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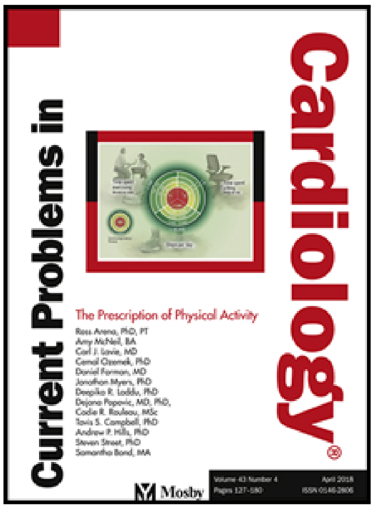

Prevention of cardiotoxicity in childhood cancer survivors: in physical exercise, we trust

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Prevention of cardiotoxicity in childhood cancer survivors: in physical exercise, we trust

Running title: Physical exercise and cardiovascular prevention in childhood cancer survivors

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Abstract

In recent years, the mean survival rate of children after a cancer diagnosis has significantly improved. At the same time, a growing interest in short and long-term cardiovascular (CV) complications of cancer therapy, as well as long-term CV risk in childhood cancer survivors (CCS) developed, along with proposals of protocols for the diagnosis, management, and prevention of cancer therapy-related CV toxicity (CTR-CVT) in this population. Many clinical and individual risk factors for CTR-CVT have been identified, and a non-negligible prevalence of traditional CV risk factors has been described in this population, potentially associated with a further worsening in both CTR-CVT and long-term CV risk. Physical exercise (PE) represents a promising, free-of-cost and free-of-complications, helpful therapy for primary and secondary prevention of CTR-CVT in CCS. The present narrative review aims to summarize the most critical evidence available about CTR-CVT in CCS, focusing on the role of PE in this clinical scenario.

Keywords: childhood cancer survivors (CCS); cancer therapy-related cardiovascular toxicity (CTR-CVT); chemotherapy (CHT); radiotherapy (RT); physical exercise (PE)

Abbreviations**:** ALL, acute lymphocytic leukemia; ANT, anthracyclines; CCS, childhood cancer survivors; CMR, cardiac magnetic resonance; CPET, cardiopulmonary test; CRF, cardiorespiratory fitness; CTR-CVT, cancer therapy-related cardiovascular toxicity; CV, cardiovascular; CVD, cardiovascular disease; ECG, electrocardiogram; GLS, global longitudinal strain; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PA, physical activity; PE, physical exercise; PI, physical inactivity; QoL, quality of life; RT, radiotherapy; TDI, tissue Doppler imaging; TTE, thansthoracic echocardiography

1. Introduction

Cancer represents the main disease-related cause of death in pediatrics, with 400,000/year children and teenagers facing a malignancy diagnosis (1,2). Cancer management innovations upgraded the 5-year survival rate, in this population, reaching 40-to-80% in low and high-income countries, respectively (3).

Neverthless, childhood cancer survivors (CCS) are at risk for short and long-term complications: cancer recurrences and functional impairments, mainly. Besides, they will also experience further complications within 30 years from their diagnosis, including cancer therapy-related CV toxicity (CTR-CVT)(4). Data from the CCS study reports an overall mortality rate 8.4 times higher than that of healthy controls, with a 40-year cumulative all-cause mortality of 23.3% (5–7). CCS experience a 2-to-10-fold increase in overall CV risk compared to the general population and a 7-fold increase in CV-related mortality, with substantial psycho-physical and economic issues, leading to a decreased quality of life (QoL), especially in females (8–13). Furthermore, frailty, defined as a condition associated with reduced physiologic reserve that is generally documented in older adults, represents an emerging, relevant issue in young adult CCS, with a prevalence among 7.9% that is comparable to that of 9.9% reported in older adults in the general population (14,15). Frailty itself determines a lower physiologic reserve and decreased physical fitness levels, leading to an increased risk of chronic disease, including CV disease (CVD) and mortality in CCS.

