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# Impaired aerobic capacity in adolescents and young adults after treatment for cancer or non-malignant haematological disease

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# Abstract

## Purpose:

Childhood cancer survivors are at increased risk for cardiovascular disease. Maximal oxygen uptake ( $VO_{2max}$ ) is a major determinant of cardiovascular morbidity. The aim of this study was to compare aerobic capacity, measured by cardiopulmonary exercise test (CPET), of adolescents and young adults in remission with that of healthy controls and to identify the predictors of aerobic capacity in this population.

## Method:

This is a controlled cross-sectional study.

## Results:

A total of 477 subjects (77 in remission and 400 controls), aged from 6 to 25 years, were included, with a mean delay between end of treatment and CPET of  $2.9 \pm 2.3$  years in the remission group. In this group, the mean  $VO_{2max}$  was significantly lower than in controls ( $37.3 \pm 7.6$  vs.  $43.3 \pm 13.1$  mL/kg/min,  $P < 0.01$ , respectively), without any clinical or echocardiographic evidence of heart failure. The VAT was significantly lower in the remission group ( $26.9 \pm 6.0$  mL/kg/min vs.  $31.0 \pm 9.9$  mL/kg/min,  $P < 0.01$ , respectively). A lower  $VO_{2max}$  was associated with female sex, older age, higher BMI, radiotherapy, and hematopoietic stem cell transplantation.

## Conclusion:

Impaired aerobic capacity had a higher prevalence in adolescents and young adults in cancer remission. This impairment was primarily related to physical deconditioning and not to heart failure.

## Trial registry:

[NCT04815447](https://www.clinicaltrials.gov/ct2/show/study/NCT04815447).

## Impact:

In childhood cancer survivors, aerobic capacity is five times more impaired than in healthy subjects. This impairment mostly reflects early onset of physical deconditioning. No evidence of heart failure was observed in this population.

# INTRODUCTION

Cancer affects around 1 in 4000 children and is the leading cause of death in children over one year of age, with 6000 deaths per year in Europe, according to the International Agency for Research on Cancer. However, thanks to the dissemination of multimodal therapeutic strategies to paediatric oncology, the 5-year remission rates currently exceed 85%.<sup>1</sup> As a result, it is nowadays more about ‘living rather than surviving’ after childhood cancer. Therefore, improving the quality of life after childhood cancer must now consider, from paediatric age, the reduction in morbidity. Indeed, childhood cancer survivors remain at high risk for obesity,<sup>2</sup> diabetes mellitus,<sup>3</sup> and cardiovascular disease as adults.<sup>4–6</sup> Furthermore, some anticancer therapies are cardiotoxic, such as radiotherapy or chemotherapy using anthracyclines, resulting in a 5% incidence of heart failure related to dilated or restrictive cardiomyopathy in adulthood.<sup>7–9</sup> Young patients with non-malignant haematological disease requiring a hematopoietic stem cell transplantation are also affected by cardiovascular complications. Overall, the mortality from cardiovascular disease in adults after childhood cancer would be seven times higher than that of the general population.<sup>10</sup> Nevertheless, early predictors of cardiovascular morbidity in childhood cancer survivors have not been clearly identified. Recent studies have suggested using aerobic capacity to promote physical activity outcomes in childhood cancer survivors.<sup>11,12</sup> In adult cancer, aerobic capacity has shown a strong, graded, and inverse association with total cancer mortality.<sup>13</sup> Moreover, in the general population, the maximum oxygen uptake ( $VO_{2max}$ ) is a strong surrogate of physical capacity, which stands as a major and independent predictor of cardiovascular risk.<sup>14</sup> In many paediatric chronic diseases, impaired physical capacity assessed by cardiopulmonary exercise test (CPET), correlates with lower health-related quality of life scores, and may indicate early onset of physical deconditioning, such as in congenital heart disease, cystic fibrosis, or kidney disease.<sup>15–18</sup>

Despite previous studies reporting the feasibility and interest of aerobic capacity assessment in cancer surveillance, routine CPET in clinical practice has not been widely disseminated in the paediatric population.<sup>19,20</sup> Moreover, the level of aerobic capacity in adolescents and young adults after childhood cancer survivors has been scarcely reported.<sup>21,22</sup>

Thus, we planned to compare the aerobic capacity of a cohort of adolescents and young adults treated for cancer or transplanted for non-malignant haematological diseases during childhood, to that of age- and sex-matched healthy controls. In this specific population, we also intended to identify the predictors of the aerobic capacity.

