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# **Use of new paediatric VO<sub>2</sub>max reference equations to evaluate aerobic fitness in overweight or obese children with congenital heart disease**

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## **Keywords**

Cardiopulmonary exercise test • VO<sub>2</sub> • Overweight • Obesity • Congenital heart defect • Reference values

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## Aims

Overweight and obesity in children with congenital heart disease (CHD) represent an alarming cardiovascular risk. Promotion of physical activity and cardiac rehabilitation in this population requires assessing the level of aerobic fitness ( $VO_{2max}$ ) by a cardiopulmonary exercise test (CPET). Nevertheless, the interpretation of CPET in overweight/obese children with CHD remains challenging as  $VO_{2max}$  is affected by both the cardiac condition and the body mass index (BMI). The new paediatric  $VO_{2max}$  Z-score reference equations, based on a logarithmic function of  $VO_{2max}$ , height and BMI, were applied to overweight/obese children with a CHD and compared with overweight/obese children without any other chronic condition

## Methods and results

In this cross-sectional controlled study, 344 children with a BMI > 85th percentile underwent a CPET (54% boys; mean age  $11.5 \pm 3.1$  years; 100 CHD; 244 controls). Using the  $VO_{2max}$  Z-score equations, aerobic fitness was significantly lower in obese/overweight CHD children than that in matched obese/overweight control children ( $-0.43 \pm 1.27$  vs.  $-0.01 \pm 1.09$ ;  $P = 0.02$ , respectively), and the proportion of children with impaired aerobic fitness was significantly more important in obese/overweight CHD children than in matched controls (17% vs. 6%,  $P = 0.02$ , respectively). The paediatric  $VO_{2max}$  Z-score reference equations also identified specific complex CHD at risk of aerobic fitness impairment (univentricular heart and right outflow tract anomalies). Using Cooper's weight- and height-based linear equations, similar matched-comparisons analyses found no significant group differences.

## Conclusions

As opposed to the existing linear models, the new paediatric  $VO_{2max}$  Z-score equations can discriminate the aerobic fitness of obese/overweight children with CHD from that of obese/overweight children without any chronic disease.

## Registration

ClinicalTrials.gov NCT04815577

## Lay summary

- The new paediatric  $VO_{2max}$  Z-score reference equations found a lower aerobic fitness in obese or overweight children with CHD than that in matched obese or overweight control children and a high proportion of children with impaired aerobic fitness in obese or overweight children with CHD and identified specific complex CHD at risk of aerobic fitness impairment.

- As opposed to Cooper's weight-based or height-based linear equations, the new paediatric  $VO_{2max}$  Z-score equations can discriminate the aerobic fitness of obese or overweight children with CHD from that of obese or overweight children without any chronic disease.

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## Graphical Abstract

### Key question

The interpretation of cardiopulmonary exercise test (CPET) in overweight or obese children with congenital heart disease (CHD) remains challenging as  $VO_{2max}$  is affected by both the cardiac condition and the body mass index (BMI).

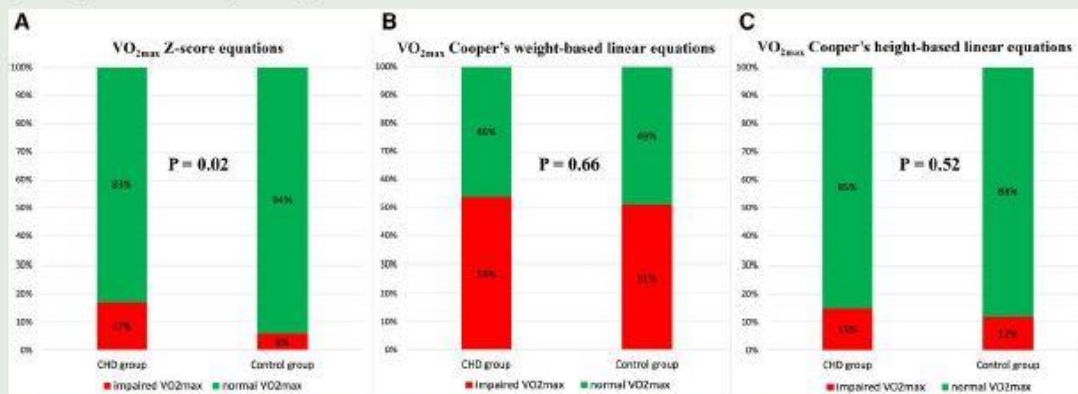
### Key finding

The new paediatric  $VO_{2max}$  Z-score reference equations found a lower aerobic fitness in obese or overweight children with CHD than that in matched obese or overweight control children and a high proportion of children with impaired aerobic fitness in obese or overweight children with CHD and identified specific complex CHD at risk of aerobic fitness impairment.

### Take-home message

As opposed to Cooper's weight-based or height-based linear equations, the new paediatric  $VO_{2max}$  Z-score equations can discriminate the aerobic fitness of obese or overweight children with CHD from that of obese or overweight children without any chronic disease.

Legend: comparison of impaired  $VO_{2max}$  in obese or overweight children with CHD with matched obese or overweight control children without any chronic disease, using the three reference models: paediatric  $VO_{2max}$  Z-score equations (A), Cooper's weight-based linear equations (B), and Cooper's height-based linear equations (C).



