms of an infection, f. written consent signed by the parents/guardians and by patients aged ≥ 16 years
	Control group
	a. the same as for the experimental group and, b. cancer treatment without use of anthracyclines, kinase inhibitors targeting BRC-ABL, hemopoietic stem cell transplantation, and radiotherapy (TBI or mediastinum irradiation)
	Both groups
Exclusion criteria	a. history of another cancer and its treatment with or without the use of anthracyclines, kinase inhibitors targeting BRC-ABL, hemopoietic stem cell transplantation, and radiotherapy (TBI or mediastinum irradiation), b. significant physical disability or a musculoskeletal disorder at the time of the enrollment (congenital or as a consequence of treatment, especially neurological complications and lower extremities conditions and amputation), c. excessive malaise (at the time of the enrollment), d. intellectual disability (on the level that disenables the participant from understanding and cooperation during the CPET procedure or ALPHA test), e. active acute inflammatory disease including the following: autoimmunological, neurological, pulmonological, endocrinological, cardiovascular, and gastrointestinal, f. platelet count < 20 G/L, g. hemoglobin concentration < 9 g/dL, h. severe residual changes (protein loss syndrome, peritoneal, pericardial or pleural effusion, arrhythmia, metabolic disorders), i. previously diagnosed congenital heart defects or other heart diseases (including cardiomyopathy, heart failure, arrythmia), j. relapse of the cancer at the time of enrollment to the study, k. severe malnutrition < 3 standard deviation (SD) body mass index (BMI) weight for age, l. chronic concomitant diseases that could affect the CPET outcome, especially endocrinological, neurological, gastrointestinal, and pulmonological[a], m. lack of patient cooperation

[a] endocrinological – decompensated thyroid disease, decompensated diabetes with hypoglycemia, neurological – conditions disabling the CPET performance due to musculoskeletal system alteration, uncontrolled epilepsy, myopathy, gastrointestinal – marasmus, decompensated hepatic insufficiency, pulmonological – asthma, interstitial lung disease, post-infection bronchiolitis obliterans (PIBO) – additionally, pulmonary embolism, lower extremity phlebitis, kidney failure

involve exercise capacity measurement, physical function and muscle strength, cardiological assessment, anthropogenic assessment, and the questionnaire assessment. The data about medical history will be collected retrospectively based on medical records. The study team will consist of 2 pediatric cardiologists (CPET and echocardiography), one physiotherapist (CPET, PA measurement, physical function tests), one pediatric oncologist, and 2 physician assistants/nurses. To optimize the enrollment and to avoid cumulation of the exams requiring physical effort, we have created a schedule of the evaluation of individual participants (Fig. 1), which will be explained to the participants and their parents/caregivers before recruitment to the study. Because the participants are children, we aim to assess each patient in a total of no longer than 90 min.

All the participants will be instructed to abstain from strenuous exercise in the 48 h preceding the testing. Also, on the day of the enrollment the participants will be encouraged to wear comfortable sports clothes and shoes. All the participants will be provided with a notable and constant level of encouragement to guarantee their maximum performance.

Objectives

Primary endpoints

The primary outcome of interest is the PA level measured by the accelerometer and the assessment of the World Health Organization (WHO) pediatric, age-adjusted PA achievement norms.

Secondary endpoints

- percentage of participants disqualified from CPET examination – secondary outcome is the assessment of the proportion of eligible pediatric oncology patients for CPET examination as well as the reasons and characteristics of the patients that were excluded from CPET examination,
- exercise capacity measured in CPET – maximal/peak oxygen consumption (VO2 max/peak) below 47 mL/kg/min for boys and 42 mL/kg/min for girls will be defined as the EC alterations – secondary outcome is the maximal/peak oxygen consumption (VO2 max/peak) measurement and defining the EC among the participants,
- assessment of the fitness in the extended ALPHA (Assessing Levels of Physical Activity) health-related fitness test battery – defining the fitness level as low, moderate, or high [33, 34] – secondary outcome is the assessment of the physical fitness among the study group in the extended ALPHA test and defining its level,
- in cardiological assessment: global longitudinal strain (GLS), global radial strain (GRS), and global circumferential strain (GCS) below average for age, left ventricle diastolic diameter (LVDd) exceeding the normal limit, and ejection fraction (EF) 55% or less will be defined as the lowered systolic function, as well as in the comparison to the control groups – secondary outcome is the contractile function assessment of the