## METHODS

### Study design and patient population

This cross-sectional controlled study was carried out from November 2010 to November 2020 in a tertiary care paediatric centre (Montpellier University Hospital, France).

Adolescents and young adults aged 6–25 years were screened during a regular outpatient visit in one of the participating centres. Two groups were identified: adolescents and young adults in complete remission after treatment for cancer or transplanted for non-malignant haematological disease during young age (i.e., the ‘remission group’), and the control subjects. Subjects from both groups were enrolled during the same period.

(1) The ‘remission group’ consisted of patients treated for paediatric cancer by chemotherapy, radiotherapy and/or hematopoietic graft, as well as patients with non-malignant paediatric haematological disease requiring a hematopoietic stem cells transplantation (before the age of 25 years). To be eligible for the study, all patients from this group needed to be in complete remission at the time CPET was performed. Patients with the following medical conditions were screened from our CPET database: haematological malignancies (acute lymphoblastic or myeloblastic leukaemia and Hodgkin or non-Hodgkin lymphoma), solid tumours, and nonmalignant haematological diseases treated with a hematopoietic stem cells transplantation (Wiskott–Aldrich syndrome, thalassemia, and medullar aplasia). The following patient characteristics were collected from electronic health records: age at diagnosis, type of treatment (chemotherapy, radiotherapy, corticosteroids, autologous or allogeneic hematopoietic stem cell transplantation), and overall length of hospital stay.

The following clinical data were systematically collected when the CPET was performed: sex, age, weight, height, body mass index (BMI), heart failure functional class (NYHA), and echocardiographic assessment of left ventricle ejection fraction (LVEF).

(2) The control group consisted of children referred for a non-severe functional symptom linked to exercise (murmur, palpitation, or dyspnoea) or for a medical sports certificate. As in our similar controlled CPET studies, these subjects were classified into the control group only after a completely normal check-up, including physical examination, electrocardiogram, echocardiography, and spirometry.<sup>16,23,24</sup>

### **CPET procedure**

The CPET laboratory used the following equipment: paediatric face masks (Hans Rudolph, Shawnee, KS), a calibrated gas analyser (Quark CPET, Cosmed Srl, Pavonna di Albano, Italy), breath-to-breath measurement software (Windows 7–10, Omnia, Cosmed), 12-lead ECG equipment (Norav, Medical, Mainz-Kastel, Germany) and pulse oxymeter (Nonin Medical Inc, Plymouth, MN), and a manual sphygmomanometer with adapted paediatric cuffs. Spirometry using a common gas device (Oxycon Pro, Jaeger, Erich Jaeger GmbH, Hoechberg, Germany).

A spirometry was systematically performed before the exercise test. From the flow volume curve, forced expiratory volume in 1 s (FEV1), forced ventilatory capacity (FVC) and Tiffeneau index (FEV1/FVC) were recorded and expressed as Z-scores using the reference spirometry equations.<sup>25</sup>

The CPET paediatric cycle ergometer protocol oversaw a homogeneous incremental overall duration between 8 and 12 min: a 1-min rest; a 3-min warm-up (10–20 watts) in increments of 10, 15, or 20 watts each minute; a pedalling rate of 60–80 revolutions per minute; a 3-min active recovery (20 watts); and a 2-min rest.<sup>16,23,24</sup>

