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STUDY PROTOCOL

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Study protocol of an early randomized intervention trial assessing the metabolic effects of two levels of exercise intensity in children undergoing cancer treatment: the APACIS study

Justine Thomas[1,4], Thomas Filleron[2], Françoise Auriol[3], Claire Laurens[4] and Marlène Pasquet[1,5*]

Abstract

Background Insulin sensitivity is a key factor of the development of metabolic diseases, highly prevalent in adult survivors of childhood cancers. The aim of the Adapted Physical Activity for children treated for Cancer and Insulin-Sensitivity (APACIS) study is to investigate the effects of two exercise programs started as early as diagnosis on metabolic profile and physical health.

Methods APACIS is a trial that includes children at diagnosis of all pediatric cancers which are randomly allocated to the Soft group – for low intensity physical activity – or to the Strong group – for mixed, high intensity exercise. Both programs are done at least twice weekly for 30 to 60 min over 6 months, adapted to the health status of the children, with a follow-up of 18 months. The primary objective is the change in insulin sensitivity measured by the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) at 0, 3, 6, 12 and 24 months between the two groups. The secondary objectives include changes in cholesterol, triglycerides and cortisol blood levels, state of undernourishment, cardiorespiratory fitness (based on peak rate of oxygen uptake of the 6 Minute Walk Test), flexibility (sit and reach flexibility test), fat mass distribution (Waist-to-Hip Ratio) and level of physical activity assessed by questionnaire at 0, 3, 6, 12 and 24 months. On-therapy metabolic adaptation in the different patient groups will also be evaluated by an integrated pipeline combining the detection of 150 metabolites, with metabolic pathway enrichment and network mapping. This approach will be complemented by an analysis of intestinal and oral microbiota, to identify the species impacted by treatments and the influence of exercise on these toxicities.

Discussion The APACIS study investigates the metabolic, motor, and nutritional effects in children with cancers performing low versus high intensity exercise with an innovative approach consisting of early practice since diagnosis. It will contribute to better personalize physical activity prescription during treatment of pediatric cancers.

Trial registration The study has been registered on ClinicalTrials.gov (NCT05383092) the 7 of November, 2022.

Keywords Cancer, Pediatric, Exercise, Physical activity, Metabolism, Rehabilitation

*Correspondence:
Marlène Pasquet
pasquet.m@chu-toulouse.fr
Full list of author information is available at the end of the article

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Background

Advances in treatment have improved the five-year survival rate of children with cancer to over 80%, in high income countries [1]. Nevertheless, treatments are often toxic, with 50% of child cancer survivors having at least one chronic health disease in adulthood [1, 2]. Worldwide, 33,6% of adult cancer survivors have excessive adiposity, impaired glucose homeostasis, dyslipidemia and hypertension, grouped under the term Metabolic Syndrome (MetS) [3–5]. Insulin is a key hormone regulating blood glucose levels, and insulin resistance has been showed as the determining factor of the development of MetS in children in remission from hematological cancers, due to an association between certain chemotherapies and altered insulin signaling [6, 7]. In addition, low-grade inflammation in cancer is known to reduce insulin sensitivity [8].

Children during or after cancer have reduced physical health partly due to inactivity and treatment side effects [9, 10]. The benefits of exercise in the management of pediatric cancers include improvements in cardiorespiratory fitness, muscle strength, body composition, quality of life and fatigue, both during and at the end of treatment, with a higher level of evidence following cessation of therapies [11–17]. Only one study has shown the effects of mixed exercise on insulin resistance performed in children in remission from cancer, and not at diagnosis [18]. Patients performed between 45 and 60 min of exercise (15 to 25 min of aerobic exercise and the rest of muscle strengthening), twice a week, for 6 months. This intervention, carried out on average 8 years after hematopoietic stem cell transplantation, shows for the first time a positive effect of mixed exercise on insulin resistance, as measured by the HOMA-IR index. Finally, intense exercise during cancer treatment does not present any risks [12].