As CVD constitutes the second cause of premature mortality in CCS, after cancer itself, primary and secondary CV prevention in this population is imperative, especially when considering the strong correlation linking CV risk, mental issues, QoL, chronic inflammatory and pro-oxidant status, and cancer (7,16). In this regard, the strong association between poor mental health and CV risk factors, such as sedentarism, PI, and weight gain, should always be kept in mind, especially in CCS, which generally report symptoms of depression and require specific medical therapy more frequently than controls (17,18). Moreover, in CCS, there is an increased risk of post-traumatic stress disorder, which is, in turn, strongly associated with CV risk factors, and CV mortality (19). In addition to the need to improve event-free and overall survival in these patients, these findings support the necessity to focus on late CV effects and QoL in CCS. In this setting, PE represents a crucial tool in CV risk factors prevention and treatment, gaining pro-oxidant status reduction and QoL improvement and working on primary and secondary prevention of CRT-CVT as well (figure 1) (20).

In line with the recommendations for cardiomyopathy surveillance for CCS, published by the Childhood Cancer Guideline Harmonization Group, regular PE should be prescribed in every survivor treated with anthracyclines or chest radiation, who have normal left ventricular (LV) systolic function. On the other hand, a cardiology consultation should be prescribed for survivors with asymptomatic cardiomyopathy or for high-risk survivors to delineate the risk type and amount for exercise. However, to date, no specific indications are available regarding specific PE protocols for each patient in terms of type, duration, amount of PE, and monitoring of potential adverse or beneficial effects (21). The aim of the present narrative review is to offer an updated review of the most critical evidence available about the role of PE in this clinical scenario. We searched MEDLINE, Scopus and Web of Science, using a combination of terms relating to childhood cancer survivors (eg, cancer; pediatrics; childhood cancer survivors), cardiotoxicity (cancer therapy-related cardiovascular toxicity; cardiotoxicity; chemotherapy; radiotherapy; primary prevention; secondary prevention; follow-up) and physical exercise (eg, physical activity; physical exercise).

2. Pathophysiology of cardiotoxicity in childhood

Significant improvements in managing oncologic diseases, including prompt diagnosis and treatment, led to a sensible increase in patient long-term survival and QoL in the last decades. Prolonged life expectancy among CCS also led to a rise in the prevalence of the comorbidities that may occur because of cancer therapy administration, which from a CV perspective are comprehensively referred to with the term CTR-CVT. The variety and severity of CTR-CVT depend on the type and dosage of the drug administered in a particular patient. Acute and early-onset CTR-CVT in children includes therapy-related cardiomyopathy (transient or progressive), myocarditis, pericarditis, arrythmias, and vascular complications (22,23). Clinical risk factors associated with more severe CTR-CVT are considered: higher lifetime cumulative doses of ANT with greater dose rates, younger age at treatment, longer follow-up after treatment, female sex, chest RT, CV risk factors (24–26).

There is a substantial heterogeneity in the definition of cardiotoxicity due to childhood cancer treatment, based on the combination of echocardiographic data, clinical indicators and biomarkers (27). Therapy-related cardiomyopathy can be described as a decline in cardiac function, either following cardiomyocyte damage, alterations of myocardial perfusion, hormonal/autonomic nervous system imbalance, or inflammatory response leading to myocardial infiltration of immune cells yielding myocardial fibrosis(28). Despite specific, less-detrimental formulations have been developed, this complication is still relevant and there may be no harmless ANT dose (29). High-dose ANT (> 250 mg/m2) and exposure to chest RT > 15 Gy are established risk factors for CTR-CVT, but even survivors who received a mean chest RT dose of 5 to 15 Gy or a cumulative ANT dose of 100-250 mg/mq have an increased risk of heart failure (HF) (30). In children, aside from symptomatic HF, ANT-related cardiotoxicity can frequently manifest as subclinical troponin elevation related to myocardial injury, due to an excessive production of free radicals, the inhibition of the topoisomerase II enzyme, and an iron/calcium homeostasis imbalance (29). Chronic ANT-related cardiotoxicity is characterized by histological changes, leading to cell loss and fibrosis (31). Other conventional chemotherapeutics, such as alkylating agents, platinum, differentiating agents, and antimetabolites, being associated to arrhythmias, myocardial ischemia, hypertension and dyslipidemia in adults, are less frequently associated with cardiotoxicity in pediatrics. Although the development of targeted therapies aimed to reduce CTR-CVT, both on- and off-target cardiotoxicity has been reported, and the use of immune checkpoint inhibitors has been related to rare, mostly reversible cases of myocarditis (22). Finally, cardiotoxicity could be influenced by genetic variability regarding the metabolic pathways of chemotherapeutics (22).