In this study, the level of aerobic capacity was determined by the  $VO_{2max}$  and the ventilatory anaerobic threshold (VAT).  $VO_{2max}$  and VAT values were normalised in a percentage of the predicted  $VO_{2max}$  using normal values from Wasserman and Cooper.<sup>26</sup> The CPET was considered as maximal when two out of the following four criteria were reached: respiratory exchange ratio ( $RER=VCO_2/VO_2$ )  $\geq 1.1$ , maximum heart rate  $>80\%$  of maximal age predicted heart rate, limit of the child's tolerance despite verbal encouragement, and plateau of  $VO_2$  ( $VO_{2max}$ ) despite the increasing exercise intensity.<sup>16</sup> When the  $VO_{2max}$  did not reach a plateau, the peak  $VO_2$  ( $VO_{2peak}$ ) was informed, as usual in paediatrics.<sup>27,28</sup> A  $VO_{2max} < 80\%$  of predicted values indicated impaired aerobic capacity.<sup>29</sup> The VAT was measured using the V-slope method.<sup>30</sup> A VAT  $< 55\%$  of predicted  $VO_{2max}$  values was in favour of physical deconditioning.<sup>16,31</sup> The ventilatory efficiency ( $VE/VCO_2$  slope), i.e., a submaximal CPET surrogate of heart failure severity, was calculated from breath-by-breath data and determined using linear regression of minute ventilation (VE) and  $CO_2$  production ( $VCO_2$ ) obtained during incremental exercise.<sup>32</sup> The  $VE/VCO_2$  slope was measured from the beginning of incremental exercise (after the warm-up period) to maximum exercise.<sup>16,24</sup> The oxygen uptake efficiency slope (OUES), i.e., a submaximal CPET surrogate of aerobic fitness, was derived from the logarithmic relation between  $VO_2$  and VE during incremental exercise, reflecting oxygen transport response to muscular oxygen consumption's increase. The OUES being influenced by anthropometric variables, we used the weight-normalised OUES kg value.<sup>23</sup> From the Fick equation, the oxygen pulse ( $O_2$  pulse), i.e., the ratio between  $VO_2$  and heart rate, was measured as an indicator of the systolic volume (SV), and, indirectly, of the left ventricular performance. The following CPET respiratory variables at maximal exercise were also collected: partial pressure of end tidal  $CO_2$  ( $PetCO_2$ ), tidal volume (Vt), breathing reserve (BR) and respiratory rate (RR).

## Statistical analysis

The study population was described with means and standard deviations (SD) for quantitative variables, and with numbers and percentages for qualitative ones. The continuous variables distributions were tested using the Shapiro–Wilk test. Quantitative variables were compared using Student's t-test when the distribution was Gaussian and with the Mann–Whitney test, otherwise. For qualitative variables, groups were compared using the  $\chi^2$  test or Fisher's exact test.

For the remission group, age- and sex-matched control comparisons were performed. For a given case, all the controls with the same sex and age (exact year of age) were matched. The case with his (or her) matched controls was considered as a cluster. Therefore, to compare CPET parameters between the two groups, mixed models were performed in which the clusters were introduced as a random effect and BMI as a fixed effect.

A multiple linear regression was used to identify the explanatory factors for  $VO_{2max}$  and VAT in the remission group. All clinically relevant variables were proposed. The best method to select variables was determined using leave-one-out cross-validation (LOO). Finally, a forward selection based on the corrected Akaike Information Criterion was applied. No collinearity between variables was detected with variance inflation factors. The normality of residues in the final model was tested using the Shapiro–Wilk test.

The statistical significance was set at 0.05 and analyses were performed using the software SAS Enterprise Guide, version 7.13 (SAS Institute, Cary, NC).

## **Formal aspects**

The study was conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles. It was approved by the institutional review board of Montpellier university hospital (IRB-MTP-2020-02-202000335) and registered on ClinicalTrials.gov (NCT04815447). Informed consent was obtained from all parents or legal guardians.

## **RESULTS**

### **Population**

During the 10-year study period, 477 patients were included, of which 77 in the remission group and 400 in the control group. No and induce a preventive action for long-term adverse health patient or legal guardian refused to participate. Adolescents and young adults in the remission group had a higher BMI than healthy matched controls ( $19.7 \pm 4.0$  vs.  $18.3 \pm 2.8$  kg/m<sup>2</sup>,  $P < 0.01$ , respectively) and were also older ( $14.8 \pm 4.9$  vs.  $11.5 \pm 2.5$  years,  $P < 0.01$ , respectively).



**Table 1.** Non-malignant or cancer survivors' characteristics.

<i>N</i>	77
Age (years)	14.8 ± 4.9
Sex ratio (male/female)	1.8
Height (cm)	157 ± 19
Weight (kg)	50.3 ± 19.0
BMI (kg/m <sup>2</sup> )	19.7 ± 4.0
Age at diagnosis (years)	10.3 ± 6.6
Delay between end of treatment and CPET (months)	34.3 ± 28.1
Diagnosis	
Acute lymphoblastic leukaemia	30 (39)
Acute myeloblastic leukaemia	12 (16)
Hodgkin lymphoma	10 (13)
Non-Hodgkin lymphoma	8 (10)
Solid tumour	5 (6)
Non-malignant haematological disease	12 (16)
Corticosteroids	
Cumulated dose of corticosteroids (mg/m <sup>2</sup> )	3212 ± 3987
Anthracyclines	
Cumulated dose of anthracyclines (mg/m <sup>2</sup> )	148 ± 121
Radiotherapy	
Total body irradiation	21 (27)
Thoracic and mediastinal	8 (10)
Other sites	3 (4)
Length of hospital stay (days)	120 ± 93
Left ventricular ejection fraction (%)	65.6 ± 6.5
NYHA functional class I	77 (100)
Chemotherapy regimen ( <i>N</i> )	
1	57 (74)
≥2	20 (26)
Hematopoietic stem cells transplantation ( <i>N</i> )	
1	43 (56)
≥2	9 (12)