Mixed Physical Activity (MPA), combining aerobic exercise and muscle strengthening, is the most used method to prevent MetS, and particularly insulin resistance, in both adults and children [19]. Aerobic activity improves cardiorespiratory fitness, carbohydrate and lipid metabolism, and mitochondrial activity in healthy adults and children [19, 20]. Muscle strengthening increases muscle mass and improves glucose uptake in healthy adults and children [19]. The combination of these benefits of MPA gives this method a systemic and prolonged effect on insulin sensitivity [19, 20]. The combined benefits of these training modalities are achieved through enhanced insulin action in muscle, adipose tissue, and liver [20]. A summary of these findings related to metabolism and physical activity in childhood cancer is presented in Fig. 1. The APACIS study is thus designed to evaluate the metabolic, motor, and nutritional impacts of low versus high intensity exercise in children with cancer, using an innovative approach that incorporates early exercise practice starting from the time of diagnosis.

Methods

Study design and objectives

This is a single center, randomized, clinical research protocol studying the evolution of metabolic, motor, and nutritional parameters between a group practicing mixed, high intensity physical activity, referred to as "Strong", and a group practicing low physical activity, referred to as "Soft". The study is taking place in the Pediatric Hematology-Oncology-Immunology Department of the Toulouse University Hospital Center.

Randomization of 60 patients is performed electronically with a 1:1 allocation ratio, using a computer minimization program incorporating a random element developed by the Department of Biostatistics, Oncopole Claudius Regaud, (Toulouse University Cancer Institute, Toulouse, France). Stratification variables are type of cancer and age (pre-pubescent and pubescent groups). Randomization is carried out by the clinical research assistant, who orally informs the families of the group in which the patient is assigned.

The first objective of the study focuses on the main parameter, the HOMA-IR index, a simple, validated method for assessing insulin resistance [21]. Indeed, it is considered as an indicator of insulin sensitivity in peripheral tissues [22] and a predictive marker of metabolic syndrome in our population [6]. It is based on the interaction between fasting glucose and insulin levels, established from the following equation: HOMA-IR = Glycemia (mmol/L) x Insulin (mUI/L)/22.5) [21]. Hence, the primary objective is to estimate the difference in the evolution of insulin sensitivity assessed by the HOMA-IR index in the two Adapted Physical Activity (APA) groups (Strong versus Soft) between the beginning (M0) and the end of the intervention (M6).

The secondary objective are to describe the longitudinal evolution between the two randomization arms over the two years of the study (at M0, M3, M6, M12 and M24) of the following variables: insulin sensitivity measured by the HOMA-IR index; plasma levels of High Density Lipoprotein-Cholesterol (HDL-Cholesterol), triglycerides and cortisol; undernutrition status; aerobic capacity based on peak rate of oxygen uptake (VO2 peak) measured by the 6 Minute Walk Test (6MWT); sit and reach flexibility test (centimeter); fat mass distribution measured by the Waist-to-Hip Ratio (WHR); physical activity level by questionnaire; and adherence to APA programs. The general study design is illustrated in Fig. 2. The Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT) checklist is provided as Additional File 1 [23].