## Introduction

Overweight and obesity are an alarming global public health issue, affecting the paediatric population, with a prevalence of 21% in Europe<sup>1</sup> and 32% in North America.<sup>2</sup> Currently, obesity has become one of the most frequent chronic diseases in childhood, which may eventually cumulate to the burden of potential pre-existing chronic health conditions,<sup>3</sup> as in children with congenital heart disease (CHD).<sup>4</sup> Indeed, CHD is the leading cause of congenital diseases,<sup>5</sup> and children with CHD are particularly affected by overweight [e.g. body mass index (BMI) > 85th percentile] or obesity (e.g. BMI > 95th percentile),<sup>6–8</sup> especially in children with low levels of physical activity. Yet, aerobic fitness after surgical or catheter-based repair is expected to be normal or subnormal in most children with CHD.<sup>9,10</sup> However, physical inactivity and sedentary behaviours precipitate many children with CHD into the vicious circle of physical deconditioning,<sup>11</sup> which negatively affects their quality of life.<sup>12</sup> Ultimately, physically inactive children are at higher risk for a sedentary lifestyle in adulthood.<sup>13</sup> As a result, obesity currently affects approximately one-third of adults with lower-complexity CHD, such as ventricular septal defects, leading to substantial cardiovascular morbidity in this population.<sup>14</sup>

The promotion of physical activity and cardiac rehabilitation may contribute to limiting the emergence of obesity in children with CHD.<sup>15</sup> This requires assessing the level of aerobic fitness by a cardiopulmonary exercise test (CPET) to measure the value of maximum oxygen uptake ( $VO_{2max}$ ), which correlates with health-related quality of life in children with CHD.<sup>12</sup>

Indeed,  $VO_{2max}$  reflects children's global health and stands as an independent predictor of all-cause mortality.<sup>16,17</sup>

Nevertheless, the interpretation of CPET in overweight or obese children with CHD remains challenging as  $VO_{2max}$  is affected by both the cardiac condition and the BMI. Moreover, the most widely used  $VO_{2max}$  paediatric reference values until now were based on Cooper's weight- or height-based linear equations and are not adapted to extreme weights.<sup>18,19</sup> Our group has recently established reference Z-score values for paediatric cycloergometer  $VO_{2max}$ , using a logarithmic function of  $VO_{2max}$ , height and BMI. External validity analyses on European and North American paediatric populations have demonstrated that these new reference  $VO_{2max}$  Z-score reference equations were applicable to children with normal and extreme weights.<sup>20</sup>

In this study, we aimed to apply the new paediatric  $VO_{2max}$  Z-score reference equations to a group of overweight and obese children with a CHD, in comparison with a group of overweight and obese children without any other chronic condition. We also intended to evaluate the contribution of these new paediatric  $VO_{2max}$  Z-score reference equations in the population of overweight and obese children with a CHD, in comparison with Cooper's linear equations.

## Methods

### Study design

This cross-sectional study was carried out from November 2010 to March 2020 in two paediatric CPET laboratories (Centre 1: M3C Regional Paediatric and Congenital Cardiology Centre, Montpellier University Hospital, France; Centre 2: Paediatric Cardiology and Rehabilitation Centre, Institut-Saint-Pierre, Palavas-Les-Flots, France).

### Patient population

All children aged 5–18 years, with a BMI > 85<sup>th</sup> percentile, and who underwent a CPET in one of the two centres, were screened. They were recruited after a regular paediatric cardiology outpatient visit. A BMI > 85<sup>th</sup> percentile defined overweight, and a BMI > 95<sup>th</sup> percentile defined obesity, according to the North American growth charts.<sup>21</sup> Two groups were identified: overweight or obese children with CHD ('CHD group') and overweight or obese children without any other chronic condition ('control group'). In both groups, subjects were from the same geographic region (e.g. Occitanie, France).

The CHD group was recruited during a routine cardiac follow-up in the regional CHD expert centre. The anatomic and clinical CHD classification was used to define the type of malformation ('CHD subgroups').<sup>22</sup>

The control group consisted of overweight or obese children, referred to the paediatric cardiology consultation by the regional specialized centre for obesity, before receiving any fitness, dietary or behavioural therapy interventions. The paediatric cardiology consultation belongs to the routine follow-up of these children. These subjects were included in the control group only after a completely normal check-up, including physical examination, electrocardiogram (ECG) and echocardiography. Children with any other chronic disease,

excluding obesity-related conditions (type 2 diabetes, high blood pressure, hyperlipidaemia and obstructive sleep apnoea), were not included in the control group.

### **Paediatric cardiopulmonary exercise test protocol**

Cardiopulmonary exercise test procedures were harmonized in both centres before the start of the study. From 2010 to 2015, the same technical devices were used in both CPET laboratories: paediatric face masks (Hans Rudolph, Shawnee, KS, USA), calibrated gas analyser (Oxycon Pro, Jaeger, Erich Jaeger GmbH, Hoechberg, Germany), breath-to-breath measurement software (Windows 98, Jaeger), 12-lead ECG equipment (CardioSoft, GE Healthcare, Little Chalfont, UK), pulse oximeter (Nellcor, Medtronic, Fridley, MN, USA) and manual sphygmomanometer with adapted paediatric cuffs. From 2015, Centre 1 used the following technical device: calibrated gas analyser (Quark CPET, Cosmed Srl, Pavonina di Albano, Italy), breath-by-breath measurement software (Windows 7–10, Omnia, Cosmed), 12-lead ECG equipment (Norav, Germany) and pulse oximeter (Nonin Medical Inc, Plymouth, MN 55441 USA).