Values are mean ± standard deviation or *N* (%).

BMI body mass index, CPET cardiopulmonary exercise test, NYHA New York Heart Association.

In the remission group, the median age at diagnosis was 10.3 [0–23] years and the mean delay between end of treatment and CPET assessment was 2.9 ± 2.3 years. By order of frequency, the patients referred to the CPET laboratory and enrolled in the study were affected by the following medical conditions: haematological malignancies (78%), non-malignant haematological diseases (16%) such as Wiskott–Aldrich syndrome, primitive medullar aplasia, or thalassemia, and solid tumours (6%). Hematopoietic stem cell transplantation was performed in 52 (68%) patients, with one (*N*=43) or two (*N*=9) transplantations, either allogeneic (*N*=53) or autologous (*N*=8). A total of 32 (42%) patients had previously undergone radiotherapy, with total body irradiation for 21 (27%) subjects. In terms of drug treatments, most patients received corticosteroids (60%) and anthracyclines (82%). Overall, the median length of hospital stay was 103 [0–495] days. All patients had a normal cardiac function as assessed by the NYHA functional class and LVEF (Table 1).



**Table 2.** CPET parameters in the youth in the remission group versus healthy controls.

	Youth in remission group	Control group	P <sup>a</sup>
N	77	400	
FEV1 (Z-score)	-0.69 ± 1.13	-0.13 ± 1.41	<0.01
FVC (Z-score)	-0.74 ± 1.18	-0.02 ± 1.43	<0.01
FEV1/FVC (Z-score)	0.06 ± 1.02	-0.14 ± 1.03	0.12
Peak heart rate (beats per min)	187 ± 10	188 ± 11	0.18
Percentage of predicted peak heart rate (%)	91 ± 5	91 ± 7	0.69
RER	1.19 ± 0.12	1.14 ± 0.16	<0.01
Maximum load (W)	125 ± 61	166 ± 123	<0.01
VO <sub>2max</sub> (mL/kg/min)	37.3 ± 7.6	43.3 ± 13.1	<0.01
VO <sub>2max</sub> predicts (%)	89.7 ± 16.4	105.2 ± 19.5	<0.01
VO <sub>2max</sub> predicts <80% (N)	29 (38)	29 (7)	<0.01
VAT (mL/kg/min)	26.9 ± 6.0	31.0 ± 9.9	<0.01
VAT predicts (%)	64.9 ± 13.6	75.8 ± 18.4	<0.01
VAT predicts <55% (N)	27 (35)	29 (7)	<0.01
VE/VCO <sub>2</sub> slope	31.8 ± 4.6	30.3 ± 6.3	0.02
OUES	1823 ± 648	2180 ± 1433	<0.01
OUES <sub>kg</sub>	40.5 ± 9.6	46.0 ± 15.3	<0.01
O <sub>2</sub> pulse (mL)	9.0 ± 3.1	10.8 ± 6.3	<0.01
PetCO <sub>2</sub> (mmHg)	35.0 ± 4.2	35.6 ± 5.3	0.2
Vt (mL/kg)	29.9 ± 5.8	31.1 ± 8.1	0.1
RR (breath/min)	47.1 ± 9.9	49.3 ± 10.6	0.08
BR (%)	31.8 ± 15.6	29.3 ± 18.7	0.18

Values are mean adjusted ± standard deviation or N (%).

CPET cardiopulmonary exercise test, FEV1 forced expiratory volume in 1 s, FVC forced vital capacity, FEV1/FVC Tiffeneau index, RER respiratory exchange ratio, W Watts, VAT ventilatory anaerobic threshold, VE/VCO<sub>2</sub> slope ventilatory efficiency, O<sub>2</sub> pulse oxygen pulse, HR heart rate, OUES<sub>kg</sub> weight-normalised oxygen uptake efficiency slope, PetCO<sub>2</sub> partial pressure of end tidal CO<sub>2</sub>, Vt tidal volume, BR breathing reserve (%), RR respiratory rate.