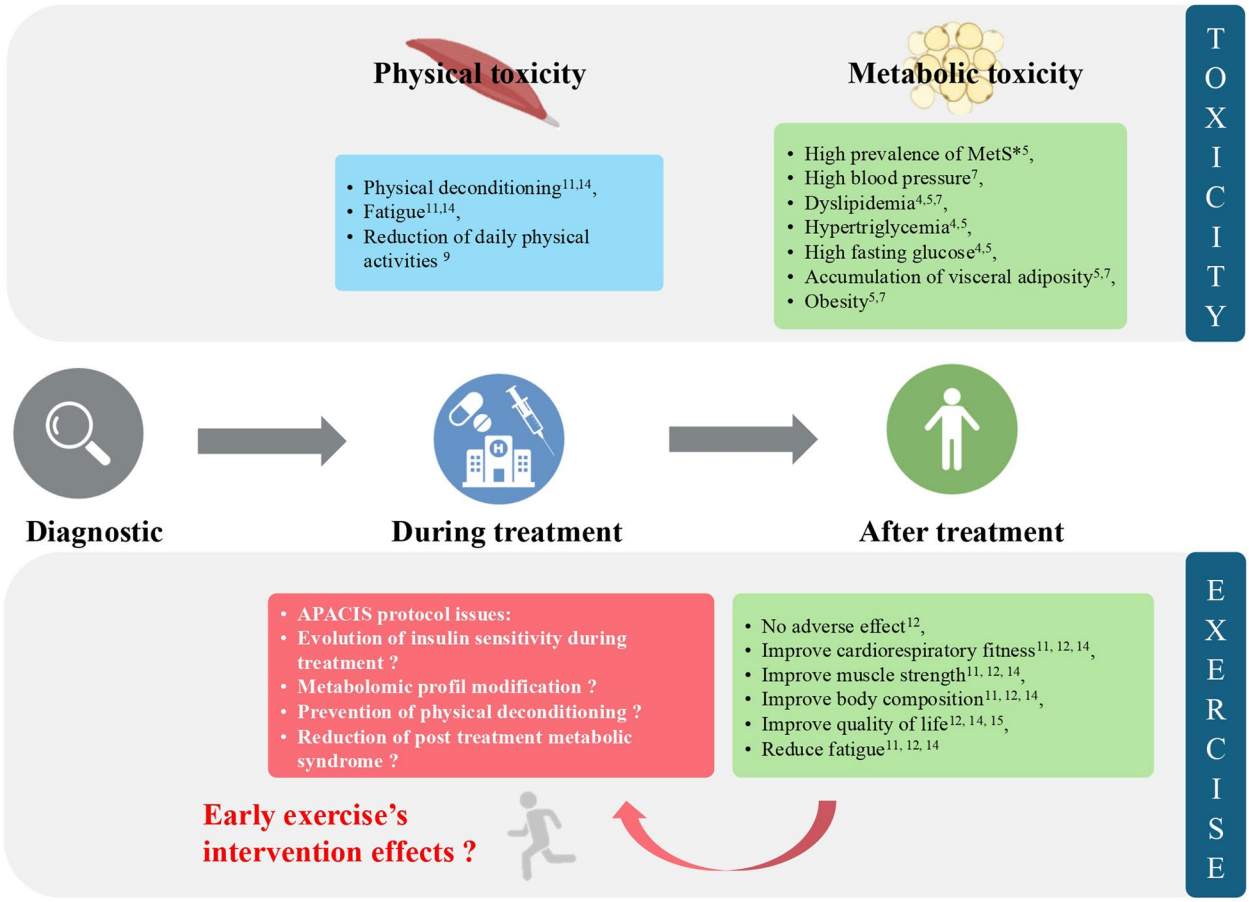

Fig. 1 Treatment and physical activity effects in childhood cancer and the needs addressed by this study. Legend: * MetS, Metabolic Syndrome; APACIS, Adapted Physical Activity for children treated for Cancer and Insulin-Sensitivity

Participants

Children and adolescents aged between 5 and 18, hospitalized at the Pediatric Hematology-Oncology-Immunology Department for the diagnosis and first chemotherapy treatment of their cancer, are included in this study. Eligible patients are those with hematological or solid cancers, and with an estimated life expectancy at diagnosis of over 6 months, and who have given free and informed consent. Patients who are physically or psychologically unable to follow an APA program are excluded. These characteristics are assessed during a clinical evaluation by the investigators and in communication with the parents. Patients with pre-existing heart disease contraindicating APA are also excluded. To study the relationship between APA intensity and insulin sensitivity in metabolic profiles that were not insulin-resistant at diagnosis, patients with type 1 diabetes or obesity (Body Mass Index (BMI) superior or equal to 25) are excluded. The study consents are presented in the Additional Files 2 to 5.

Intervention

Patients are randomly assigned to either the Soft program (low intensity APA) or the Strong program (mixed, high intensity APA). To ensure that the programs are tailored to patients'needs, two intervention arms are defined for each group, based on age. Patients aged 5 to 12 are in the pre-pubescent group and practice 30 min of APA. Patients aged 13 to 18, in the pubescent groups, practice 45 to 60 min of APA. Both programs run for 6 months, at least twice a week, at the hospital when patients are hospitalized and via videoconferencing when they are at home. Hospitalized participants can receive up to 5 supervised sessions per week. Programs are supervised by APA professionals trained to address the specific needs of this population. APA sessions are either individual or group sessions (with a maximum of 6 children per group), performed seated, lying down, or standing, depending on the patient's health condition. They are mediated by equipment chosen by the professional in collaboration with the child. For videoconferencing

