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# Correlation between cardio-pulmonary exercise test variables and health-related quality of life among children with congenital heart diseases☆

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☆ The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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## Abstract

**Background:** Health-related quality of life (HR-QoL) stands as a determinant “patient-related outcome” and correlates with cardio-pulmonary exercise test (CPET) in adults with chronic heart failure or with a congenital heart disease (CHD). No such correlation has been established in pediatric cardiology.

**Methods and results:** 202 CHD children aged 8 to 18 performed a CPET (treadmill  $n = 96$ , cycle-ergometer  $n = 106$ ). CHD severity was stratified into 4 groups. All children and parents filled out the Kidscreen HR-QoL questionnaire. Peak  $VO_2$ , anaerobic threshold (AT), and oxygen pulse followed a downward significant trend with increasing CHD severity and conversely for  $VE/VCO_2$  slope. Self-reported and parent-reported physical well-being HR-QoL scores correlated with peak  $VO_2$  (respectively  $r=0.27$ ,  $p < 0.0001$  and  $r=0.43$ ,  $p < 0.0001$ ), percentage of predicted peak  $VO_2$  ( $r = 0.28$ ,  $p = 0.0001$  and  $r = 0.41$ ,  $p < 0.0001$ ), and percentage of predicted  $VO_2$  at AT ( $r = 0.22$ ,  $p < 0.01$  and  $r = 0.31$ ,  $p < 0.0001$ ). Significant correlations were also observed between several HRQoL dimensions and dead space to tidal volume ratio ( $VD/VT$ ), oxygen uptake efficiency slope (OUES), oxygen pulse but never with  $VE/VCO_2$  slope. The strongest correlations were observed in the treadmill group, especially between peak  $VO_2$  and physical well-being for parents ( $r=0.57$ ,  $p < 0.0001$ ) and self ( $r=0.40$ ,  $p < 0.0001$ ) reported HR-QoL.

**Conclusions:** Peak  $VO_2$  and AT are the two CPET variables that best correlated with HR-QoL in this large pediatric cohort, parents' reports being more accurate. If HR-QoL is

involved as a “PRO” in a pediatric cardiology clinical trial, we suggest using parents related physical well-being HR-QoL scores.

## 1. Introduction

Quality of life (QoL) now stands as a determinant “patient-related outcome” [1] and is frequently used as a secondary endpoint in cardiovascular clinical trials [2]. The “overall life satisfaction” [3] being a quite subjective definition, most studies refer to “health-related quality of life” (HR-QoL) and use multidimensional questionnaires including at least physical, social, psychological, mental, and functional aspects [4]. Validation of these HR QoL instruments is based on good psychometric properties such as validity, reproducibility, and sensitivity to change [3,5,6]. Good correlations between HR-QoL and the severity of the disease are a prerequisite for these clinical studies. The World Health Organization stated that functional capacity explorations best reflect the impact of chronic diseases on QoL [7]. In cardiology, cardio-pulmonary exercise test (CPET) is considered as a “gold standard” to quantify the disease severity. Indeed, in chronic heart failure, CPET (peak VO<sub>2</sub> and VE/VCO<sub>2</sub> slope) correlates with both HR-QoL and prognosis [8–11]. Similar results have been found in adults with CHD [12–16]. However, no data about correlations between HR-QoL and physical capacity from a large CPET cohort is available in pediatric cardiology. This study therefore aimed to identify the correlations between self and parents reported HR-QoL and CPET variables on a cohort of children with CHD, considering the severity of the disease.

## 2. Method

### 2.1. Study design

This prospective cross-sectional study was carried out between April 2009 and October 2011 (18 months) in two tertiary care pediatric and congenital cardiology departments (Montpellier University Hospital, France and Brussels Saint-Luc University Hospital, Belgium). We included all children who performed a complete CPET among our previously reported QoL study [17].

### 2.2. Patients' population

Children aged 8 to 18 years with CHD were prospectively recruited during a regular pediatric cardiology outpatient visit. Children without CHD (cardiac exploration for syncope/faint, thoracic pain, palpitations, dyspnea, etc.) were not eligible. We did not include children with any other severe chronic disease (neuro-developmental disorder, chronic renal or respiratory failures) and children and/or families unable to understand the QoL questionnaire. Children with recent surgical or catheter cardiac intervention (6 months delay) and hospitalized children were temporarily excluded but could be recruited during their following annual outpatient visit.

### 2.3. QoL questionnaires

Right before CPET was performed, children filled in the Kidscreen-52 questionnaire, a generic validated pediatric HR-QoL instrument [18,19]. The Kidscreen is a reliable, valid, sensitive, and conceptually/linguistically appropriate HR-QoL measure in 38 countries/languages [20]. Designed for healthy and chronically ill children and adolescents aged between 8 and 18 years, it measures 10 dimensions: physical wellbeing (5 items), psychological well-being (6

items), moods & emotions (7 items), self-perception (5 items), autonomy (5 items), parent relations & home life (6 items), social support & peers (6 items), school environment (6 items), social acceptance (bullying) (3 items), financial resources (3 items). At the same time, in a separate room, before they learned the results of their child's CPET, parents filled in the Kidscreen-27 proxy questionnaire, which measures 5 dimensions: physical well-being (5 items), psychological well-being (7 items), autonomy & parent relations (7 items), social support & peers (4 items), and school environment(4 items) [21,22]. HR-QoL scores are given for each dimension and vary from 0 (lowest HR-QoL) to 100 (highest HR-QoL).

Table 1 CHD severity classification [32].

Severity class 1	Mild CHD requiring no therapy or effectively treated non-operatively (catheter therapy)
Severity class 2	Moderate CHD requiring no therapy or surgically corrected (curative)
Severity class 3	Surgically treated CHD with significant residua or need for additional surgery
Severity class 4	Complex or severe CHD, uncorrectable or palliated (includes single ventricle)

Table 2 Socio-demographic characteristics.

	CHD total N = 202	CHD		p-value
		France N = 106	Belgium N= 96	
Sex ratio (male/female)	1.9	2.2	1.7	0.34
Age (mean (SD))	12.4 (3.0)	12.2 (2.9)	12.6 (3.2)	0.39
School class				0.38
Elementary school	62 (31%)	34 (33%)	28 (29%)	
Middle school	95 (48%)	51 (49%)	44 (46%)	
High school	26 (13%)	13 (13%)	13 (13%)	
Specialized education	16 (8%)	5 (5%)	11 (12%)	
School level				0.41
Normal	131 (66%)	68 (65%)	63 (66%)	
Advanced	2 (1%)	2 (2%)	0 (0%)	
Repeated	64 (32%)	32 (31%)	32 (34%)	
Dropout	2 (1%)	2 (2%)	0 (0%)	

Table 3 Medical characteristics.