Spirometry using a common gas device was systematically performed before the exercise test, providing a flow-volume curve and measurements of the forced expiratory volume in 1 s (FEV1), the forced vital capacity (FVC) and the FEV1/FVC ratio (FEV1%). Spirometry was repeated at least three times to ensure reproducibility, following the current guidelines in children.<sup>23</sup> Results were expressed as Z-scores from the spirometry reference equations.<sup>24</sup>

Both centres used the same CPET paediatric cycle ergometer protocol adapted to CHD children to obtain a homogeneous incremental overall duration of 8–12 min: a 1-min rest; a 3-min warm-up (20–40 W) in increments of 10, 15, 20 or 30 W each minute; a pedalling rate of 60–80 revolutions per minute; a 3-min active recovery (20 W); and a 2-min rest. The CPET was considered as exhaustive when the following criteria were reached: maximum heart rate  $\geq 80\%$  of maximal age-predicted heart rate (220-age) and inability to maintain a pedalling rate above 60 despite verbal encouragement. When the  $VO_{2max}$  did not reach a plateau, the peak  $VO_2$  was recorded, as usual in children.<sup>25</sup>

### **$VO_{2max}$ reference equations**

Two mathematical models for paediatric cycloergometer  $VO_{2max}$  reference values were used in this study:

(1) The  $VO_{2max}$  reference values defined by Cooper *et al.*<sup>18,19</sup> in 1984 were based on linear equations according to body weight or height, from a cohort of 109 American healthy children with normal weight. The weight-based linear equations are as follows:  $VO_{2max} = [52.8 \times \text{weight (kg)} - 303.4]$  in boys;  $VO_{2max} = [28.5 \times \text{weight (kg)} + 288.2]$  in girls.<sup>18</sup> The height-based linear equations are as follows:  $VO_{2max} = [43.6 \times \text{height (cm)} - 4547.1]$  in boys;  $VO_{2max} = [22.5 \times \text{height (cm)} - 1837.8]$  in girls.<sup>19</sup>

(2) Our group recently established reference Z-score values for paediatric cycloergometer  $VO_{2max}$ , applicable to normal and extreme weights, from a cohort of 1141 healthy children of contemporary anthropometric profile, including 909 subjects in the development cohort and

232 European and North American subjects in the validation cohort.<sup>20</sup> For both sexes, the Z-score equations were modelled using a logarithmic function of  $VO_{2max}$ , height and BMI:

$$\text{Z-score} = \frac{\ln VO_{2max}(\text{mL}/\text{min}) + 4.448 - 2.305 \times \ln_{\text{height}(\text{cm})} - 0.139 \times \ln_{\text{BMI}(\text{kg}/\text{m}^2)}}{0.142}$$

in boys;

$$\text{Z-score} = \frac{\ln VO_{2max}(\text{mL}/\text{min}) + 2.826 - 1.863 \times \ln_{\text{height}(\text{cm})} - 0.285 \times \ln_{\text{BMI}(\text{kg}/\text{m}^2)}}{0.146}$$

in girls.

Impaired  $VO_{2max}$  was defined as  $VO_{2max} < 80\%$  using Cooper's equations<sup>11</sup> and  $VO_{2max} < -1.64$  Z-score using the  $VO_{2max}$  Z-score equations.

### Formal aspects

The study was conducted in compliance with the Good Clinical Practice guidelines and the Declaration of Helsinki principles. Informed consent was obtained from all parents or legal guardians. The use of the CPET database was approved by our Institutional Review Board. The study was registered on ClinicalTrials.gov (NCT04815577).

### Statistics

The study population was described using means and standard deviations (SD) for quantitative variables and frequencies for qualitative variables. Quantitative variables were compared using the Student's *t*-test (sample size > 30 in both groups). For qualitative variables, groups were compared using the chi-squared test or Fisher's exact test. As  $VO_{2max}$  is influenced by gender, age and BMI, and because these anthropometric characteristics differed between the two groups, we reconstituted a posteriori two groups matched according to sex, age ( $\pm 2$  years) and BMI ( $\pm 3$  kg/m<sup>2</sup>). This matching process was performed with a 1:1 ratio using the greedy algorithm. The groups were then compared using conventional statistical tests.

Statistical analyses were performed at the conventional two-tailed  $\alpha$  level of 0.05 using SAS version 9.4 (SAS Institute, Cary, NC, USA).

**Table 1** Cardiopulmonary exercise test parameters in obese or overweight children with congenital heart disease vs. obese or overweight control children without chronic disease