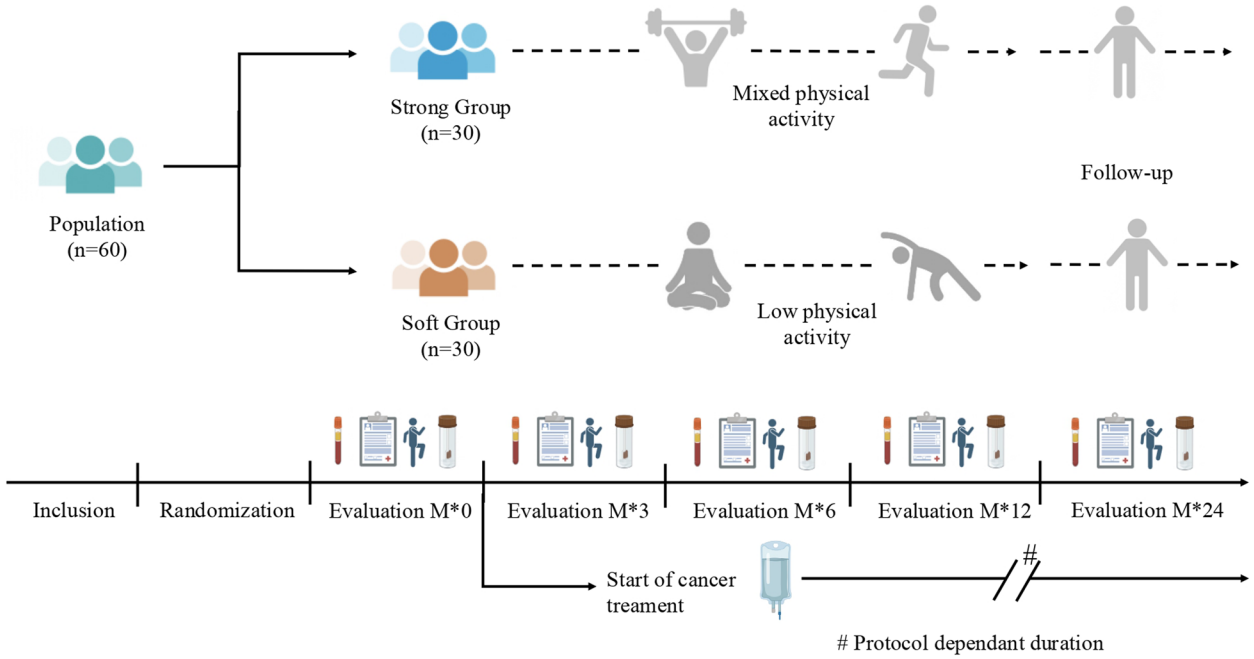

Fig. 2 Flowchart of APACIS study. Legend: * M, Month

sessions, equipment is provided, consisting of a box with a Twister game, balls, studs and elastic bands. Activity intensity is assessed during sessions using the modified Borg visual analog scale adapted to children [24]. Heart rate is not used because of its limitations in young children, especially in their movement. For clinical consistency, patients and their families are encouraged to be active daily, respecting the intensity assigned to their group. The physical activity questionnaire enables us to monitor the level of physical activity undertaken independently. Statical analysis will be normalize the results by these levels, to adjust the results to the autonomous practice evaluated.

Strong program sessions consist of (i) a warm-up with joint mobility, breathing and cardio-respiratory activation exercises; (ii) a main body of session consisting of fractional aerobics, muscular strengthening of the main muscle groups (biceps femoris, quadriceps, hamstrings, erectors of the spine, abdominals, pectorals, biceps brachii) and static stretching of these muscles; (iii) a cool-down consisting of breathing exercises and a discussion of feelings during the session.

Soft program sessions consist of (i) a warm-up involving joint mobility and breathing exercises; (ii) a main body session consisting of low intensity activities involving static sequences aimed at improving coordination and precision, joint mobility work through static stretching (stretching of the main muscle groups), relaxation through dynamic massage of the main muscle groups; (iii) and a cool-down involving breathing exercises and discussion of the feelings experienced during the session. Details of the Strong and Soft program sessions are shown in Table 1.