Severity Class	CHD		
	Total N = 202	France N = 106	Belgium N = 96

Class 1	45(23%)	22(21%)	23(24%)
Class 2	28(14%)	13(12%)	15(15%)
Class 3	99(49%)	59(57%)	40(42%)
Class 4	28(14%)	10(10%)	18(19%)
Total	200(100%)	104(100%)	96(100%)
<b>CHD</b>			
Heterotaxy	0(0%)	0(0%)	0(0%)
Anomalies of venous return	4(1%)	2(1%)	2(1%)
Anomalies of the atria and interatrial Communications	14(5%)	5(3.5%)	9(5%)
Anomalies of the atrioventricular junctions and valves	16(5%)	4(3%)	12(7%)
Complex anomalies of the atrioventricular Connections	10(3%)	1(1%)	9(5%)
Functionally univentricular hearts	53(17%)	17(12%)	36(22%)
Ventricular septal defects (VSD)	17(6%)	11(8%)	6(4%)
Anomalies of the ventricular outflow tracts	140(46%)	64(46%)	76(46%)
Anomalies of the extrapericardial arterial Trunks	38(12%)	26(19%)	12(7%)
<b>Congenital anomalies of the coronary Arteries</b>			
Other CHD (HCM, DCM, LQTS, CPVT) <sup>a</sup>	8(3%)	5(3.5%)	3(2%)
<b>Invasive treatment</b>			
Cardiac surgery	144(72%)	77(73%)	67(70%)
Patients with at least one cardiac surgery	76(53%)	50(65%)	26(39%)
1 intervention	30(21%)	19(25%)	11(16%)
2 interventions	38(26%)	8(10%)	30(45%)
≥3 interventions	144(100%)	77(100%)	67(100%)
<b>Total</b>			
Intervention catheter	64(32%)	20(19%)	44(47%)
Patients with at least one intervention	43(67%)	17(85%)	26(59%)
1 intervention	8(13%)	2(10%)	6(14%)
2 interventions	13(20%)	1(5%)	12(27%)
≥3 interventions	64(100%)	20(100%)	44(100%)
Total	144(72%)	77(73%)	67(70%)
<b>Medical treatment</b>			
Patients with at least one treatment	60(30%)	29(28%)	31(32%)
Beta-blockers	11(18%)	7(24%)	4(13%)
Angiotensin-converting enzyme inhibitors	6(10%)	1(3%)	5(16%)
Calcium channel blockers	2(3%)	2(7%)	0(0%)
Diuretics	5(8%)	3(10%)	2(6%)
Oral anticoagulants	14(23%)	6(21%)	8(26%)
<b>Medical device</b>			
Pacemaker	5(2%)	1(1%)	4(4%)
Mechanical valve	1(1%)	1(1%)	0(0%)
Implantable defibrillator	1(1%)	0(0%)	1(1%)

a HCM: hypertrophic cardiomyopathy. DCM: dilated cardiomyopathy. LQTS: long QT syndrome. CPVT: catecholaminergic polymorphic ventricular tachycardia.

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#### 2.4. CPET procedures

Both university hospitals are referral tertiary care pediatric and congenital cardiology centers with regular practice of CPET in the follow-up of children and adults with CHD. Children referred to one of the two CPET laboratories in their routine follow-up were offered to participate to the study. The investigator coordinator of the study participated to CPET in both centers where procedures were harmonized before the study started. Both laboratories used the same following devices: pediatric face masks (Hans Rudolph), calibrated gas analyzer (Oxycon Pro, Jaeger), breath-to-breath measurements software (Windows 98, Jaeger), 12-lead ECG equipment (Cardiosoft, GE Healthcare), pulse oximeter (Nellcor), manual sphygmomanometer with adapted pediatric cuffs.

Systematic spirometry using common gas device (Oxycon Pro, Jaeger) was performed before exercise test with flow volume curve and measurement of forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), FEV1/FVC ratio (FEV1%), with normalization to theoretical values [23].

Both centers used CPET pediatric protocols adapted to CHD children [24]. French center used a cycle-ergometer protocol: 1-min rest, 3-min warm-up (10 to 20W), increments of 10, 15 or 20W each minute, pedaling rate of 60 to 80 rpm, 3-min active recovery (20 watts), 2-min rest. Belgian center used a treadmill modified Bruce protocol: 1 min rest, 3-min warm-up (1 km/h, slope 0%), increments every 2 min in terms of speed (from 2.5 to 10.5 km/h) and slope (from 3 to 18%), 3-min active recovery (2.5 km/h, 3% slope), 2-min rest.

Exercise was pursued until the limit of the child's tolerance was reached, despite verbal encouragement.

The following CPET variables were measured: oxygen uptake ( $\text{VO}_2$ ; ml/kg/min), carbon dioxide production ( $\text{VCO}_2$ ; ml/kg/min), respiratory exchange ratio ( $\text{RER} = \text{VCO}_2/\text{VO}_2$ ), minute ventilation ( $\text{VE}$ ; breaths/min), ventilatory equivalent for oxygen ( $\text{VE}/\text{VO}_2$ ), ventilator equivalent for carbon dioxide ( $\text{VE}/\text{VCO}_2$ ), dead space to tidal volume ratio ( $\text{VD}/\text{VT}$ ), heart rate ( $\text{HR}$ ; beats per minute — bpm), maximum load (watts), and oxygen pulse ( $\text{VO}_2/\text{HR}$ ; ml). For all CPET performed within the study, the same investigator coordinator manually calculated the peak oxygen uptake (peak  $\text{VO}_2$ ), the ventilatory anaerobic threshold (AT) using Beaver's method [25], the ventilation efficiency ( $\text{VE}/\text{VCO}_2$  slope with  $\text{VE} = \text{slope} \times \text{VCO}_2 + b$ ) and the oxygen uptake efficiency slope (OUES with  $\text{VO}_2 = \text{OUES} \times \log_{10} \text{VE} + b$ ) [26–28]. Peak  $\text{VO}_2$  and AT were normalized in percentage of predicted peak  $\text{VO}_2$  using normal values from Wasserman and Cooper [29–31].

#### 2.5. CHD severity

In adult population, heart failure is classically stratified upon the NYHA functional class but this classification does not apply to pediatric cardiology and is rarely used by physicians. We chose to classify our pediatric CHD population into 4 severity groups using previous classification from Uzark et al. (Table 1) [32]. ACC-CHD classification from Houyel et al. was used to define the type of malformation [33].



## 2.6. Formal aspects

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. It was approved by Ethics Committees in France (South Mediterranean IV) and Belgium (UCL Medical School) and was registered on [ClinicalTrials.gov](https://clinicaltrials.gov) (number NCT01202916). Informed consent was obtained from all parents.