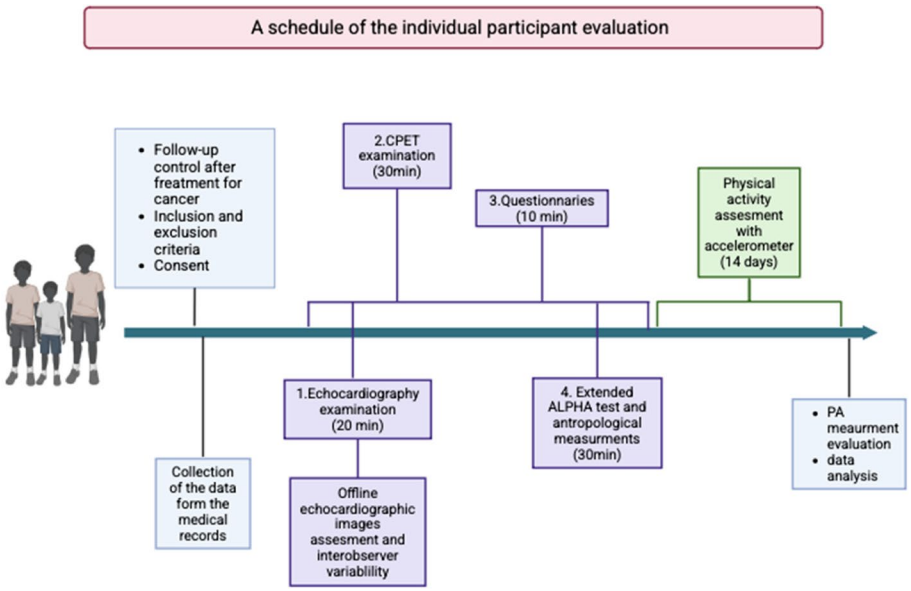

Fig. 1 Figure showing the study schedule of the evaluation of an individual participant (created in BioRender.com)

heart among the study group and in comparison to the control group.

Project duration and expected outcomes

The estimated period of enrollment will be 2 years. Estimated study completion will be at the end of 2027.

The results of the proposed project will contribute to the development of the diagnostic standards and improvement of the future management of cardiac adverse effects of the oncological treatment in pediatric patients. Management of the complications will result in possible minimization of the adverse effects in the population of childhood cancer survivors. Through this study we hope to understand the main reason for the level of physical capacity and activity in this population, which may have a crucial impact on further development of follow-up recommendations to improve their physical fitness.

Exercise capacity assessment

The exercise capacity will be measured by symptom-limited, upright-sitting CPET. The CPET will be only conducted on eligible participants. The percentage of participants from both the study group and the control group who prove to be ineligible for the CPET examination will be counted.

The CPET is going to will be performed on a bicycle ergometer. The procedure will be explained to the participant and the parent/caregiver. The participants will be informed that they may end the examination at any time, but they will be encouraged to continue the CPET to achieve the maximal level of physical effort. The CPET will be performed according to the Ramp protocol (10, 15, or 20 W/min Ramp) [35].

During the CPET baseline parameters including heart rate, blood pressure and ECG changes during rest and during effort will be recorded.

After a 3-min rest period, unloaded paddling will be set at a rate of 60 rotations per minute (rpm) for 2 min. The effort will be progressively increased by 10–15 watts/minute until the patient no longer maintains a cycling frequency of at least 40 rpm. Cardiopulmonary parameters, such as heart rate, oxygen uptake (VO_2), and carbon dioxide production (VCO_2), will be continuously monitored. The respiratory exchange ratio (RER) (VCO_2/VO_2) will be simultaneously calculated and used to assess maximal effort. The trial will be stopped when the patient is unable to maintain the pedal cycle rhythm. CPETs will be considered valid if the VO_2 reaches a plateau (for >1 min) despite an increasing workload and/or a complementary RER ≥ 1.05 combined with peak heart rate above 85% of predicted. Peak oxygen uptake (VO_{2peak}), directly reflective of $VO_{2\,max}$ (oxygen uptake during maximal exercise), will be the highest value of VO_2 attained upon CPET, defined as the limit of exercise capacity, and will be indexed to body weight and time and expressed in milliliters per kilo per minute [5, 35].