<sup>a</sup>Comparison between subjects in the youth in remission group and age- and gender-matched healthy controls (random cluster) adjusted on BML.

## CPET results

No CPET-related adverse events were observed. Both groups were similar in terms of Tiffeneau ratio, peak heart rate, and percentage of peak heart rate. In the remission group, the FEV1, FVC, and maximum load were lower than in healthy matched subjects, and the RER was higher. In the control group, the mean VO<sub>2max</sub> was normal (43.3 ± 13.1 mL/kg/min), representing 105.2 ± 19.5% of the predicted values (Table 2).

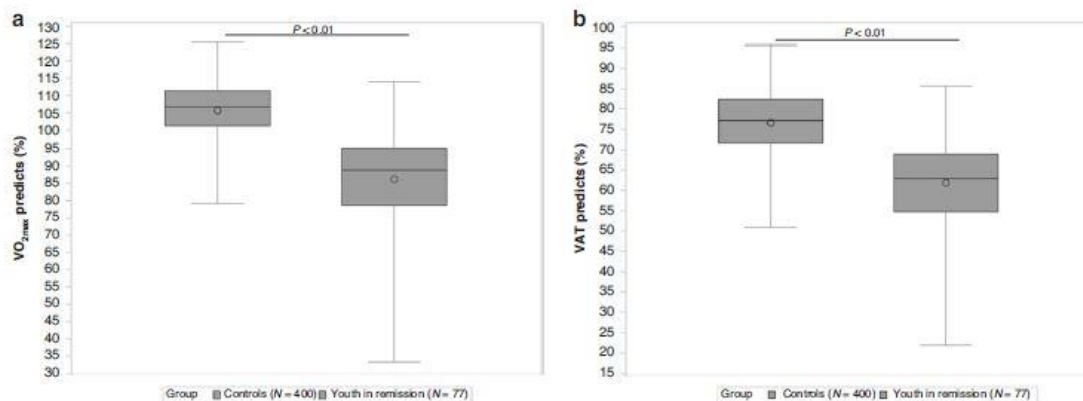
In the remission group, the mean level of VO<sub>2max</sub> was good, overall (37.3 ± 7.6 mL/kg/min), and in percent-predicts (89.7 ± 16.4%), but was significantly lower than that of healthy controls, with a magnitude of the difference of 6 mL/kg/min (P < 0.01) (Fig. 1a and Table 2).

The proportion of subjects with an impaired  $VO_{2max}$  was 5.4 times more important in the remission group than in matched healthy controls (38% vs. 7%,  $P < 0.01$ , respectively). No significant  $VO_{2max}$  difference was observed between non-malignant and malignant cancers ( $88.1 \pm 17.0$  mL/kg/min vs  $84.6 \pm 23.7$  mL/kg/min,  $P = 0.31$ , respectively).

The VAT was significantly lower in the remission group, overall ( $26.9 \pm 6.0$  mL/kg/min vs.  $31.0 \pm 9.9$  mL/kg/min,  $P < 0.01$ , respectively) and in percent-predicts ( $64.9 \pm 13.6\%$  vs.  $75.8 \pm 18.4\%$ ,  $P < 0.01$ ) (Fig. 1b and Table 2). The proportion of patients with a decreased VAT was five times more important in the remission group than in matched healthy controls (35% vs. 7%,  $P < 0.01$ ).

Moreover, in the remission group, the OUES and the oxygen pulse were significantly lower and the  $VE/VCO_2$  slope was significantly higher, than in healthy subjects (Table 2).

No significant difference was observed for the other ventilatory parameters at maximum exercise ( $PetCO_2$ ,  $V_t$ , BR, and RR).



**Fig. 1** Percent-predicted  $VO_{2max}$  and VAT in the remission group and in healthy controls. Box plot of percent-predicted  $VO_{2max}$  values (a) and percent-predicted VAT values (b) in the remission group and in healthy controls. The bottom and top of the box represent the first and third quartiles. Inside each box, the band represents the second quartile (median) and the circle represents the mean value. The whiskers represent the minimum and maximum values.