Measures

Evaluation measurements are taken at three time points: at diagnosis, before the first course of chemotherapy and corticosteroid therapies, at 3 months and at 6 months. Follow-up data are collected at 12 and 24 months. The schedule of enrolment, interventions and evaluations in the APACIS trial is presented in Table 2.

Clinical and biological data

Clinical data collected include age, sex, pubertal stage, weight, height, resting blood pressure, past acute and chronic illnesses, surgical history, concomitant pathologies (metabolic, cardiac and others), concomitant pathologies, type of cancer, treatment protocol, and the initiation and duration of enteral and parenteral nutrition. Minimal Residual Disease, regularly collected in care protocols, is recorded in clinical parameters to study the effect of exercise-induced metabolic regulation on the molecular response for leukemia and lymphoma.

Biological blood parameters are taken as part of a routine check-up in hospital, during long-term hospitalization, day hospitalization or consultation. They are taken between 8 and 10 a.m., after an overnight fast of 8 to 12 h. Plasma concentrations studied include glucose,

Table 1 Overview of the intervention programs

	Strong for pre-pubescent children	Strong for pubescent children	Soft for pre-pubescent children	Soft for pubescent children
Age	5- 12 years old	13- 18 years old	5- 12 years old	13- 18 years old
Intensity	High intensity	High intensity	Low intensity	Low intensity
Duration	30 min	45–60 min	30 min	45–60 min
Frequency	Minimum of 2/week	Minimum of 2/week	Minimum of 2/week	Minimum of 2/week
Warm-up				
Duration	5 min	10 min	5 min	10 min
Fractional aerobics				
Duration	10 min	15 min		
Muscle strengthening				
Duration	10 min	15 min		
Repetition	5	7		
Sets	2	3		
Static activities (coordination, precision)				
Duration			8 min	20 min
Static stretching				
Duration	3 min	10 min	8 min	20 min
Dynamic massage				
Duration			4 min	10 min
Cool-down				
Duration	2 min	10 min	5 min	10 min

insulin, HDL-Cholesterol, triglycerides, and cortisol. The HOMA-IR index is calculated afterward.

As part of two ancillary studies, a biological collection for metabolomic and microbiota analyses is taken at every measurement, on optional participation, subject to consent. This consists of a 5 mL plasma sample, a 5 mL saliva sample, 3 periodontal plaque tip samples from the periodontal sulcus, and a 5 g feces sample. Plasma samples are stored at the Biological Resources Center of the Toulouse University Hospital Center, in the form of aliquots of 500µL frozen at −80 °C. Samples relating to salivary microbiota (saliva and periodontal plaque) and intestinal microbiota (feces) are sent to a partner laboratory for bacterial collection. This biological collection will give rise to further studies on the effect of APA on the metabolomic profile and microbiota, in children undergoing treatment.

Motor and nutritional data

Aerobic capacity is measured by the 6MWT test, determining the maximum rate of oxygen uptake (VO2peak) [25]. The participant must walk as far as possible in 6 min, in 25 m round trips. Walking with mechanical assistance is permitted. Breaks, their duration and the reasons for them are recorded. The evaluator accompanies the participant, informing him of the progress of the time. At the end of the test, heart rate, blood pressure, saturation, intensity of effort with the children Borg scale [24] and total distance covered are recorded. VO2peak is calculated using the Cahalin's equation [25], validated for children [26].

The flexibility is measured by the sit and reach flexibility test [27], performed on a mat, without shoes. The participant sits with legs straight, a 60 cm ruler at heel level. The arms are stretched forward, as far as possible, and held for 2 s. Legs must remain straight. The distance of flexibility is marked by the participant's fingers on the ruler. Three attempts are made, the best being retained.

The WHR is used to determine the distribution of body fat mass, between subcutaneous and visceral fat [28]. It is based on waist and hip circumference, measured with a constant-tension tape. The calculation is as follows: waist circumference (cm)/hip circumference (cm) [28].

The level of physical activity is assessed by two questionnaires created for the study, based on the questionnaires Youth Risk Behavior Survey of Guedes & Lopes [29] and the International Physical Activity Questionnaire [30]. The questionnaires (one for 5–12-year-olds and the other for 13–18-year-olds) provide information on the frequency and weekly duration of low and intense physical activity and sedentary behavior. Analysis with the pediatric-specific compendium by Butte et al. [31] calculates weekly energy expenditure in physical activity.