## 2.7. Statistics

The study population was described with means and standard deviations (SD) for quantitative variables and with frequencies for qualitative variables. The continuous variable distributions were tested with the Shapiro–Wilk statistic. Quantitative variables were compared with Student's t-test when the distribution was Gaussian, and with the Mann–Whitney test otherwise. For qualitative variables, groups were compared with Chi-square or Fisher test. The two-sided Jonckheere trend test investigated the existence of a trend according to the severity class. ANOVA or Kruskal–Wallis tests were used for comparisons between severity classes. To measure the strength and direction of the relationships between HR-QoL scores and CPET variables, a Pearson or Spearman correlation coefficient was used. And to test the linearity of the relation between the main CPET variables and HR-QoL scores, the normality of residues was tested with Shapiro–Wilk test. Sensitivity analysis for age and gender was performed. Statistical significance was set at 0.05 and analyses were performed using SAS version 9 (SAS Institute, Cary, NC).

Table 4 CPET results: stratification on CHD severity.

	CHD total	Severity class				p-Value <sup>a</sup>
		Class 1	Class 2	Class 3	Class 4	
Age (years)	12.4 ± 3.0	12.4 ± 3.3	12.0 ± 2.8	12.4 ± 2.9	12.9 ± 3.2	0.40
Sex ratio (M/F)	1.9	1.5	1.5	2	3	0.17
Weight (kg)	43.4 ± 15.0	44.5 ± 15.6	45.1 ± 19.0	43.2 ± 14.3	41.2 ± 12.8	0.62
Size (cm)	151.0 ± 16.0	152.1 ± 16.8	148.8 ± 13.6	151.4 ± 16.0	149.9 ± 18.0	0.99
BMI (kg/m <sup>2</sup> )	18.5 ± 3.6	18.6 ± 3.2	19.6 ± 5.3	18.3 ± 3.4	17.9 ± 2.9	0.24
Peak HR (bpm)	174.1 ± 20.4	180.3 ± 15.5	179.3 ± 16.8	172.9 ± 20.5	163.3 ± 25.6	<0.01 <sup>**</sup>
% predicted HR	83.9 ± 10.0	86.8 ± 7.7	86.3 ± 8.1	83.3 ± 9.9	79.0 ± 12.8	<0.01 <sup>**</sup>
Maximum load (watt)	148.5 ± 62.3	157.8 ± 64.8	152.5 ± 66.2	150.0 ± 61.4	125.7 ± 56.9	0.13
Peak RER	1.13 ± 0.11	1.16 ± 0.14	1.12 ± 0.11	1.12 ± 0.10	1.10 ± 0.11	0.08
Peak VO <sub>2</sub> (ml/kg/min)	39.4 ± 8.9	41.3 ± 9.4	42.5 ± 9.7	39.5 ± 7.5	33.0 ± 9.3	<0.001 <sup>***</sup>
% predicted peak VO <sub>2</sub>	91.5 ± 21.5	97.8 ± 21.2	98.1 ± 22.2	91.6 ± 19.1	74.7 ± 21.6	<0.001 <sup>***</sup>
AT (ml/kg/min)	27.4 ± 6.5	28.0 ± 6.8	28.5 ± 7.1	27.4 ± 6.4	25.4 ± 5.3	0.17
% predicted AT	63.5 ± 15.0	66.4 ± 16.3	65.8 ± 16.2	63.4 ± 14.2	57.3 ± 12.6	0.01 <sup>*</sup>
VO <sub>2</sub> /HR <sub>rest</sub> (ml/beat)	3.8 ± 1.6	3.6 ± 1.5	4.1 ± 1.4	3.8 ± 1.6	4.0 ± 1.8	0.48
VO <sub>2</sub> /HR <sub>AT</sub> (ml/beat)	8.3 ± 2.7	8.3 ± 2.8	8.6 ± 2.5	8.5 ± 2.7	7.4 ± 2.9	0.24
VO <sub>2</sub> /HR <sub>peak</sub> (ml/beat)	9.6 ± 3.3	10.0 ± 3.7	9.8 ± 2.9	9.7 ± 3.1	8.2 ± 3.5	0.05 <sup>**</sup>
VE/CO <sub>2</sub> slope	31 ± 6	30 ± 6	30 ± 4	30 ± 6	37 ± 8	0.02 <sup>***</sup>
OUES	732.5 ± 276.5	765.5 ± 349.7	772.1 ± 195.8	739.0 ± 260.7	637.0 ± 261.6	0.20
VD/VT <sub>rest</sub>	19.7 ± 8.9	20.0 ± 7.7	18.3 ± 12.6	19.5 ± 8	21.9 ± 9.5	0.47
VD/VT <sub>AT</sub>	21.1 ± 9.4	21.6 ± 7.9	18.4 ± 9	20.2 ± 9.1	26.2 ± 11.1	0.39 <sup>**</sup>
VD/VT <sub>peak</sub>	21.8 ± 9.6	20.8 ± 9.3	18.6 ± 9.2	19.7 ± 8.3	26.4 ± 12.6	0.22 <sup>**</sup>

Values are presented as mean ± SD.

BMI: body mass index.

<sup>a</sup> Two-sided Jonckheere trend test.

\* p < 0.10 for significant comparison (Chi-square, ANOVA or Kruskal–Wallis test).

\*\* p < 0.05 for significant comparison (Chi-square, ANOVA or Kruskal–Wallis test).

\*\*\* p < 0.01 for significant comparison (Chi-square, ANOVA or Kruskal–Wallis test).

\*\*\*\* p < 0.001 for significant comparison (Chi-square, ANOVA or Kruskal–Wallis test).

## 3. Results

### 3.1. Population

During the study period, 261 CHD children aged 8 to 18 years were referred for CPET; 25 were not eligible because of recent intervention catheter procedure (n= 5), recent surgical

procedure (n= 7), impossibility to answer the questionnaire (Down syndrome n = 5, DiGeorge syndrome n=5), other significant disease (n=3); 35 families refused to participate.

Table 5 CPET results: stratification on gender and type of protocol.