	Overall cohort (n = 344)			Matched cohort (n = 190)		
	CHD group	Non-matched control group	P-value <sup>a</sup>	CHD group	Matched control group	P-value <sup>b</sup>
n	100	244		95	95	
Age (years)	12.1 ± 3.0	11.3 ± 3.1	<b>0.02</b>	11.9 ± 3.0	11.5 ± 2.7	0.41
Height (cm)	153.1 ± 16.2	152.0 ± 15.8	0.54	152.1 ± 15.9	153.4 ± 15.2	0.57
Weight (kg)	59.4 ± 18.4	67.7 ± 29.4	<b>&lt;0.01</b>	58.2 ± 17.9	59.2 ± 18.3	0.70
BMI (kg/m <sup>2</sup> )	24.6 ± 3.7	28.0 ± 7.8	<b>&lt;0.01</b>	24.4 ± 3.7	24.5 ± 3.9	0.86
BMI (percentiles)	92.8 ± 3.9	95.4 ± 4.4	<b>&lt;0.01</b>	92.8 ± 3.9	93.2 ± 4.2	0.14
Sex ratio (male/female)	1.7	1.0	<b>0.04</b>	1.57	1.57	1
FEV1 (Z-score)	-0.39 ± 1.21	0.09 ± 1.28	<b>&lt;0.01</b>	-0.37 ± 1.21	0.21 ± 1.34	<b>&lt;0.01</b>
FVC (Z-score)	-0.21 ± 1.38	0.31 ± 1.37	<b>&lt;0.01</b>	-0.18 ± 1.37	0.41 ± 1.56	<b>&lt;0.01</b>
FEV1/FVC (Z-score)	-0.24 ± 1.20	-0.37 ± 1.14	0.37	-0.25 ± 1.22	-0.26 ± 1.15	0.99
Peak heart rate (b.p.m.)	177.0 ± 17.9	185.6 ± 14.2	<b>&lt;0.01</b>	177.1 ± 17.9	186.4 ± 10.3	<b>&lt;0.01</b>
Percentage of predicted peak heart rate (%)	85.1 ± 8.7	88.9 ± 6.8	<b>&lt;0.01</b>	85.1 ± 8.7	89.4 ± 5.1	<b>&lt;0.01</b>
RER	0.96 ± 0.07	0.96 ± 0.07	0.72	0.96 ± 0.07	0.96 ± 0.06	0.79
VO <sub>2max</sub> (mL/min)	1841 ± 593	1899 ± 553	0.39	1813 ± 576	1952 ± 596	0.1
VO <sub>2max</sub> (mL/kg/min)	31.8 ± 7.0	30.7 ± 8.6	0.22	32.1 ± 7.0	33.8 ± 7.5	0.09
VO <sub>2max</sub> predicts using weight-based Cooper's equations (%)	77.2 ± 21.3	76.2 ± 17.8	0.68	77.1 ± 17.6	81.6 ± 17.6	0.08
VO <sub>2max</sub> <80% using weight-based Cooper's equations (n/%)	56 (56)	134 (55)	0.95	51 (54)	48 (51)	0.66
VO <sub>2max</sub> predicts using height-based Cooper's equations (%)	97.5 ± 22.3	106.4 ± 20.2	<b>&lt;0.01</b>	98.5 ± 22.0	102.2 ± 17.9	0.20
VO <sub>2max</sub> <80% using height-based Cooper's equations (n/%)	16 (16)	22 (9)	0.09	14 (15)	11 (12)	0.52
VO <sub>2max</sub> predicts using Z-score equations (Z-score)	-0.46 ± 1.31	-0.10 ± 1.03	<b>&lt;0.01</b>	-0.43 ± 1.27	-0.01 ± 1.09	<b>0.02</b>
VO <sub>2max</sub> < 1.64 using Z-score equations (n/%)	17 (17)	17 (7)	<b>&lt;0.01</b>	16 (17)	6 (6)	<b>0.02</b>

Values are expressed as mean ± standard deviation. Significant P-values are marked in bold.

BMI, body mass index; CPET, cardiopulmonary exercise test; RER, respiratory exchange ratio; FEV1, normalized forced expiratory volume in 1 s; FVC, normalized forced vital capacity; FEV1/FVC, normalized Tiffeneau index.

<sup>a</sup>Comparison between CHD and non-matched control groups.

<sup>b</sup>Comparison between CHD and matched control groups.

## Results

### Population

During the 10-year study period, a total of 344 children (54% boys, mean age 11.5 ± 3.1 years) with overweight (n = 151) or obesity (n = 193) were enrolled in the study, of which 100 subjects with CHD and 244 control subjects without any other chronic disease. In the CHD group, the proportions of overweight (64%) and obese (36%) children were significantly different to those in the control group (36% and 64%, respectively, P < 0.01). The demographic data are summarized in [Table 1](#).

### Comparison of cardiopulmonary exercise test parameters in obese or overweight children with congenital heart disease vs. controls

Group comparisons are reported in [Table 1](#), presenting the overall sample ( $n = 344$ ) and the matched groups according to sex, age and BMI (95 in the CHD group and 95 in the control group).

The FEV1, FVC and peak heart rate were significantly lower in the CHD group than those in controls, with both non-matched and matched group comparisons.

Using the  $VO_{2max}$  Z-score equations, the aerobic fitness was significantly lower in obese or overweight children with CHD than that in obese or overweight control children, in both non-matched ( $-0.46 \pm 1.31$  vs.  $-0.10 \pm 1.03$ ;  $P < 0.01$ , respectively) and matched ( $-0.43 \pm 1.27$  vs.  $-0.01 \pm 1.09$ ;  $P = 0.02$ , respectively) group comparisons. However, no significant  $VO_{2max}$  differences were observed between CHD and controls using raw values (expressed in mL/min and mL/kg/min) or per cent-predicted values from Cooper's equations, in both non-matched and matched group comparisons, apart from a significantly lower  $VO_{2max}$  in the CHD group than in non-matched controls, using Cooper's height-based equations ( $97.5\% \pm 22.3\%$  vs.  $106.4\% \pm 20.2\%$ ,  $P < 0.01$ , respectively).

### **Impaired aerobic fitness in obese or overweight children with congenital heart disease vs. matched controls**

Using the  $VO_{2max}$  Z-score equations, the proportion of children with impaired aerobic fitness was significantly more important in obese or overweight children with CHD than in matched obese or overweight control children (17% vs. 6%,  $P = 0.02$ , respectively). However, no significant group differences in the proportion of children with impaired aerobic fitness were observed using Cooper's weight-based linear equations (54% vs. 51%,  $P = 0.66$ ) or Cooper's height-based linear equations (15% vs. 12%,  $P = 0.52$ ). These data are reported in [Table 1](#) and [Figure 1](#). Patients with impaired aerobic fitness in CHD and control groups, according to the three  $VO_{2max}$  equations, were also represented using Venn diagrams, to highlight which equations identified the same children ([Figure 2](#)).