Table 2 Schedule of enrolment, interventions and evaluations in the APACIS study

	STUDY PERIOD					
	Enrolment	**Intervention**			**Follow-up**	
TIMEPOINT	**M[a]-1**	**M[a]0**	**M[a]3**	**M[a]6**	**M[a]12**	**M[a]24**
Enrolment						
Eligibility screen	x					
Information, delivery of consents	x					
Medical exam	x					
Collecting consents	x					
Randomization	x					
Interventions						
APA group Strong		♦	—	♦		
APA group Soft		♦	—	♦		
Biological collection						
Plasma sample		x	x	x	x	x
Saliva sample		x	x	x	x	x
Periodontal sample		x	x	x	x	x
Faeces sample		x	x	x	x	x
Assessments						
Clinical data		x	x	x	x	x
Blood parameters		x	x	x	x	x
State of undernourishment		x	x	x	x	x
6 Minute Walk Test		x	x	x	x	x
Sit and reach flexibility test		x	x	x	x	x
Waist circumference		x	x	x	x	x
Hip circumference		x	x	x	x	x
Waist-to-Hip Ratio		x	x	x	x	x
Level of physical activity		x	x	x	x	x
Number of sessions carried		x	x	x	x	x
Adverse events of APA		x	x	x	x	x

[a] Months

The assessment of undernourishment is based on the BMI plotted on the body curves and its evolution, according to the criteria of the French National Authority for Health [32].

Compliance with the Strong and Soft APA programs will be defined by the ratio of the number of sessions carried out to the number of theoretical sessions. Adherence to the programs is measured by a satisfaction questionnaire created for the study. Adherence to prescribed exercises is monitored in the Case Report Forms (CRF), with details of posture types (sitting, lying down, standing), social context (individual, group), location (room, different department rooms, videoconferencing) and duration. Exercise intensity is self-assessed for each main part of the session (warm-up, main body of session, cool-down).

Data monitoring

The APACIS study is funded by the Toulouse University Hospital Center, the trial's sponsor. Study data control is carried out by the Department of Biostatistics, Oncopole Claudius Regaud, (Toulouse University Cancer Institute, Toulouse, France), an independent institution experienced in controlling clinical studies and guaranteeing patient and data safety.

CRF are entered into a secure online database. Authorized staff at sites require an individual secure login username and password to access this online data entry system. The data are captured on paper and entered onto the CRF by the researchers. The data in each CRF must be consistent with the source data, or discrepancies must be explained. Any unknown or missing information must be clearly indicated on the CRF and be the subject of a query. All sections must be completed. All documents relating to the trial are archived and stored securely for a minimum of 10 years. No documents will be destroyed without the prior agreement of the sponsor. The Toulouse University Hospital Center holds all final study data and is responsible for the controlled sharing of anonymized trial data with the research community, to ensure the privacy and confidentiality of participants. The research is monitored by a clinical research technician, following standard operating procedures. A clinical research associate appointed by the center carries out regular monitoring visits, at set-up, several times during and at the end of the research. These monitoring visits check compliance with informed consent and the protocol, the quality of data collected and the management of samples.

Data analysis is carried out in collaboration with the Biostatistics Department. As the data in the CRF are filled in by the department's team of researchers or clinicians, they are provided confidentially to the Biostatistics Department, which can be considered the Data Monitoring Committee. It is consulted regularly on the adequacy of the accumulated data. It will be consulted once the inclusions have been completed to produce the analyses.

Confidential information collected during the trial will be stored in accordance with the General Data Protection Regulation. As specified in the consent, patients will be identified using their unique registration number. Authorized personnel may have access to records for quality assurance and auditing purposes.

A meeting will be organized after the end of the study to allow discussion of the main results between the collaborators before publication. The results of the primary and secondary endpoints will be submitted for publication in a journal. Results from ancillary studies will also be submitted for publication in a journal. Manuscripts will be prepared by the responsible investigators and authors will be determined by mutual agreement. Patients who have made a request to the main sponsor will receive the results of the study. Reports on the results are also sent to the funding associations, according to a set schedule.