3. Diagnosis of cardiotoxicity in childhood: from imaging to cardiac biomarkers

3.1 Non-invasive tests

Electrocardiogram (ECG)

The ECG can identify early signs of cardiotoxicity, e.g. resting tachycardia, ST-T wave abnormalities, conduction disorders, prolonged QT interval, or arrhythmias. These findings are non-specific and may be unrelated to CTR-CVT. Furthermore, as they are often reversible, the use of 24-hours Holter monitoring may be needed to assess any dynamic changes in cardiac conduction (32).

Cardiopulmonary exercise testing (CPET)

CPET may represent a first-line tool to detect subclinical cardiac dysfunction in CCS, with reduced peak oxygen consumption and exercise capacity being related to previous exposure to ANT (33,34). To date, the research landscape on CPET in the workup of CCS is still sparse and based on retrospective studies.

3.2 Imaging

Echocardiography

Two-dimensional transthoracic echocardiography (TTE) is the most widely used method for evaluating CTR-CVT in children. As standard TTE parameters have a low predictive value in identifying cardiotoxicity, the use of global longitudinal myocardial strain (GLS) and Tissue Doppler Imaging (TDI) has been strongly, routinely recommended in both adult and CCS since they allow earlier identification of myocardial damage (35–39). Studies regarding the use of three-dimensional TTE in pediatrics are ongoing (40).

Cardiac Magnetic Resonance imaging (CMR)

The use of CMR to monitor CTR-CVT in children has been sparsely investigated (41,42). On a general note, due to limited availability, long procedural times, and high cost, CMR is not routinely recommended in the workup of CCS; however, it could become the screening modality in high risk patients with poor-quality echocardiographic images or pre-existing CVD (43).

3.3 Biomarkers

Serum cardiac troponin

An acute increase in serum troponin levels following ANT in children with acute lymphocytic leukemia (ALL), due to cardiac cell damage, has been demonstrated (44). However, no definite data support a strong association between troponin release and LV dysfunction in CCS (45,46).

Natriuretic peptides

N-terminal pro-brain natriuretic peptide (NT-proBNP) has been used to predict early cardiotoxicity in children with ALL, before the onset of pathological LV remodeling (47).

Nevertheless, as for its low sensitivity, it has to be appraised in the context of clinical assessment and TTE (48).

D-Dimer

D-dimer represents a marker for deep vein thrombosis and pulmonary embolism, with high negative predictive value and poor specificity (49). Thus, it is recommended to use D-Dimer levels only to rule out suspected venous thromboembolism, and no evidence supports its use for CTR-CVT or survival estimate in CCS.

Others

Several potential cardiotoxicity biomarkers, such as C-reactive protein, growth/differentiation factor 15, myeloperoxidase, placental growth factor, soluble Fms-like tyrosine kinase receptor 3, and galectin 3, have been recently investigated (50). However, they significantly changes only after heart damage occurs, with uncertain incremental value in CTR-CVT. Omics science, comprising genomics, transcriptomics, proteomics, and metabolomics, is investigating their possible integration in the workup of CCS (51).