Physical function and anthropometric measurements

The physical function of the participants will be assessed by the extended ALPHA health-related fitness test battery. The extended ALPHA test consists of (1) the 20 m shuttle run test to assess cardiorespiratory fitness; (2) the handgrip strength; (3) the standing broad jump to assess musculoskeletal fitness; (4) body mass index; (5) skinfold thickness; and (6) waist circumference to assess body composition. The ALPHA test will be performed according to the detailed manual [33, 34].

The preferred order of participant assessment will be as follows:

1. pubertal status assessment,
2. weight and height, BMI measurement,
3. waist circumference measurement,
4. skinfold thickness (triceps and subscapular) measurement,
5. handgrip strength, standing long jump, and 4× 10 m shuttle run test,
6. 20 m shuttle run test.

Assessment by the extended ALPHA test will be performed by a study team of more than 2 testers to enable full evaluation in the planned time frame of 30 min.

Handgrip strength, an indirect indicator of global muscle strength, will be measured with a hand dynamometer. The measurement of grip strength will be performed on the dominant hand in triplicate, and the highest value will be recorded. The posture for measuring the grip strength will involve standing with legs straight and weight bearing balanced on both feet; the feet will be positioned shoulder-width apart, shoulders will be adducted and neutrally rotated, elbows will be flexed to 90°, forearms will be in a neutral position, and the wrists will be between 0° and 30° of dorsiflexion and between 0° and 15° of ulnar deviation [36]. The grip span of the dynamometer will be adjusted to the hand size of the child to obtain the maximal handgrip strength according to sex- and age-specific equations. The main advantages of the extended ALPHA test are the normative values for each of the suggested components of the test. which will enable a correct interpretation of the fitness status and the identification of children and adolescents at risk for fitness impairment [33].

The participants' weight, height, BMI, and waist-to-hip ratio will be measured, compared to the WHO norms for girls and boys, and represented as centiles for age.

Although the extended ALPHA test is a validated and widely used testing method in children, especially those frequenting PE classes, the group of children after cancer treatment is at risk of all of the possible complications during the testing. Therefore, the study team will prioritize the participants' instruction, and the testing will be performed under physician observation.

Cardiological assessment

The cardiological assessment will include baseline vital parameters: resting heart rate and blood pressure, and echocardiography. The echocardiography will be performed according to the international recommendations on an EPIQ CVx 5.0 ultrasound machine (Philips Medical System, USA), and it will be obtained from at least 3 cardiac cycles. All recordings will be reviewed by 2 experienced echocardiographers, providing interobserver reliability. The echocardiographic assessment will involve the following: left ventricle (LV) end-diastolic dimension (LVDd, mm) and end-systolic dimension (LVSd, mm), interventricular septal diastolic diameter (IVSDd, mm), interventricular septal systolic diameter (IVSSd, mm), left ventricular posterior wall diastolic diameter (LVPWDd, mm), and left ventricular posterior wall systolic diameter (LVPWSd, mm)—measured at the level of the top of the papillary muscles in M-mode imaging. These parameters will be indexed to the body surface area and expressed as the z-score (normal values from −2 to +2) [37, 38].

Left ventricular ejection fraction (LVEF), representing LV systolic function, will be determined using the Simpson method from 4-chamber and 2-chamber apical view imaging. The normal systolic function will be defined as a LVDd within the normal limit and EF 55% or more.