As this protocol corresponds to category 2 research involving the human body, and as no serious risks are associated with the practice of APA in the population of children with cancer [12], information on serious Adverse Events (AEs) is not expected. AEs due to interventions are documented during the whole duration of the protocol. They are defined as an event occurring in a person undergoing research involving the human body when this event is related to the research.

Statistical analysis

As the aim of the protocol is to estimate the difference in progression between the randomization arms with a certain degree of accuracy, randomizing 50 patients at a 1:1 ratio (i.e. 25 per arm) enables us to estimate a two-sided 95% confidence interval for the difference between the two groups with an accuracy of ± 0.28 (standard deviation of 0.5) [33]. Considering 15% of non-evaluable patients, 60 patients are expected to be randomized to ensure a manageable number of patients. Data acquired prior to premature patient discontinuation will be considered in the analyses.

Clinical data will be described by randomization arm using standard descriptive statistics. Qualitative variables will be presented by randomization arm as follows: number of missing data, number and percentage for each modality of the variable. Quantitative data will be presented by randomization arm as follows: number of missing data, minimum, maximum, median, quartiles. Comparisons between randomization arms will be made using Fisher's exact test for qualitative variables and the

Mann Whitney test for quantitative variables, to check group comparability.

The primary objective is the change in insulin sensitivity as measured by the HOMA-IR index at 6 months compared with baseline. The difference between the two groups will be evaluated with its 95% confidence interval. The evolution of the HOMA-IR index will also be presented by randomization arm, using the usual descriptive statistics: number of missing data, mean, variance, standard deviation, minimum, maximum, median, quartiles. For exploratory purposes, this evolution will be compared using the Student test or Mann–Whitney test. A sensitivity analysis will be carried out to assess the impact of the number of sessions carried on the evolution of the HOMA-IR index.

The secondary objective will be presented at each measurement time using a strategy similar to that used for the primary objective, for motor and nutritional parameters. The difference between the randomization arms will be presented at each time point with its 95% confidence interval. Quantitative variables will be presented at each measurement time for each group using the usual descriptive statistics used for the primary endpoint.

Discussion

Pediatric cancers are associated with chronic diseases that develop in adulthood [1, 2], partly due to treatment toxicity [8, 34], and a major risk factor is related to treatment burden over time [35]. Among them, MetS has been found to develop worldwide at higher rates in pediatric cancer survivors than in the general population in numerous studies [4, 5, 34, 36], thereby increasing the risk of developing cardiovascular and metabolic diseases [5]. Worldwide, 33.6% of adults in remission from leukemia have metabolic syndrome, and 49.9% have insulin resistance [3, 4]. In France, the prevalence varies between 6.9% and 10.3%, two to four times higher than the general population [34, 36]. The development of MetS is largely explained by insulin resistance in peripheral tissues, which favors other MetS components such as dyslipidemia, arterial hypertension, and abdominal obesity [37]. Very few studies have examined the evolution of insulin sensitivity during the treatment of pediatric cancer [7], and no study has yet investigated whether the early initiation of physical activity in this population can improve treatment tolerance and insulin sensitivity to prevent MetS. We acknowledge that the euglycemic-hyperinsulinemic clamp is the gold standard method to assess insulin sensitivity [38]. However, given the fragile nature of our pediatric cancer population, we will use the HOMA-IR index as a less invasive alternative in this study [39]. In addition, to get deeper into early metabolic profile changes under APA, analyses of a biological collection will be carried out longitudinally. Metabolomic signatures will be studied to generate mechanistic hypotheses on the metabolic pathways affected by cancer and to explain changes in insulin sensitivity resulting from APA programs. Anti-cancer treatments induce dysbiosis, which is a risk factor for MetS [40]. Because exercise can modulate gut microbiota [41], we will study this dysbiosis in children undergoing anti-cancer treatment within our cohort using stool, saliva, and periodontal samples. This will allow us to identify which bacteria are the most affected by treatment and to evaluate the impact of APA intensity on this treatment-related toxicity.