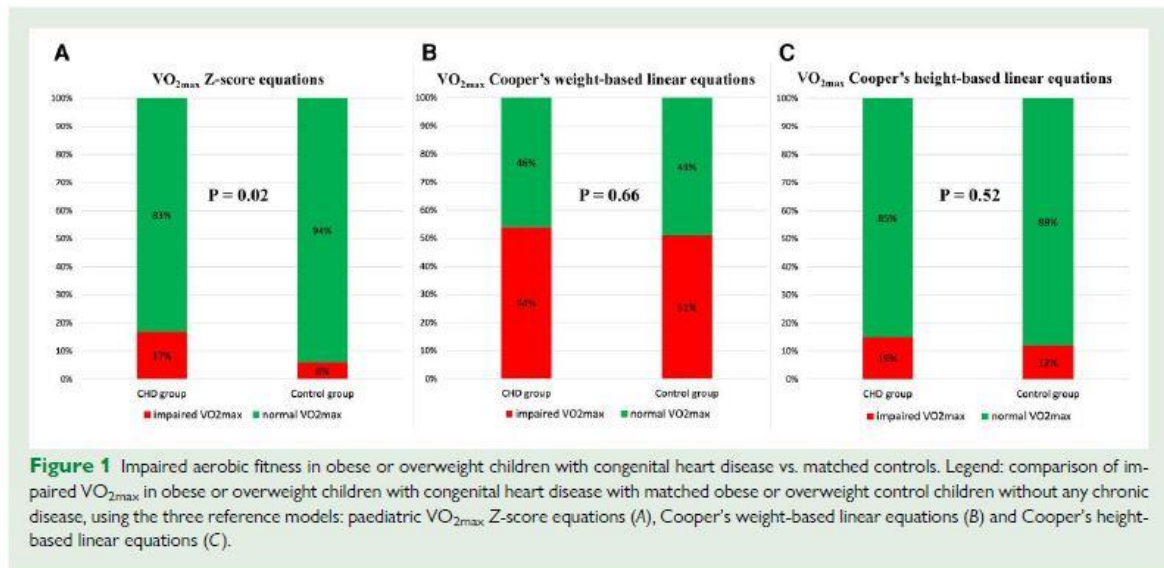
### **Aerobic fitness in congenital heart disease subgroups expressed with the three different $VO_{2max}$ reference equations**

Congenital heart disease subgroups are presented in [Table 2](#). Comparisons were not performed in CHD subgroups with a low number of subjects  $<3$  (e.g. Group 5, complex anomalies of atrioventricular connections; and Group 10, congenital anomalies of the coronary arteries).

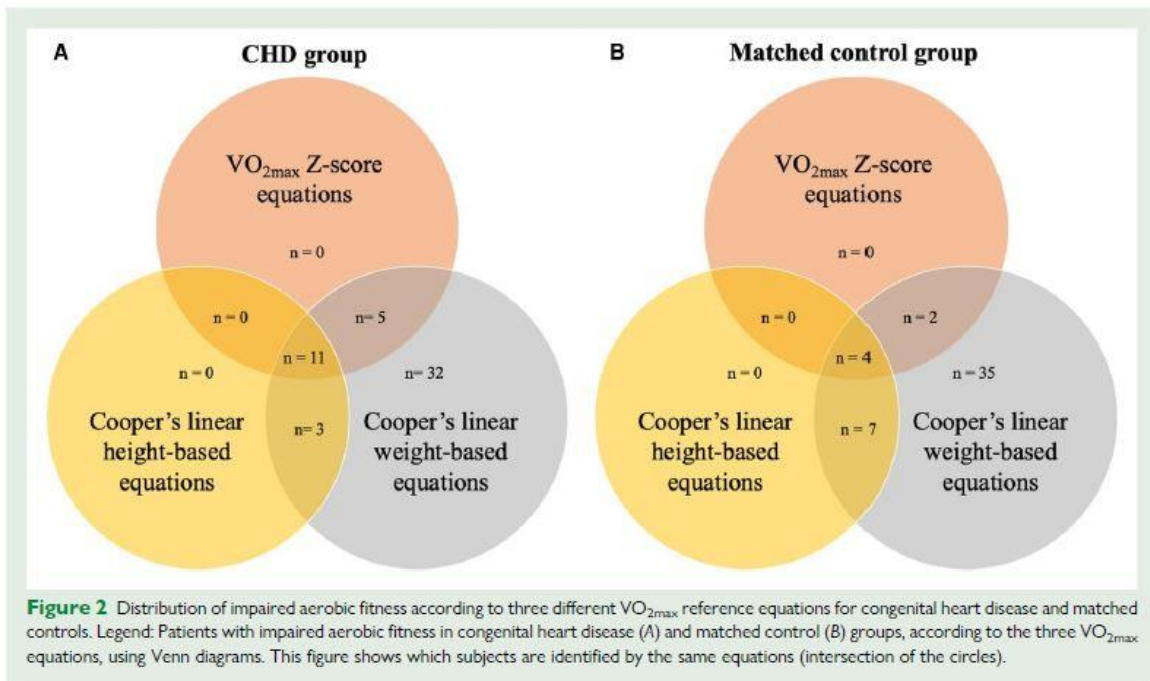
Using the  $VO_{2max}$  Z-score equations, the greatest aerobic fitness impairment was observed in Group 6 (univentricular heart), with a median  $VO_{2max}$  Z-score of  $-1.64$  ( $-2.82$ ;  $-0.31$ ) and Group 8.2 (tetralogy of Fallot, truncus arteriosus, pulmonary atresia and double outlet right ventricle), with a median  $VO_{2max}$  Z-score of  $-1.63$  ( $-2.20$ ;  $-0.23$ ). As illustrated in the [Figure 3](#), the median  $VO_{2max}$  Z-scores ranged between 0 and  $-1.64$  in most CHD subgroups.