### Predictors of $VO_{2max}$ and VAT in the remission group (Table 3)

In both univariate and multivariate analyses, a lower  $VO_{2max}$  in the remission group was associated with female sex, higher BMI, and previous treatment with radiotherapy (regardless the site) or hematopoietic stem cells transplantation. The final multivariate model explained 47% of the  $VO_{2max}$  variability in the remission group.

In both univariate and the multivariate analyses, a lower VAT in the remission group was associated with female sex, older age, higher BMI, and previous treatment with hematopoietic stem cell transplantation. The final multivariate model explained 43% of the VAT variability in the remission group.

## DISCUSSION

This controlled cross-sectional study on 477 subjects showed that aerobic capacity was decreased in adolescents and young adults treated for cancer or non-malignant haematological disease during childhood, in comparison with healthy matched controls and despite the

absence of any clinical or echocardiographic evidence of heart failure. Moreover, the decrease in physical capacity was associated with female sex, higher BMI, and previous treatment with radiotherapy or hematopoietic stem cell transplantation.

The physical aerobic capacity in the examined population was overall good, with mean  $VO_{2max}$  values reaching nearly 90% of the predicted values. This level of  $VO_{2max}$  and the absence of any heart failure reflect good cardiopulmonary fitness in the young population in remission. This result seems to be in contrast with few data previously published.<sup>22,33–36</sup> However, factors such as the short distance from the end of cancer therapy,<sup>33,34</sup> the inclusion of older population samples,<sup>34</sup> or the use of different techniques to assess exercise capacity<sup>35</sup> might have influenced those results. Nevertheless, the magnitude of the difference in  $VO_{2max}$  in our cohort was clinically relevant, being 6 mL/kg/min lower in the remission group in comparison with healthy matched controls. Of note, in the general population, a  $VO_{2max}$  decrease superior to 3.5 mL/kg/min (1-MET) is a predictor of all-cause mortality and cardiovascular events in healthy men and women.<sup>14</sup> Moreover, nearly 40% of the young patients in remission enrolled in this study had an impaired  $VO_{2max}$ , which is higher than our previous results in paediatric asthma (24%)<sup>37</sup> and congenital heart disease (25%).<sup>16</sup> This result represents a strong alert, considering that childhood cancer survivors are at high risk for premature cardiovascular disease.<sup>10</sup> Indeed, a recent review on impairments of cardiopulmonary fitness level in previous childhood cancer reported poor levels of physical capacity in this population, despite limited number of high-quality studies on this subject.<sup>22</sup>

Lastly, this study found significant differences in VAT, suggesting an early entry of young childhood cancer survivors into the vicious circle of muscular deconditioning. Despite good overall values, the VAT was decreased in the remission group by 4.1 mL/kg/min, and this magnitude of discrepancy is close to the 4.6 mL/kg/min difference previously reported.<sup>38</sup> Moreover, the proportion of patients with abnormal VAT (37%) was similar to the one of patients with abnormal  $VO_{2max}$  (38%). This deconditioning is probably multifactorial, involving the lack of physical activity in the paediatric population,<sup>39</sup> the change in body composition during the first year of chemotherapy,<sup>40</sup> with fatty mass increase and muscle mass decrease, as well as the alteration of aerobic muscular fibers by corticosteroids.<sup>41</sup> The VAT is a submaximal CPET parameter which reflects muscular conditioning and provides additional value to  $VO_{2max}$  in cancer survivors.<sup>42</sup> The VAT commonly strongly correlates to  $VO_{2max}$  <sup>16</sup> and, in our study, the predictors of VAT and  $VO_{2max}$  were interestingly almost the same. While sex, age and therapies received are unmodifiable factors, preventive actions such as cardiac rehabilitation programmes can help in controlling BMI<sup>43</sup> and avoiding overweight/obesity which, in turn, is responsible for scarce physical activity.<sup>44</sup>

Overall, the decreased exercise capacity was most apparent in decreased workload and decreased oxygen pulse with no change in peak heart rate and comparable efforts as measured by peak RER. Moreover, the severity of decreased exercise tolerance in this study seemed limited, and at a level where most patients would not be aware of it daily. Further studies remain necessary to precisely determine why childhood cancer survivors have a reduced exercise capacity, among combinations of deconditioning over the treatment and recovery period, and subclinical consequences of therapy (such as chest radiation and anthracyclines) on cardiac performance.<sup>45,46</sup> Our results seem to support both systematic evaluation of long-term cancer survivors and systematic fitness or rehabilitation programmes, which have the potential to shift the long-term trajectory of exercise capacity.<sup>43</sup>