4. Management of CTR-CVT in childhood

The management of CCS encompasses CTR-CVT prevention, pharmacological approaches, and implementation of PE interventions. Primary prevention strategies include RT exposure reduction protocols and cardioprotective antineoplastics' formulations, the latter being experimented in different randomized controlled trials (52). To date, only dexrazoxane (DRZ) received Food and Drug Administration and European Medicines Association approval in adults as a cardio-protectant agent and recently it showed to play a significant cardioprotective effect in young adult-aged CCS nearly 20 years after ANT exposure (53–57). Enalapril demonstrated cardiac function improvement in patients treated with ANT high-doses, whereas the latest data from literature do not support the administration of carvedilol for secondary HF prevention in CCS after ANT exposure. The use of statins in the same scenario is under study (22,58–60). Other potential, long-term, CV side effects in CCS include arterial hypertension, dyslipidemia, glucose intolerance, and adiposity. Cranial, abdominal, and total body irradiation represent specific risk factors for metabolic dysfunction. Nephrectomy, abdominal irradiation, and antineoplastic alkylating agents can contribute to nephrotoxicity. The epidemiological and clinical manifestations of these complications will be defined in the KINDEST-CCS and the Dutch LATER METS studies (61–63). According to the specific clinical history and risk factors, each CCS should undergo periodic laboratory tests to monitor cardio-nephro-metabolic parameters and serial ambulatory blood pressure evaluation. Furthermore, lifestyle factors management, focused on PE and balanced diet, should be warranted, despite the lack of research on the PE and nutritional interventions for CCS, with no adequate recommendations about the usefulness of dietary interventions in this population (64,65).

4. Prevention of CTR-CVT in childhood: the paramount role of physical exercise

CV risk factors and CTR-CVT vs exercise intervention in CCS

Successful management in CCS requires a multidisciplinary approach in which caregivers, health professionals, and patients cooperate to pursue children's short and long-term health. CCS experience a two-to-tenfold increase in overall CV risk compared to the general population and a 7-fold increase in mortality due to CV complications, such as severe LV dysfunction or sudden cardiac death, with the prevalence of CV risk factors significantly increasing with time (9,25,66). CCS exhibit a higher risk for future CVD even when compared with a non-cancer age-, sex-, and ethnicity-matched control population with similar cardiometabolic profiles, with a probability of 3% and 10% of developing CVD, respectively, at 30 and 45 years of age (66,67). Moreover, they suffer from a significant burden of modifiable CV risk factors at an earlier age than the general population, and this burden significantly increases with time, enhancing more than 5-fold their risk of severe CVD (7,11,25,66,68,69). We must keep in mind that cancer and CVD share common traditional and novel risk factors, and antineoplastic therapies, along with health behavioral changes and psychological issues, negatively impact CV risk (70–74). These considerations warrant the need for CCS to undergo long-term clinical follow-up and lifestyle assessment (75). CV risk factors in CCS are generally underdiagnosed and undertreated, whereas they could be counteracted by effective PE interventions, with a significant mortality reduction (7,22,76). PI represents a weighty modifiable CV risk factor in CCS, as it affects more than 70% of CCS and is associated with a higher cardiometabolic burden (77–79). While anxiety, fatigue, and lack of motivation may explain this deteriorating attitude, it is also likely that CV prevention campaigns do not systematically target these patients, which are easily lost to follow-up (71,72). CCS significantly reduce the total amount and the average time spent in PA, especially in moderate-to-vigorous PA, negatively impacting cardiorespiratory fitness (CRF) (80–82). CRF represents an essential health indicator in youth and a primary prognostic marker of survival and CV risk in CCS (83,84).