Using Cooper's height-based linear equations, the greatest aerobic fitness impairment was observed in Group 8.2, with a median per cent-predicted  $VO_{2max}$  of 81.7% (69.3%; 87.4%), and Group 4 (anomalies of the atrioventricular junctions and valves), with a median per cent-predicted  $VO_{2max}$  of 89.8% (68.2%; 103.9%). As illustrated in the [Figure 3](#), a median per

cent-predicted VO<sub>2max</sub> of ~100% was observed in most CHD subgroups, with a wide distribution of per cent-predicted VO<sub>2max</sub> values in the Group 6 (univentricular heart).



Using Cooper's weight-based linear equations, the greatest aerobic fitness impairment was observed in Group 8.2, with a median per cent-predicted VO<sub>2max</sub> of 62.8% (54.1%; 67.2%), and Group 4, with a median per cent-predicted VO<sub>2max</sub> of 68.1% (47.0%; 82.9%). As illustrated in *Figure 3*, a per cent-predicted VO<sub>2max</sub> under 80% was observed in most CHD subgroups.



## Discussion

This study applied, for the first time, the new paediatric VO<sub>2</sub>max Z-score reference equations on a cohort of 344 children with overweight or obesity, including 100 subjects with CHD and 244 controls, and who underwent a complete CPET assessment of their aerobic fitness.

In this study, the paediatric VO<sub>2</sub>max Z-score reference equations showed a better ability than Cooper's equations to discriminate the aerobic fitness of obese or overweight children with CHD from that of obese or overweight children without any chronic disease. We confirmed that Cooper's weight-based and height-based linear equations struggled to identify any VO<sub>2</sub>max difference between these two groups and therefore were not adapted to children with overweight or obesity. From a general perspective, the use of linear models for reference equations in the paediatric population has been previously criticized, as the relationship between anthropometric and physiological parameters is not strictly linear, especially for extreme ranges of age or weight. Therefore, new mathematical models have emerged in paediatrics, such as lung function Z-score equations<sup>24</sup> or echocardiographic spline equations.<sup>26</sup> Similarly, allometry should be considered to define reference equations for aerobic fitness in children.<sup>27</sup> During growth and pubertal stages, the relationship between VO<sub>2</sub>max and its main determinants, such as total mass, lean mass and height, is not necessarily linear. Physiologically, the oxygen uptake (VO<sub>2</sub>) is a product of cardiac output and peripheral oxygen extraction, and classically, the oxygen extraction capacity of the metabolically active muscle is constant.<sup>28</sup> However, the use of body weight normalization to express aerobic fitness is irrelevant in obesity, as body fat does not reflect metabolically active muscle mass.<sup>27</sup>

Furthermore, this study found that the paediatric VO<sub>2</sub>max Z-score reference equations contributed to a better assessment of aerobic fitness impairment in children with CHD and overweight or obesity than the existing linear models. This result is of great value in the routine follow-up of children with CHD and overweight or obesity, as the existence of a decreased VO<sub>2</sub>max may be related to both the cardiac condition and obesity or overweight. Cardiopulmonary exercise test studies on physical capacity in CHD have highlighted the intricate relation between heart failure,<sup>4</sup> muscular deconditioning,<sup>9</sup> restrictive lung disease<sup>29</sup> and overweight or obesity,<sup>6</sup> which all together contribute to impaired aerobic fitness. Therefore, the expression of VO<sub>2</sub>max using Z-score values adapted to extreme weight can help identify the early onset of aerobic fitness impairment, in order to enrol children with CHD suffering from physical deconditioning in rehabilitation programs, <sup>11,30</sup> and, ultimately, limit cardiovascular risk and mortality in adults with CHD.<sup>14</sup> As previously stated by Cooper *et al.*,<sup>31</sup> 'finding obesity in a child is not a reliable indicator of poor fitness but that testing cardiorespiratory responses to exercise can be used to identify subjects with serious impairment and to individualize therapy'.

In the CHD subgroup analysis, the paediatric VO<sub>2</sub>max Z-score reference equations identified specific complex CHD at risk of aerobic fitness impairment in children with overweight or obesity, such as univentricular heart and complex right outflow tract anomalies. Similar results were previously reported in the literature, in the overall paediatric CHD

population,<sup>9,32</sup> as in children with univentricular heart<sup>33</sup> or tetralogy of Fallot,<sup>34</sup> but without focusing on overweight or obesity. In this study, VO<sub>2max</sub> values in obese or overweight children with univentricular heart were overestimated by Cooper's height-based equations and underestimated by Cooper's weight-based equations, as recently shown in the general paediatric population.<sup>20</sup>

Therefore, access to reliable VO<sub>2max</sub> Z-score reference values for obese or overweight children with complex CHD, e.g. a population particularly concerned with cardiovascular risk, will contribute to avoid misestimating the specific role of the cardiac disease because of overweight or obesity in aerobic fitness impairment. Ultimately, this will help congenital cardiologists define specific therapeutic targets for these patients.