	CHD	GENDER		p-Value	CPET protocol		p-Value
	total N = 202	Female N = 69	Male N = 133		Cycle ergometer N = 106	Treadmill N = 96	
Age (years)	12.4 ± 3.0	12.8 ± 3.1	12.2 ± 3.0	0.14	12.2 ± 2.9	12.6 ± 3.2	0.39
Sex ratio (M/F)	1.9	-	-	-	2.2	1.7	0.34
Weight (kg)	43.4 ± 15.0	43.8 ± 13.5	43.2 ± 15.7	0.41	43.3 ± 15.0	43.8 ± 15.1	0.65
Size (cm)	151.0 ± 16.0	150 ± 15	151 ± 17	0.85	151 ± 16	152 ± 16	0.54
BMI (kg/m <sup>2</sup> )	18.5 ± 3.6	18.9 ± 3.4	18.3 ± 3.7	0.11	18.5 ± 3.7	18.5 ± 3.5	0.96
Peak HR (bpm)	174.1 ± 20.4	176.4 ± 19.2	172.8 ± 21.0	0.23	171.0 ± 20.3	177.8 ± 20.0	<b>0.001</b>
% predicted HR	83.9 ± 10.0	85.2 ± 9.5	83.1 ± 10.2	0.15	82.3 ± 9.8	85.8 ± 9.9	<b>&lt;0.001</b>
Maximum load (watt)	148.5 ± 62.3	139.9 ± 60.0	152.9 ± 63.3	0.13	132.3 ± 43.7	164.1 ± 73.0	<b>0.01</b>
Peak RER	1.13 ± 0.11	1.14 ± 0.10	1.13 ± 0.12	0.34	1.12 ± 0.12	1.14 ± 0.10	0.06
Peak VO <sub>2</sub> (ml/kg/min)	39.4 ± 8.9	34.5 ± 7.5	41.9 ± 8.5	<b>&lt;0.001</b>	39.3 ± 8.3	39.5 ± 9.5	0.89
% predicted peak VO <sub>2</sub>	91.5 ± 21.5	90.5 ± 20.8	92.0 ± 21.9	1.00	92.4 ± 20.3	90.5 ± 22.8	0.54
AT (ml/kg/min)	27.4 ± 6.5	24.0 ± 5.3	29.0 ± 6.4	<b>&lt;0.001</b>	26.9 ± 6.2	27.9 ± 6.7	0.31
% predicted AT	63.5 ± 15.0	63.4 ± 14.5	63.6 ± 15.2	0.92	63.4 ± 14.8	63.7 ± 15.2	0.87
VO <sub>2</sub> /HR <sub>peak</sub> (ml/beat)	3.8 ± 1.6	3.6 ± 1.3	4.0 ± 1.7	0.10	3.8 ± 1.7	3.9 ± 1.4	0.38
VO <sub>2</sub> /HR <sub>AT</sub> (ml/beat)	8.3 ± 2.7	7.3 ± 2.0	8.8 ± 2.9	<b>0.001</b>	8.3 ± 2.8	8.3 ± 2.7	0.91
VO <sub>2</sub> /HR <sub>peak</sub> (ml/beat)	9.6 ± 3.3	8.3 ± 2.3	10.2 ± 3.5	<b>&lt;0.001</b>	9.7 ± 3.3	9.4 ± 3.3	0.60
VE/VC <sub>02</sub> slope	31 ± 6	32 ± 8	31 ± 6	0.84	-	-	-
OUES	732.5 ± 276.5	683.1 ± 241.5	762.5 ± 293.7	0.19	-	-	-
VD/VT <sub>rest</sub>	19.7 ± 8.9	20.7 ± 10.2	19.1 ± 8.2	0.43	18.0 ± 9.7	21.2 ± 7.9	<b>&lt;0.01</b>
VD/VT <sub>AT</sub>	21.1 ± 9.4	22.2 ± 9.0	20.4 ± 9.5	0.19	16.9 ± 7.1	24.5 ± 9.6	<b>&lt;0.001</b>
VD/VT <sub>peak</sub>	21.8 ± 9.6	21.9 ± 10.7	20.1 ± 8.9	0.39	16.8 ± 5.2	24.0 ± 11.1	<b>&lt;0.001</b>

Values are presented as mean ± SD. Significant p-values <0.05 are marked in bold.

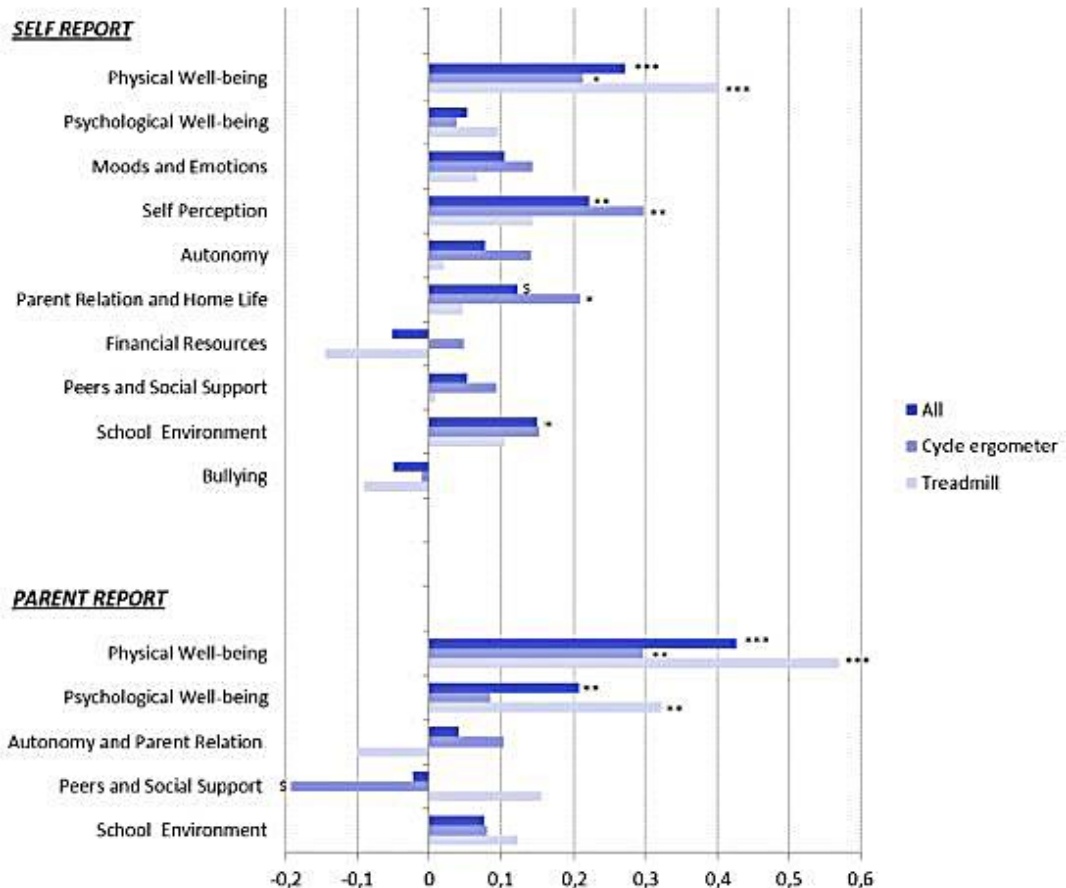


Fig. 1. Correlations between QoL scores (self-reported and parents-reported) and peak VO<sub>2</sub>. Legend: Significant correlation was denoted by \$ for p b 0.10, \* for p b 0.05, \*\* for p b 0.01 and \*\*\* for p b 0.001.