On the other hand, regular exercise training exerts its cardioprotective mechanisms in cancer patients in several ways. Firstly, it increases cardiac muscle adaptation and growth, reducing cardiomyocyte apoptosis and improving cardiovascular reserve in terms of better endothelial and autonomic function and cardiac perfusion. Secondly, it reduces inflammatory markers and endogenous stress, ameliorating antioxidant status. Thirdly, it improves cardiometabolic risk profile in terms of reduced CV risk burden, counteracting sarcopenic effects of anticancer treatment, and ameliorating CRF during and after treatment in children (85–93). High PA (≥ 60 minutes per day of moderate-to-vigorous PA) in CCS improves cardiometabolic profile in terms of fat mass reduction and lowers CV risk at a long-term follow-up, as compared to low

PA (94). Conversely, low PA, high screen time, old age, female gender, and high waist-to-height ratio represent predictive factors for worse CRF (95).

In CCS, the cumulative incidence of CV events is inversely correlated with the increase in the reported PE levels, with a 10-year incidence of CV events of 12.2% for survivors reporting a low exercise exposure compared with 5.2% for those describing adherence to vigorous-intensity PE (96). Moreover, ≥ 2.5 hours of intense PA/week for at least one year can determine a substantial CVD risk score reduction (97).

Exercise guidelines for CCS following antineoplastic treatments have been published, but compared to literature evidence in adults, cardioprotective properties of PE in CCS have received less attention. There is a significant heterogeneity among the available studies in terms of patients' characteristics, exercise protocols, and the time interval between cancer diagnosis and therapy, and exercise prescription (98–100). A Cochrane systematic review by Braam et al., including 171 CCS, undergoing a PE training program within the first five years following the diagnosis of a childhood cancer, demonstrated that although some positive results were found in terms of CRF, body composition, and QoL, the overall data were inadequate due to the heterogeneous study methodology regarding the number of participants and the characteristics of the exercise intervention (101). Analogously, Bourdon et al. demonstrated that aerobic PE determines a statistically and clinically significant positive effect of CRF in CCS when compared to the change in CRF experienced by a control, standard-of-care group (102). The same Authors underlined that the impact of aerobic PE training on CRF seems to be less significant among CCS as compared to adult cancer survivors, as for the adverse effects of cancer itself and related therapies on physiological growth and development, and for the lower adherence to PE experienced by CCS (103). Furthermore, they highlighted the meaningful heterogeneity of clinical characteristics and intervention parameters across the available studies, thus supporting the need for more high-quality randomized controlled trials in this clinical scenario. Recently, Kendall et al. published the first scoping review exploring the impact of PE on the development of CTR-CVT in CCS. The authors included six reports, carried out from 1993 to 2020, that significantly varied according to patients' characteristics, PE protocol, and impact of PE on CTR-CVT (104–109). Regarding PE interventions, one study included only aerobic PE, whereas the other five entered a combination of aerobic and resistance training; moreover, the PE protocol was administrated during cancer treatment in one study and 4- to-30 years after the diagnosis in the other reports and none met the current World Health Organization's guidelines exercise standards for CCS (2.5 hours/week of aerobic exercise for adults and strength training twice a week for adults; 1h/day of aerobic exercise and strength training twice a week for children) (110). The cancer diagnosis and the CV health-related findings significantly differed among the studies. However, all reports suggested the benefit of PE in mitigating CTR-CVT risk in CCS (111). Finally, an umbrella review by Rapti et al., including 13 studies, provided a comprehensive overview of the positive effects of PE on many CV health outcomes in CCS, especially in terms of CRF, LVEF, and endothelial function, describing a limited number of adverse effects, even when exercise intervention was provided during hospitalization (112–116).

One final consideration is that it seems that CCS do not benefit from regular PA as much as it happens in the non-cancer population. Firstly, ANT and RT interfere with mechanisms of CV adaptation to PA causing premature myocyte and cardiac progenitor cells apoptosis, thus limiting the physiological process of PA-related cardiac hypertrophy. Secondly, cancer therapies affect many cardiac and vascular adaptative mechanisms to PA, particularly endothelial function. These mechanisms decrease CCS physiological reserve as compared to the cancer-free population, with a potential increased risk of age-related chronic conditions. These considerations underline the need for more research to understand why CCS react differently than their peers to exercise training and to define which specific exercise interventions could amplify CV health benefits in this population (117).