## Study limitation

Several general parameters influencing aerobic fitness were not collected in this study, such as pubertal status, fat-free mass or the level of physical activity.

Various factors related to metabolic syndrome and potentially associated with aerobic fitness were not analysed, such as hyperlipidaemia, hypertension and insulin resistance.

The cut-off value of  $-1.64$  Z-score to define impaired aerobic fitness is based on a statistical approach to define abnormality from normality (5th percentile value). However, further studies remain necessary to determine a clinically meaningful prognostic threshold for these Z-score values.

**Table 2** Aerobic fitness in the congenital heart disease subgroups expressed with the three different VO<sub>2max</sub> reference equations

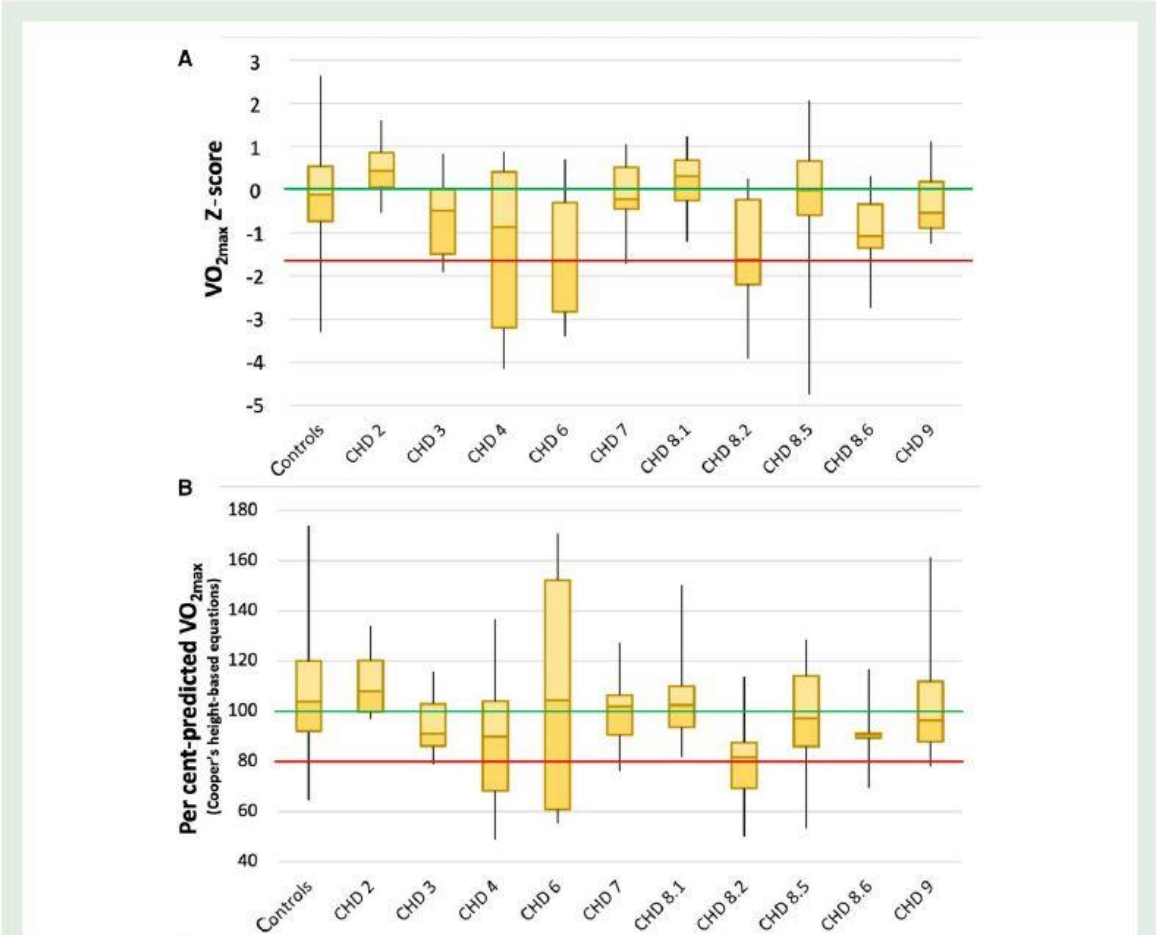
ACC-CHD group		VO <sub>2max</sub> Z-score equations		Cooper's linear height-based equations		Cooper's linear weight-based equations		
		n	VO <sub>2max</sub> Z-score median (Q1; Q3)	Z-score <1.64 (n, %)	Per cent-predicted VO <sub>2max</sub> median (Q1; Q3)	Per cent-predicted VO <sub>2max</sub> <80% (n, %)	Per cent-predicted VO <sub>2max</sub> median (Q1; Q3)	Per cent-predicted VO <sub>2max</sub> <80% (n, %)
2	Anomalies of the venous return	4	0.43 (0.05; 0.86)	0 (0)	108.0 (99.7; 120.2)	0 (0)	94.7 (82.6; 109.2)	1 (25)
3	Anomalies of the atria and interatrial communications	10	-0.49 (-1.49; 0.01)	3 (30)	91.0 (86.0; 102.8)	1 (10)	73.9 (65.8; 80.0)	7 (70)
4	Anomalies of the atrioventricular junctions and valves	6	-0.87 (-3.20; 0.41)	3 (50)	89.8 (68.2; 103.9)	2 (33)	68.1 (47.0; 82.9)	4 (67)
6	Univentricular heart	4	-1.64 (-2.82; -0.31)	2 (50)	104.3 (60.8; 152.2)	2 (50)	68.6 (49.6; 88.1)	2 (50)
7	Ventricular septal defects	13	-0.22 (0.45; 0.52)	1 (8)	101.8 (90.5; 106.3)	1 (8)	82.2 (75.4; 88.7)	6 (46)
8.1	Transposition of the great arteries	18	0.31 (-0.25; 0.69)	0 (0)	102.4 (93.6; 109.9)	0 (0)	76.8 (67.4; 90.5)	11 (61)
8.2	Tetralogy of Fallot; truncus arteriosus; pulmonary atresia; double outlet right ventricle	9	-1.63 (-2.20; -0.23)	4 (44)	81.7 (69.3; 87.4)	4 (44)	62.8 (54.1; 67.2)	8 (89)
8.5	Aortic valve stenosis; Shone syndrome	12	-0.02 (-0.59; 0.66)	1 (8)	97.1 (85.9; 114.1)	1 (8)	75.3 (70.4; 83.0)	7 (58)
8.6	Pulmonary valve stenosis	6	-1.08 (-1.35; -0.34)	1 (17)	90.7 (89.4; 91.2)	1 (17)	80.7 (79.2; 82.1)	2
9	Anomalies of the extrapericardial arterial trunks	15	-0.54 (0.89; 0.18)	0 (0)	96.4 (87.8; 111.8)	2 (13)	81.3 (65.4; 88.8)	6