Mitral inflow velocities will be obtained from pulsed-wave Doppler in the apical 4-chamber view. Early diastolic mitral inflow velocity (E, cm/s), atrial diastolic mitral inflow velocity (A, cm/s), and E deceleration time (Edt, ms) of the E wave will be measured as diastolic echocardiographic variables. Isovolumic relaxation time (IVRT, ms), early diastolic (E', cm/s), and late diastolic (A', cm/s) velocities will be measured at the septal mitral annulus using the tissue Doppler imaging method (TDI). The ratio between E and E' (E/E') will be calculated as an indicator of LV filling pressure.

Evaluation of LV regional wall abnormalities and subclinical LV dysfunction will be performed by GLS measurement through speckle tracking echocardiography (STE). The GLS of the left ventricle will be assessed in 2D by QLAB 2D stain software (Philips Medical System, USA) and 3D strain imaging by 4D LV-Analysis software (Philips Medical System, USA). Additionally, global radial strain (GRS) and global circumferential strain (GCS) in 3D strain assessment will be used. Three apical views 2D (4-chamber, 2-chamber, and 3-chamber) will be used for 2D assessment, and 4-chamber 3D acquisition will be used for 3D assessment. The obtained echocardiographic records will be precisely evaluated offline on the computer software after the examination. The borders of the studied LV myocardial segments will be adjusted manually. An adjustment for body surface area will be performed and represented by the z-score [39].

Questionnaire assessment

Study participants and their parents/caregivers will be given a questionnaire to fill in. The questionnaire for children and their parents/caregivers will include issues such as self-efficacy, lifestyle, socio-demographic, and anthropogenic factors and their knowledge about the positive impact of PA that might affect the PA level in these children. This questionnaire was developed by the authors specifically for this study. Next, the children will be given Pediatric Quality of Life Inventory (PedsQL) [40] questionaries to assess their QoL and Physical Activity and Leisure Motivation Scale (PALMS) [41] questionaries to assess their motivation to undertake PA.

PA level assessment

An ActiGraph GT3X accelerometer will be used to monitor the time spent in PA (LPA), moderate-to-vigorous PA (MVPA), sedentary behavior (min/day), and sleep/wake time (hours/day). The ActiLife software program (ActiGraph, LLC, Fort Walton Beach, USA) will be used to perform all analyses. The patients will wear the monitors for 14 consecutive days, including 2 weekend days, for at least 10 h per day of "usage time", including nighttime sleep. The accelerometers will be fixed at the waist and positioned on another axillary line at the iliac crest level of the right or left hip (equipped with a flexible and adjustable elastic belt). Patients will be instructed not to change their daily routine, and the accelerometer will be removed only for water activities. Additionally, patients will be instructed to keep a diary of the equipment use, in which they should write down the time they woke up and the time they went to sleep at night every day, in addition to the times when the monitor was removed and then put back on the body. The accelerometer will be initialized to collect data at a sampling rate of 30 Hz with normal filter in 1 s epochs, and then the data will be reintegrated into 15 s epochs. Sedentary behavior periods will be defined by < 100 counts per minute. Values between 100 and 1999 counts per minute will be recorded as light PA. The time spent on moderate PA (MPA) and vigorous PA (VPA) will

be calculated based on cutoffs of 2000 and 4000 counts per minute, respectively [42].

Treatment modalities

Treatment protocols, anthracycline type, dosage (including maximal dose per m^2 of body surface) and total time of treatment, radiation type and dosage, kinase inhibitors targeting BRC-ABL use, hemopoietic stem cell transplantation procedure, and subsequent treatment complications, as well as follow-up information, will be collected from medical records.

Age-validation of the obtained data

Facing the inevitable growth, development, and puberty of the children, the study group will be compared within 4 groups: (I) 6 < age < 8 years; (II) 8 < age < 10 years; (III) 10 < age < 12 years; and (IV) 12 < age < 14 years. This classification is in accordance with other studies in which participants younger than 10 years were considered as children and those between 10 and 14 years as preadolescents or early adolescents [43–45]. Also, the control group will be adjusted according to age and sex to the study group. Although children treated for cancer may present with precocious or delayed puberty, it is generally rare [46]. In the case of pubertal incompatibility with age, the individual will be assigned to their pubertal (children, adolescents, late adolescents) group according to the Tanner stage [47].