Finally 202 children were included (France  $n = 106$ , Belgium  $n=96$ ). Belgian and French populations were not significantly different for all demographic and school characteristics (Table 2). Simple CHD, such as atrial (ASD) and ventricular (VSD) septal defects (15%), were less represented than complex CHD (Table 3). Sixty-three percent of the patients belonged to severity class 3 or 4. Only 15% of children had never had any treatment before inclusion (no drugs, no cardiac surgery, no intervention catheter); 72% had had at least one cardiac surgery procedure, and 13 (7%) were on drugs only. The two recruiting center populations were comparable for most medical data especially distribution of severity classes, medication and medical devices. However, surgical procedures were significantly more frequent in the Belgian group ( $p < 0.0001$ ).

### 3.2. CPET results

Patients' distribution was homogeneous in terms of age, gender, weight and height between the four severity classes (Table 4) and between CPET procedures (treadmill or cycle ergometer). Few differences were observed between treadmill and cycle ergometer, except for maximum HR, maximum load, and VD/VT ratio (higher values in the treadmill group) (Table 5). Male and female groups were similar in terms of weight, size, and body mass index; male values were higher for peak VO<sub>2</sub> and AT, but after normalization with theoretical peak VO<sub>2</sub>, both variables were not significantly different between males and females (Table 5). A downward trend was observed with increasing CHD severity for peak HR, percentage of predicted HR, peak VO<sub>2</sub>, percentage of predicted peak VO<sub>2</sub>, percentage of predicted VO<sub>2</sub> at AT, peak oxygen pulse, and conversely for VE/VCO<sub>2</sub> slope (Table 4).

### 3.3. Correlations between CPET and HR-QoL scores

The HR-QoL dimension which most correlated to CPET variables was “the physical well-being”, for parents and self-reports and for treadmill and cycle-ergometer procedures. These correlations with the physical well-being scores were particularly significant for three CPET variables: peak VO<sub>2</sub>, percentage of predicted peak VO<sub>2</sub> and percentage of predicted VO<sub>2</sub> at AT (presented in Figs. 1, 2 and 3, respectively).

#### 3.3.1. Self-reported HR-QoL scores (Fig. 4)

The self-reported physical well-being score correlated with peak VO<sub>2</sub> ( $r = 0.27$ ,  $p < 0.001$ ), percentage of predicted peak VO<sub>2</sub> ( $r = 0.28$ ,  $p = 0.0001$ ), and percentage of predicted VO<sub>2</sub> at AT ( $r = 0.22$ ,  $p < 0.01$ ). Such correlations were particularly strong among treadmill CPET for peak VO<sub>2</sub> ( $r = 0.40$ ,  $p < 0.0001$ ), percentage of predicted peak VO<sub>2</sub> ( $r = 0.34$ ,  $p < 0.01$ ) and percentage of predicted VO<sub>2</sub> at AT ( $r = 0.26$ ,  $p = 0.01$ ).

“School environment” was the “non-physical” dimension that correlated to more CPET variables, with low ( $r < 0.3$ ) correlation rates (percentage of predicted peak VO<sub>2</sub>, percentage of predicted VO<sub>2</sub> at AT, OUES, oxygen pulse at AT, oxygen pulse at peak).

Oxygen pulse at peak was the CPET variable that correlated to more non-physical HR-QoL dimensions, with low ( $r < 0.3$ ) correlation rates (financial resources, autonomy, social acceptance).

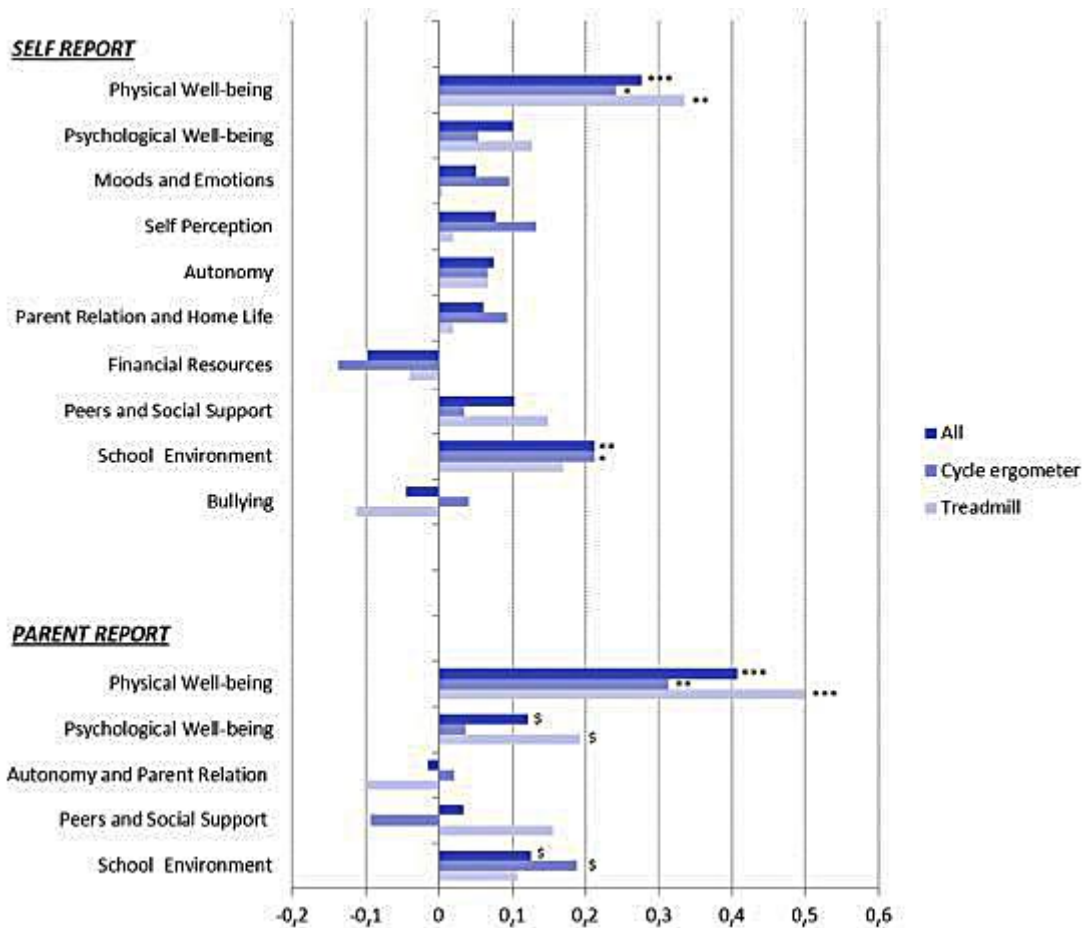


Fig. 2. Correlations between QoL scores (self-reported and parents-reported) and percentage of predicted peak VO<sub>2</sub>. Legend: Significant correlation was denoted by \$ for p < 0.10, \* for p < 0.05, \*\* for p < 0.01 and \*\*\* for p < 0.001.