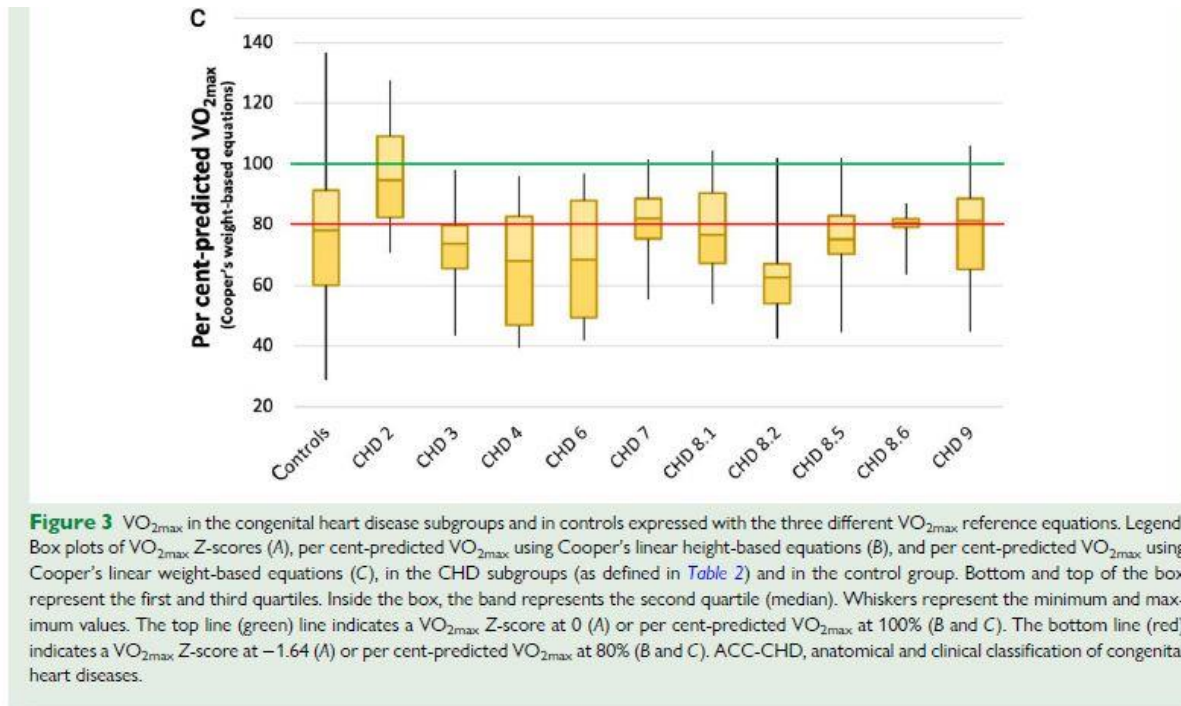
ACC-CHD, anatomical and clinical classification of congenital heart diseases.

## Conclusion

The newly established reference Z-score values for paediatric cycloergometer VO<sub>2max</sub> can discriminate the aerobic fitness of obese or overweight children with CHD from that of obese or overweight children without any chronic disease. These Z-score equations, based on a logarithmic function of VO<sub>2max</sub>, height and BMI, contribute to a better assessment of aerobic fitness impairment in the contemporary population of children with CHD and overweight or

obesity, than the existing linear weight-based or height-based models, especially in the most complex CHD. Considering the increasing prevalence of overweight and obesity in the paediatric population with chronic disease, the results of this study are of importance and in line with the public health-oriented dynamics towards the promotion of physical activity in paediatrics.





### Authors' contributions

P.A., L.K. and A.G. directed, conceptualized and designed the study, enrolled patients, drafted the initial manuscript and reviewed and revised the manuscript. S.M., S.G., A.R. and C.J. enrolled patients and reviewed and revised the manuscript. T.M. supervised the data management, performed the statistical analyses and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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### Conflict of interest:

None declared.

### Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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