Ethical committee approval

This study will be conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving patients will be approved by the local Ethic Examining Committee of Human Research of the Medical University of Warsaw, Poland (Decision of Approval: KB/54/A2023).

Sample size calculation

The sample size was calculated for an unmatched case–control study with the input parameters of a 2-sided confidence level of 0.95, power 80%, ratio of controls to cases 1:1, and odds an ratio of 2.0. The sample size calculation by Fleiss with CC method showed 144 participants for each group. Considering a dropout rate of 10%, the total sample size required is 300.

Participant dropout mitigation

This study protocol includes a one-time in-hospital participant assessment (approximately 3 h long) and 14-day accelerometer assessment. The relatively short but adequate observation time was planned to mitigate participant dropout. What is more, the study protocol and aims will be explained by a pediatric oncologist while obtaining consent to participate, and the in-hospital assessment will be scheduled in advance with the participant parent/caregiver. The study protocol does not involve any unpleasant assessment methods, and all the exams will be performed by a study team experienced in working with children and their caregivers. Also, in the case of refusal, the children will be encouraged to comply, especially during the CPET examination. A dropout rate of no more than 10% is expected.

Statistical analysis

Statistical analysis will to be performed using SPSS. Medians, proportions, and percentages will be used to describe the population and resulting observations. The comparisons between groups will be performed with the T-test for normally distributed data and the U-Mann–Whitney test for non-normally distributed data. For nominal variables Fisher's exact test will be used if the number of observations per group is below 5; in other cases Pearson's chi-square test will be applied.

For determinant assessment univariate and multivariate analysis will be applied.

Figures

Figure 1 illustrating the schedule of the individual participant assessment was created via BioRender.com.

Data monitoring

Individual data will be monitored by the study team during the participants' in-hospital evaluation as well as 14-day accelerometer monitoring. A data monitoring committee will compromise a pediatric oncologist, pediatric cardiologist, and physiotherapist and will have access to the final trial dataset. Quarterly auditing of the study will be completed by the investigators.

Adverse events will be identified and documented by the study team over the course of the study. Participant data will be stored on 2 different secure password-protected external drives. The study will be concluded once the target sample size has been reached.

The study data will be stored for a maximum of 5 years.

Dissemination of findings

The results of the study will be shared through conferences and publications in peer-reviewed journals. Regardless of the study's direction or magnitude, the results will be released. The study team (pediatric oncologist, pediatric cardiologist, and physiotherapist) will decide whether to publicize and/or publish any interim results.

Discussion

The overall favorable prognosis in childhood cancers justifies major efforts towards not only minimizing, detecting, and early management of chemotherapy-induced cardiotoxicity, but also improvement of physical efficiency and consequently the quality of life of these children. The main finding of the above study will be the key determinants of the physical activity level in child cancer survivors treated with cardiotoxic therapy.

Establishing the key determining factors of the PA level in the group of patients after cardiotoxic cancer therapy can be used to develop targeted exercise prescriptions and exercise programs. It may enable the prescription of different exercise intensities for each patient that are independent of disease severity or baseline fitness. Exercise prescriptions based on estimated baseline physiological end points have high clinical applicability but increase the susceptibility for underdosing or overdosing of exercise therapy [48].

Previous studies mainly based on heterogenic, small groups of patients showed that children after oncological treatment did not meet the recommendations related to the appropriate level of everyday moderate-to-vigorous PA [48–50].

Decreased PA was associated with higher cancer-related fatigue 12 months after cancer treatment [18, 19]. Children and young adults on and off cancer therapy pointed out fatigue and psychological issues, as well as physical complaints and safety concerns as the most prevalent barriers to PA [18]. Treatment-related factors including chemotherapy or a combination of treatment modalities were not significantly associated with activity behavior despite observed low CRF [17, 19]. The data about the social versus treatment impact on PA level remain inconclusive [19, 25, 51]. Lower CRF was significantly associated with increased fatigue during cancer treatment, having a higher percentage of fat mass and lower belief of one's own athletic competence [17]. Social support has been addressed as a strong facilitator to activity [18, 20]. However, parents of children with cancer highlighted the treatment, subsequent isolation, and loss of independence as major factors determining the decline in the PA level of their children, excluding their lack of support to participate in PA [21, 22]. The environmental factors impacting the PA of children after cancer treatment may include school and peers [22]. Schools who welcome back cancer survivors are often unsure how to behave towards the children in regard to PA [25]. Peer support was analyzed and found to have a positive association with PA and self-efficacy [23]. Friends were also identified as a critical part of support [24].