### 3.3.2. Parents-reported HR-QoL scores (Fig. 5)

The parent-reported physical well-being score correlated to peak VO<sub>2</sub> ( $r = 0.43$ ,  $p < 0.0001$ ), percentage of predicted peak VO<sub>2</sub> ( $r = 0.41$ ,  $p < 0.0001$ ) and percentage of predicted VO<sub>2</sub> at AT ( $r = 0.31$ ,  $p < 0.0001$ ), and negatively correlated with VD/VT at AT ( $r = -0.29$ ,  $p < 0.001$ ) and VD/VT at peak exercise ( $r = -0.30$ ,  $p < 0.0001$ ). Correlations between physical well-being score and VO<sub>2</sub> values were significant with both CPET methods, with particularly high correlation coefficients in the treadmill subgroup: peak VO<sub>2</sub> ( $r = 0.57$ ,  $p < 0.0001$ ), percentage of predicted peak VO<sub>2</sub> ( $r = 0.50$ ,  $p < 0.0001$ ) and percentage of predicted VO<sub>2</sub> at AT ( $r = 0.42$ ,  $p < 0.0001$ ). Moreover, in this treadmill subgroup, negative correlations were observed between parents reported physical well-being scores and VD/VT at AT ( $r = -0.32$ ,  $p < 0.01$ ) and at peak exercise ( $r = -0.32$ ,  $p < 0.01$ ).

Significant but low correlation rates ( $r < 0.3$ ) were observed between parents reported psychological well-being, parents reported school environment and peak VO<sub>2</sub>.

Sensitivity analysis for age and gender showed that the correlations between the physical dimension of the Kidscreen and peak VO<sub>2</sub> remained significant and globally concordant with

the global results excepted for youngest children self-reports (non significant) and for male self-reports ( $r = 0.2$ ) (Table 6).

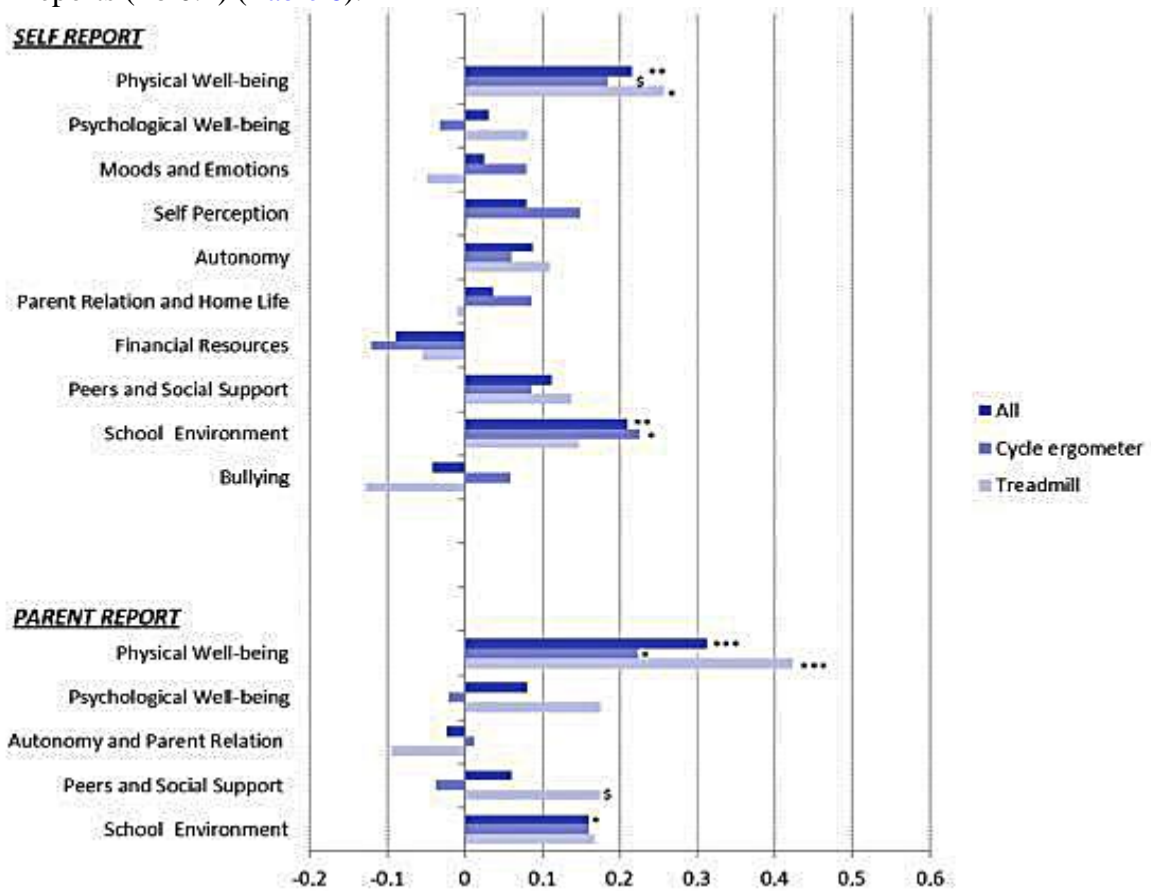


Fig. 3. Correlations between QoL scores (self-reported and parents-reported) and percentage of predicted VO<sub>2</sub> at anaerobic threshold. Legend: Significant correlation was denoted by \$ for  $p < 0.10$ , \* for  $p < 0.05$ , \*\* for  $p < 0.01$  and \*\*\* for  $p < 0.001$ .

#### 4. Discussion

This large pediatric cohort of 202 CHD patients aged 8 to 18 years identified interesting correlations between CPET indices and HR-QoL as reported by both the children themselves and their parents.

The main result lies in the important correlations found between the physical well-being scores of the Kidscreen and the maximum oxygen uptake, with or without normalization. Interestingly, this maximum effort is probably rarely performed in the child's everyday life and is nevertheless related to the HR-QoL which meanwhile mostly reflects daily life. Peak VO<sub>2</sub> is considered as a “gold standard” to objectively measure the physical impairment in adult heart failure population [11]. The fact that we found significantly lower peak VO<sub>2</sub> values with increasing CHD severity reinforces the idea of such an analogy between pediatric and adult cardiology.