**Table 3.** Predictors of  $VO_{2max}$  and VAT in the youth in the remission group.

Variables	$VO_{2max}$ (mL/kg/min)			VAT (mL/kg/min)			
	Description	Univariate analysis	Multivariate analysis (N = 77)	Description	Univariate analysis	Multivariate analysis (N = 77)	
	r	P value	P value				
Age (years)		-0.26	0.03		-0.37	<0.01	0.06
BMI (kg/m <sup>2</sup> )		-0.45	<0.01	<0.01	-0.47	<0.01	<0.01
Cumulated dose of prednisone (mg/m <sup>2</sup> )		-0.10	0.41		-0.14	0.38	
Cumulated dose of anthracyclines (mg/m <sup>2</sup> )		-0.12	0.17		-0.10	0.45	
Number of HCST		-0.11	0.31		-0.14	0.43	
Number of regimens		-0.26	0.04		-0.25	0.07	
Delay between end of treatment and CPET		0.15	0.56		0.14	0.49	
		<b>Mean ± SD</b>	<b>P value</b>	<b>P value</b>	<b>Mean ± SD</b>	<b>P value</b>	<b>P value</b>
Sex	Female	31.6 ± 7.938.4 ± 9.4	<0.01	<0.01	22.7 ± 5.927.5 ± 7.7	<0.01	<0.01
	Male						
Prednisone	No	38.9 ± 7.935.0 ± 10.2	0.41		26.6 ± 6.325.0 ± 8.0	0.35	
	Yes						
Anthracyclines	No	37.5 ± 7.835.6 ± 9.8	0.49		26.8 ± 6.825.5 ± 7.5	0.56	
	Yes						
Radiotherapy	No	37.1 ± 9.334.2 ± 9.6	0.19	0.03	26.1 ± 7.325.3 ± 7.7	0.65	
	Yes						
Total body irradiation	No	36.5 ± 9.534.3 ± 9.3	0.37		25.9 ± 7.325.4 ± 7.8	0.81	
	Yes						
HCST	No	37.4 ± 9.935.2 ± 9.2	0.32	0.10	26.9 ± 7.425.2 ± 7.4	0.35	0.10
	Yes						
Number of HCST	0	37.4 ± 9.935.6 ± 8.633.1 ± 11.9	0.48		26.9 ± 7.425.3 ± 6.624.8 ± 10.8	0.64	
	1						
	≥2						
Type of HCST	No HCST	37.4 ± 9.935.4 ± 8.733.4 ± 12.8	0.53		26.9 ± 7.425.4 ± 7.223.9 ± 8.8	0.57	
	Allogeneic tissue						
	Autologous tissue						
Number of chemotherapy regimen(s)	1	37.6 ± 9.231.0 ± 8.5	<0.01		26.9 ± 7.422.4 ± 6.6	0.02	
	≥2						

Values for 'r' are coefficient correlation. Values are mean adjusted ± SD (standard deviation).

BMI body mass index, HCST hematopoietic stem cell transplantation,  $VO_{2max}$  maximum oxygen uptake, VAT ventilatory anaerobic threshold.

## Study limitation

In this cross-sectional observational study, the paediatric oncologists may have referred the most severe patients for CPET assessment, and further prospective studies are necessary to determine the aerobic capacity in larger and more heterogeneous cohorts. Moreover, this study did not precisely identify the mechanisms behind the decline in physical capacity (cardiotoxicity, type of cancer, level of physical activity, muscle function, etc.) in childhood cancer survivors.

The control group was recruited at the hospital and may not be considered as healthy as if they were recruited from the general population.

Physical capacity has been estimated by CPET parameters, but data on muscular function (handgrip), physical activity (fitness tracker) or patient-reported outcomes (health-related quality of life) have not been collected.



## CONCLUSION

Adolescents and young adults treated for oncologic or nonmalignant disease by chemotherapy, radiotherapy, and/or hematopoietic stem cell transplantation, have lower aerobic capacity compared to matched controls. Female sex, older age, higher BMI, radiotherapy, and hematopoietic stem cell transplantation are associated with a lower  $VO_{2max}$ . The absence of any evidence of heart failure in this population and the association with a low VAT suggest that physical deconditioning plays an important role in determining this impairment. The early screening of aerobic capacity could improve supportive care in addressing patients with impaired cardiopulmonary fitness to cardiac rehabilitation programs.

## DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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