The acute and late effects of anti-cancer treatments create overall physical deconditioning, fatigue, pain, and impaired quality of life [12], as well as adverse medium-term effects on physical and mental health, and socio-economic and social conditions [42]. One consequence is the reduction in children's physical activity levels during treatment [9] and after remission [10]. Physical activity during treatment is safe [12] and has positive effects on muscle strength, functional and aerobic capacity, fatigue, body composition and quality of life [11–17]. Although exercise is recommended from the start of treatment to prevent medium-term effects [12], the optimal duration and intensity of PA remain unknown, as well as its consequences in terms of MetS prevention. The recommendations for healthy children can be adapted to children with cancer, provided that the modalities are adapted to the side effects of treatment and the children's health status [11, 43]. However, starting an APA program at diagnosis remains a real challenge for clinicians due to several limitations (asthenia, pain, anxiety).

To prevent MetS, the gold standard for healthy children relies on MPA [20], which we chose for this study. The combination of muscle strengthening and aerobic exercise reduces body fat mass, increases muscle mass, and improves the metabolic profile [20, 36], giving this exercise modality a systemic effect on insulin sensitivity [44]. Based on these findings and the conclusions of Davis et al. [18], which demonstrated the benefits of MPA eight years after the cessation of leukemia treatment, the APA-CIS protocol is the first study to examine these effects from diagnosis.

Lack of evidence on the APA management of children undergoing cancer treatment do not allow us to identify an optimal training program [12]. Recommendations for physical activity in pediatrics involve a personalized, comprehensive approach targeting major muscle groups, with at least two sessions per week, incorporating 1 to 3 sets of 6 to 12 repetitions per exercise [45]. These principles have been taken up and adapted in our program for children undergoing cancer treatment.

An individualized, supervised program has more effect and seems to have higher adhesion than free programs [14]. Thus, supervision of the protocol in small groups by level of intensity and pubertal stage enables the program to be suitable to the participants. In addition to these aspects, the collective approach strengthens social ties and supports children's educational development. Finally, the program's professionals provide recommendations for PA following the end of intensive treatment (i.e. usually 6 months post-diagnosis), thereby promoting active behavior.

In conclusion, the APACIS protocol will, for the first time, provide data on the effects of APA introduced at the time of pediatric cancer diagnosis on metabolism, physical condition, tolerance to treatment toxicities, metabolomic profile, microbiota diversity, and the prevention of medium-term sequelae.

Abbreviations

AEs	Adverse events
APA	Adapted Physical Activity
APACIS	Adapted Physical Activity for children treated for Cancer and Insulin-Sensibility
BMI	Body Mass Index
CRF	Case Report Forms
HDL-Cholesterol	High Density Lipoprotein- Cholesterol
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
MPA	Mixed Physical Activity
MetS	Metabolic Syndrome
SPIRIT	Standard Protocol Items: Recommendations for Intervention Trials
WHR	Waist-to-Hip Ratio
6MWT	6 Minute Walk Test

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14235-4.

Additional file 1. SPIRIT Checklist.

Additional file 2. Consent for the APACIS study, issued to patients' parents.

Additional file 3. Consent for the APACIS study, issued to patients aged between 5 and 7 years.

Additional file 4. Consent for the APACIS study, issued to patients aged between 8 and 12 years.

Additional file 5. Consent for the APACIS study, issued to patients aged between 13 and 17 years.

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Authors' contributions
MP and JT designed the study and were the major contributors in writing the manuscript. FA and TF designed the methodology and biostatistics. CL and FA reviewed the study and the manuscript. All authors read and approved the final manuscript.

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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 has been approved by the French Consultative Committee for the Protection of Persons Ile de France VIII (RC31/22-0061). The study is registered on ClinicalTrials.gov (NCT05383092). It is a single-center randomized, prospective, two-armed intervention study organized and actually conducted by the Toulouse University Hospital Center. As ancillary studies, a biological collection is taken at every measurement, as optional participation, subject to consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Pediatric Hematology and Immunology, Toulouse University Hospital Center, 339 Avenue de Grande Bretagne, Toulouse 31059, France. [2]Department of Biostatistics, Claudius-Regaud Institute, Toulouse University Cancer Institute Oncopole, Toulouse, France. [3]Pediatric Clinical Research Unit, CIC1436, Children Hospital, Toulouse University Hospital Center, Toulouse, France. [4]University of Toulouse, Institute of Metabolic and Cardiovascular Diseases, UMR 1297 Inserm, Team Metadiab, Toulouse, France. [5]University of Toulouse, Toulouse Cancer Research Center, UMR1037 Inserm, UMR5077 CNRS, Toulouse, France.

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