Besides peak VO<sub>2</sub>, the anaerobic threshold (AT) was well correlated to the physical dimension of the Kidscreen for both self and parents' reports. Moreover we found significantly lower AT values with increasing CHD severity, suggesting the potential

importance of this variable in pediatric cardiology patients. Low AT in adult population is known to be associated with deconditioning, which may affect many cardiac patients. Therefore, among 4415 CPET performed in adults with CHD, Kempny et al. estimated the AT values to help congenital cardiologists advise patients on activities of daily life, sports participation, and choice of occupation [34]. Besides, adults with CHD and deconditioning are classically eligible to a rehabilitation program aiming to improve physical performances and QoL. However few pediatric centers have such a structured medical care. The correlation found in our study between impaired HR-QoL and low AT among CHD children opens up horizons in pediatric rehabilitation programs. The effects of physical exercise training programs in children and young adults with CHD were recently reviewed: among the 31 published studies only four took the QoL outcome into account [35]. Therefore, when managing transition to adulthood for adolescents with congenital heart diseases [36], the evaluation of the impact of an educational program could use the AT and the HR-QoL before and after rehabilitation as original endpoints. Moreover, it is sometimes difficult to obtain a maximum CPET in the most severe CHD: the AT might then replace the peak VO<sub>2</sub> if not reached.

Our study pointed out the correlations between CPET variable and parents-reported HR-QoL scores, which appeared to be stronger than with their children self-reported scores, especially for the physical dimension. Among the youngest children, parents could identify a significant correlation between peak VO<sub>2</sub> and the physical dimension of the Kidscreen, while children themselves did not. Moreover, some correlations were also present in other dimensions such as the psychological well-being which correlated with peak VO<sub>2</sub> for parents' reports and not for children's. Similarly, some ventilatory parameters such as dead space to tidal volume ratio (VD/VT) correlated to parents reported HR-QoL (physical well-being, school environment) but not to children's reports. Previous QoL studies in pediatric chronic diseases [37–40] and in pediatric cardiology [17,32,41] have shown that proxies underscored HR-QoL compared to the child's own estimation. Our results stated that parents' reported HR-QoL in the physical dimension of the Kidscreen was more related to the actual physical performance of their child as objectively measured by CPET. Moreover, parents seemed to be more accurate in identifying the impact of the CHD on the psychological wellbeing of their child.

This study also considered some other main CPET variables: the VE/ VCO<sub>2</sub> slope and the oxygen pulse. Both are classically associated with prognosis in adult heart failure [9–11] and were interestingly also affected by the severity of the CHD in our pediatric cohort. However, we did not find any correlation between the VE/VCO<sub>2</sub> slope and any HR-QoL dimension. Similarly, the oxygen pulse did not correlate with the physical well-being but with most of the “non physical” dimensions (school, autonomy, financial resources, social acceptance) for self reports only. One more last controversial CPET variable was finally considered: the oxygen uptake efficiency slope (OUES). Some authors have identified it as a reliable CPET variable when peak VO<sub>2</sub> is not reached [26–28]; however in our study, OUES was neither impacted by the severity of the CHD nor related to impaired physical well-being.

When considering the “non-physical” HR-QoL dimensions, we found many correlations between school environment and CPET, for both self and parents' reports. Through these questions related to school, the Kidscreen questionnaire possibly identified some impact of the CHD on these children everyday life. Upon pediatric cardiologists' statements, CHD children might be more brooded by their parents, more stigmatized by their teachers and because of their CHD some of them don't participate to physical activity at school. In most cases, physical activity and sports are authorized under individual pediatric cardiologist's

prescription [42,43], but these barriers to physical activity for youngsters with CHD put them on the sidelines [44]. Therefore, caregivers, parents and teachers need to consider this potential impact of the CHD on school life.

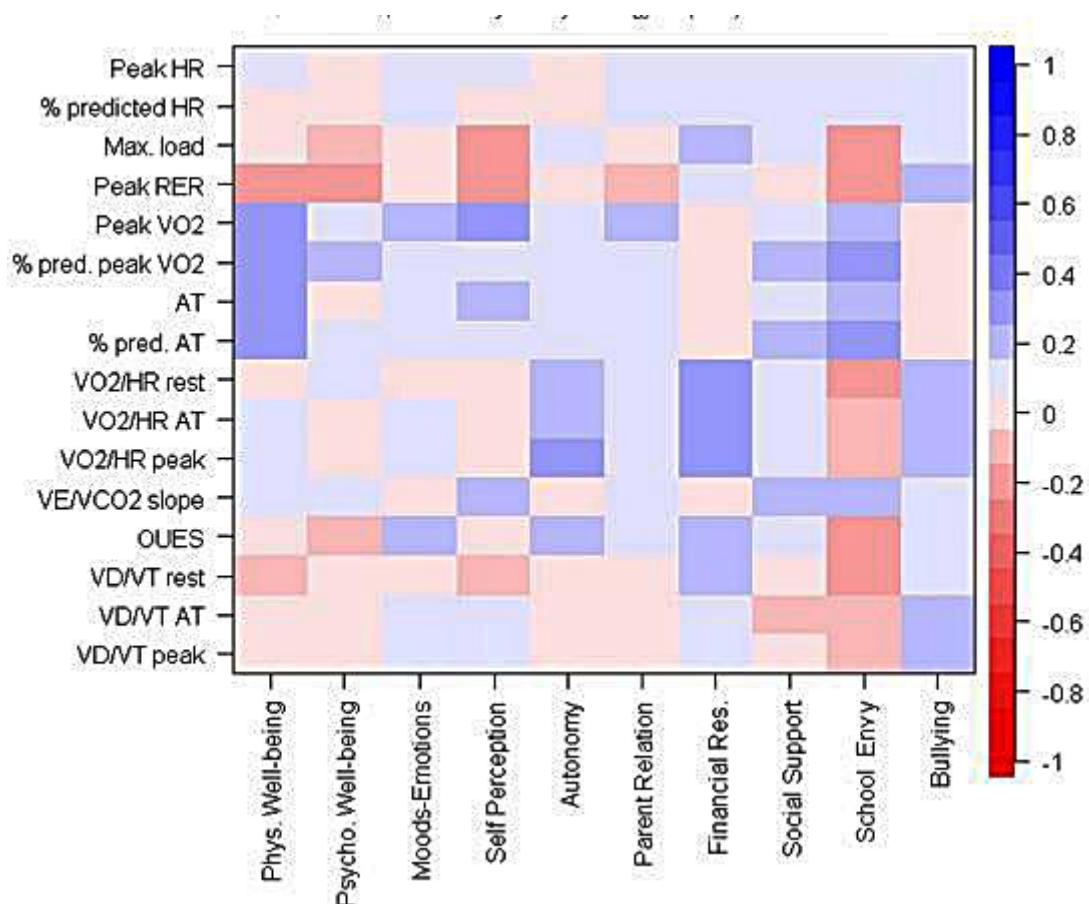


Fig. 4. Correlations between self-reported QoL scores and CEPT. Legend: Correlation matrix between self-reported QoL scores (10 dimensions of the Kidscreen-52) and CPET variables. . (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

#### 4.1. Study limitation

Due to habits of each center on the use of different ergometers, Belgian children performed treadmill CPET and French children performed cycle ergometer CPET. However, the two groups did not differ in terms of age, sex, school characteristics and CHD severity, suggesting limited bias. Moreover, most CPET results were not different between the two methods, especially for the two main variables, i.e. the percentage of predicted oxygen uptake at peak and at anaerobic threshold. Although we cannot overlook a potential center effect, the fact that similar results were found globally and separately in two different populations and Shades of blue indicate increasing positive correlation coefficient; shades of red indicate increasing negative correlation coefficient with two CPET procedures, reinforces the idea of a strong link between the physical well-being HR-QoL dimension and CPET among CHD children. Interestingly, in our cohort, treadmill CPET results were particularly well correlated with HR-QoL dimensions, with a correlation coefficient up to 0.57 between parents-reported



physical dimension and peak VO<sub>2</sub>. However, the design of our study does not allow us to conclude that treadmill best reflects the impact of CHD on the child's HR-QoL. Besides, even if the two cultures are very close, the QoL of French and Belgian children cannot be assimilated.