Future perspectives

Given these premises, trials are ongoing to enhance our understanding of the positive effects of PE on CTR-CVT in CCS (118).

The HIMALAYAS Trial (NCT05023785) will provide data about the most effective PE prescription for CCS at risk of cardiotoxicity, comparing a strategy of cardio-oncology rehabilitation to standard of care concerning many outcomes of cardiac function (75).

The BEACON (BEing Active after ChildhOod caNcer) study aims to create a person-centered, evidence-based intervention for promoting and supporting sustainable PA behavioral change in CCS, identifying the barriers and facilitators to PA in CCS (119). In the LIFE Cancer Survivorship and Transition Program (Children's Hospital, Los Angeles) specific and practical evidence-based PE recommendations in CCS have been developed (120).

PE protocols should be tailored for each patient, and periodically re-evaluated, based on CPET parameters and specific short and long-term effects of cancer therapy, to ensure the patient's safety and adherence to exercise (120,121).

We must face, identify, and treat the causes of the "PI pandemic" in CCS to increase their adherence to exercise prescription. Three orders of factors influence PA participation among cancer patients: physiologic factors, psychosocial and cultural factors, environmental and economic factors (122). Physiologic issues are related to cancer itself or to treatment-related side effects, such as cancer-related fatigue that has a prevalence of 0-62% and a multifactorial etiology, and lack of PA engagement (123,124). Psychosocial features include low self-esteem and lack of motivation, whereas financial hardship and inaccessible services are among economic and environmental factors. According to the COG guidelines, clinicians should be aware about the psychosocial late effects experienced by CCS, with an active referral to mental health services and a tailored socioeconomic risk assessment (99). These factors should be accurately screened and treated in CCS, and an accurate motivational lifestyle counseling should be offered (124). Parental support, as well as the role of nurse-led intervention in early CV prevention and motivational interviewing with parents, should always be advocated in this context (125–127). Both mHealth (medical and public health practice supported by mobile devices) and eHealth (the use of communication tools to upgrade health care) might play a relevant role among CCS (128).

The PanCareFollowUp Consortium identified lack of time, unhealthy environment, and social media, as barriers to health behavior adherence in CCS and is gathering data about the feasibility and effects of an eHealth intervention to support sustainable PA and nutritional changes in CCS (129,130). The PACCS study aims to broaden the available knowledge about the physiological, psychological, and social barriers to exercise that can be targeted in interventions to contribute to the development of an evidence-based PA intervention for young CCS to increase their long-term adherence to rehabilitation programs (131).

Finally, the gender disparity in PA, especially in childhood and adolescence, must be considered, as in most countries girls are less physically active than boys, with a consequent additional increase in PI into adulthood, significantly impacting short and long-term CV health of women and offspring (132–134). As female CCS experience a greater risk of maternal CV outcomes compared to general pregnancy, being greatly influenced by CV risk factors, especially PI, concrete attention must be paid to raising awareness of PE in the female CCS population (135).

6. Conclusions

Substantial advances in cancer management have considerably upgraded the survival rate of CCS. However, these patients are still at risk of short and long-term complications. The effects of PE improving QoL, fatigue, and functional capacity in CCS have been demonstrated. However, to date, there are still poor data regarding the role of PE in primary and secondary prevention of CVT-CTR, the best PE training program for children with active cancer and CCS and the clinical characteristics of patients who can benefit the most from PE program. Future studies should include a higher number of participants affected by different cancer diagnoses; consider analogous material and methods and comparable PE training programs, defining the right time interval between cancer diagnosis and therapy and exercise prescription; identify the proper protocol of PE for the right patient in terms of type and duration of training, to ameliorate cardio-metabolic outcomes in CCS; highlight the clinical and social risk factors for PI and gender disparity in PA involvement in CCS; focus on personalized PA components and tailored PE programs supporting behavior change methods to decrease CV risk, amplify CV health and QoL as well, reducing long-term CV risk and CV morbidity and mortality (135)