Physical function was assessed as a 6-min walking test, without validated test batteries [52]. Most of the previous studies in the topic were based on questionaries and/or interviews [19–25], whereas the actual PA was not measured objectively with, for example, activity trackers [27]. Studies in which the activity trackers were used included a very short time of accelerometer assessment, i.e., 4–7 days [17, 29–31].

Studies in adult populations have shown that anthracycline chemotherapy led to a significant decrease in VO2peak or VO2 max, and that this downward trend is closely linked to the occurrence of cardiotoxicity. Lower VO2peak indicated a direct reduction in cardiorespiratory fitness [53–55].

The determining factors of physical activity in children with another risk factor of possible physical activity decline – cardiotoxic treatment and its influence on the cardiovascular system – have not been yet studied.

The determinants of the PA level in children after oncological treatment remain unknown and may provide key information in the future therapeutic management of long-term adverse effects and a route to quality-of-life enhancement among childhood cancer survivors. These determinants may include treatment impact on somatic and psychological aspects, as well as level of awareness, social factors, lifestyle, self-efficacy, and QoL.

Abbreviations

ALL	Acute lymphoblastic leukemia
BRC-ABL	Breakpoint cluster region protein-abelson
TBI	Total body irradiation
CRF	Cardiorespiratory fitness
PA	Physical activity
QoL	Quality of life
SD	Standard deviation
BMI	Body-mass index
CPET	Cardiopulmonary exercise test
WHO	World Health Organisation
VO2 max	Maximal oxygen consumption
ALPHA health-related fitness test battery	Assessing Levels of Physical Activity health-related fitness test battery
GLS	Global longitudinal strain
LVDd	Left ventricle diastolic diameter
EF	Ejection fraction
rpm	Rotations per minute
VO_2	Oxygen uptake
VCO_2	Carbon dioxide production
RER	Respiratory exchange ratio
$VCO2/VO_2$	ratio of carbon dioxide (CO_2) produced (VCO2) to oxygen consumed (VO_2)
LV	Left ventricle
LVSd	Left ventricle end-systolic dimension
IVSDd	Interventricular septal diastolic diameter
IVSSd	Interventricular septal systolic diameter
LVPWDd	Left ventricular posterior wall diastolic diameter
LVPWSd	Left ventricular posterior wall systolic diameter
LVEF	Left ventricular ejection fraction
E	Early diastolic mitral inflow velocity
A	Atrial diastolic mitral inflow velocity
Edt	E deceleration time
IVRT	Isovolumic relaxation time
E′	Early diastolic velocity
A′	Late diastolic velocity

TDI	Tissue doppler imaging method
STE	Speckle tracking echocardiography
GRS	Global radial strain
GCS	Global circumferential strain
PedsQL	Pediatric Quality of Life Inventory
PALMS	Physical Activity and Leisure Motivation Scale
MPA	Moderate physical activity
VPA	Vigorous physical activity
GFCI	Greedy Fast Causal Inference

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Authors' contributions
Conceptualization, J.H.S., J.S.G., K.A., P. Ł. and B.W.; methodology, J.H.S., J.S.G, K.A., P. Ł. and B.W.; formal analysis, J.H.S. and J.S.G; data curation, J.H.S. and J.S.G.; writing—original draft preparation, J.H.S. and J.S.G; writing—review and editing, B.W.; visualization, J.H.S.; supervision, B.W.; project administration, J.H.S.; funding acquisition, J.H.S. and J.S.G. All authors have read and agreed to the published version of the manuscript. All the authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study will be conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving patients are approved by the local Ethic Examining Committee of Human Research of the Medical University of Warsaw (Decision of Approval: KB/54/A2023).
Informed consent will be obtained from all subjects involved in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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