Parents' reports seemed to identify a correlation between CPET and some non-physical HR-QoL dimensions such as “psychological wellbeing” and “school environment”. We previously showed that these two dimensions were affected by the severity of the CHD in multivariate analysis [17]. Therefore, their association with CPET might only be due to the confounding effect of the severity of the disease. Moreover, it is also possible that children have learned to “cope” with their CHD and don't express any psychological wrong-being [45]. Therefore, even though other dimensions than “the physical well-being” are useful for the follow-up of patients, their use as endpoints in pediatric cardiology clinical trials is subject to many limitations.

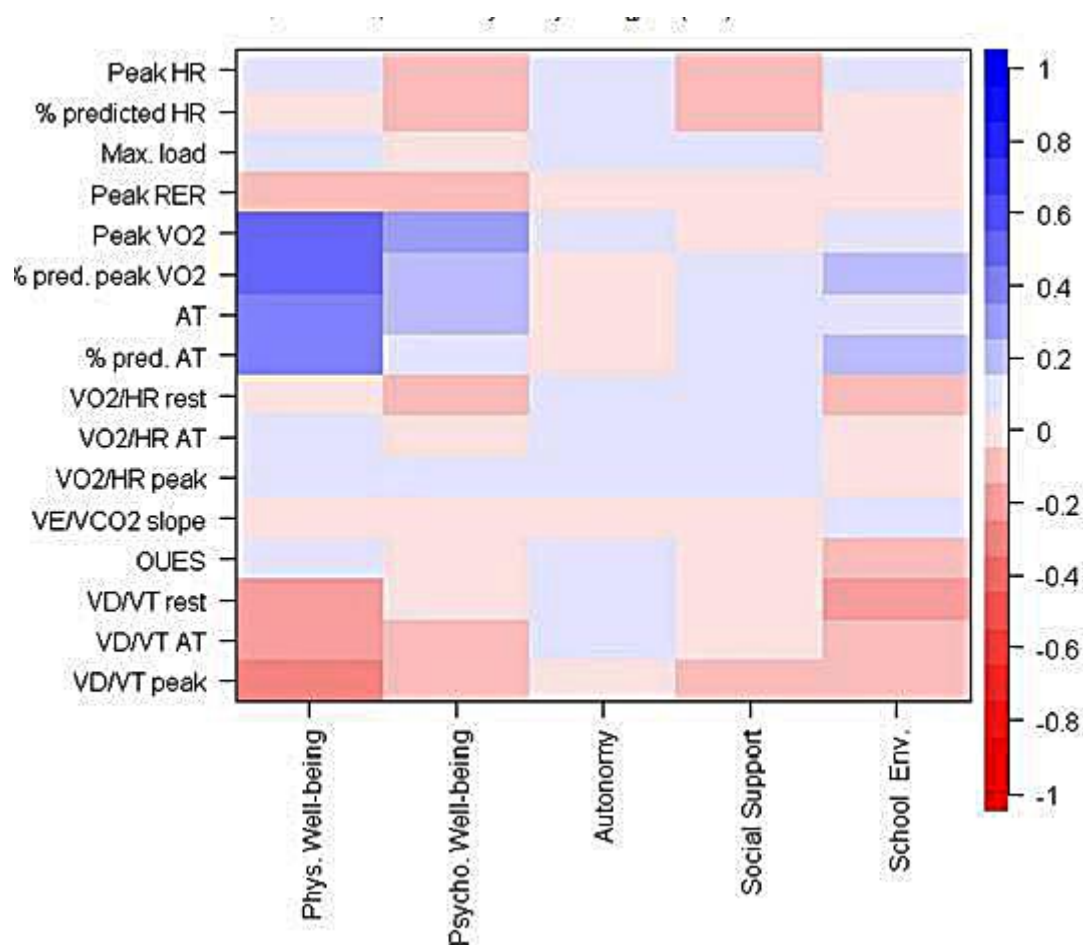


Fig. 5. Correlations between parents-reported QoL scores and CEPT. Legend: Correlation matrix between parents-reported QoL scores (5 dimensions of the Kidscreen-27) and CPET variables. Shades of blue indicate increasing positive correlation coefficient; shades of red indicate increasing negative correlation coefficient. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

## 5. Conclusion

In this large pediatric CHD cohort, peak VO<sub>2</sub> and anaerobic threshold were the two CPET variables that best correlated with the physical wellbeing dimension of the Kidscreen HR-QoL questionnaire as reported by the children themselves or by their parents. These two CPET variables were significantly lowered with increasing CHD severity. CPET variables appeared to be better correlated with parents reported HR-QoL scores than with children self-reported scores. Precisely, parents' reported HR-QoL in the physical dimension of the Kidscreen was well related to the actual physical performance of their child as objectively measured by CPET. If HR-QoL is involved as a “PRO” in a pediatric cardiology clinical trial, we suggest using parents related physical well-being HR-QoL scores. Further studies are necessary to measure the dynamic aspect of HRQoL in the follow-up of children with CHD.

Table 6 Correlations between peak VO<sub>2</sub> and the physical dimension of the Kidscreen.

		Self-reports			Parents' reports		
		r	N	p	r	N	p
Overall		0.27	194	<b>0.0001</b>	0.43	190	<b>&lt;0.0001</b>
Age groups	8–9 years old	0.04	44	0.8	0.38	45	<b>0.01</b>
	10–12 years old	0.33	58	<b>0.01</b>	0.45	58	<b>&lt;0.001</b>
	13–15 years old	0.37	49	<b>0.01</b>	0.41	47	<b>0.005</b>
	16–18 years old	0.26	41	<b>0.04</b>	0.42	39	<b>0.007</b>
Gender	Male	0.18	129	<b>0.04</b>	0.40	126	<b>&lt;0.0001</b>
	Female	0.37	65	<b>0.003</b>	0.39	64	<b>0.001</b>

Significant p-values are marked in bold.

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### *Conflict of interest*

None.

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