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Author Contributions

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Ethics approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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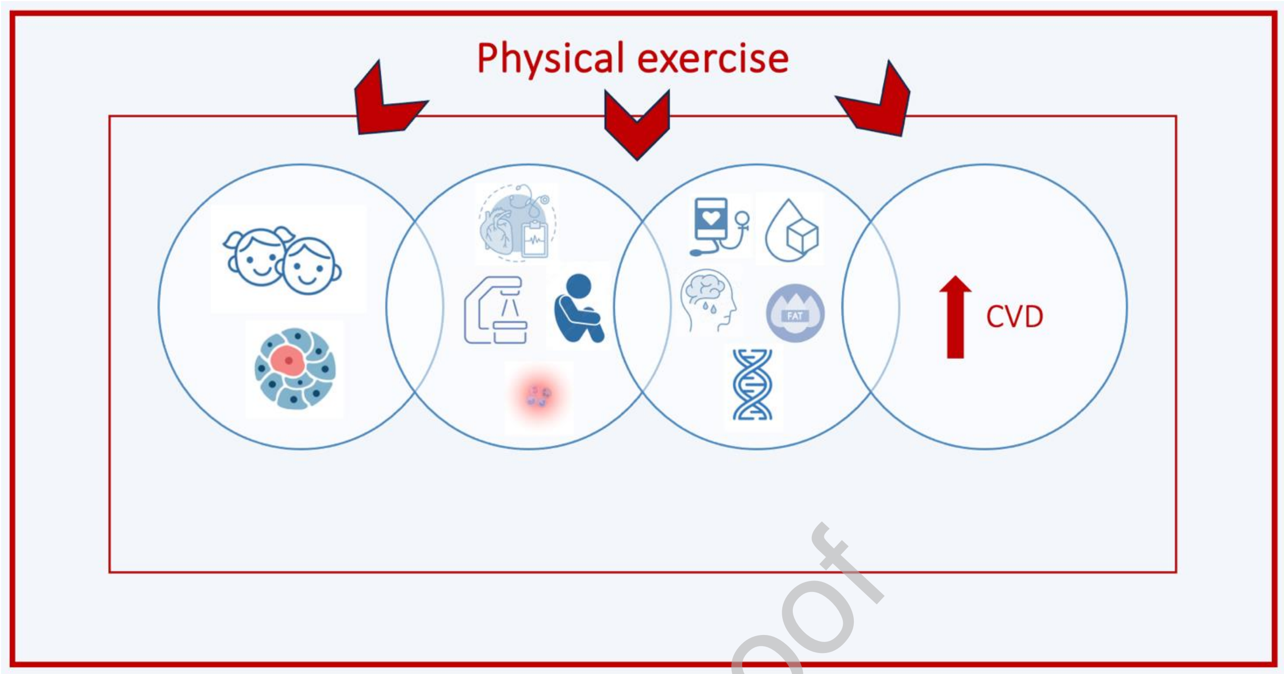

Figure 1. Physical exercise in primary and secondary CV prevention in childhood cancer survivors (CCS). CCS experience an increased long-term risk of cardiovascular diseases (CVD) that is influenced by cancer-therapy related cardiovascular toxicity (CTR-CVT), radiation exposure, chronic inflammatory status related to cancer itself, fatigue and sedentarism and traditional CV risk factors as well (arterial hypertension, dyslipidemia, altered glucose metabolism, mental health issues, genetic predisposition). Physical exercise can play a relevant role in primary and secondary prevention of CTR-CVT, reducing CV risk factors prevalence and impact, improving chronic inflammatory and pro-oxidant status associated with cancer and its related therapies, and enhancing cardiorespiratory fitness and short and long-term risk of CVD.

Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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