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# Reference values of aerobic fitness in the contemporary paediatric population

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## Keywords:

Cardiopulmonary exercise test; Obesity; Paediatrics; VO<sub>2</sub>; Z-score.

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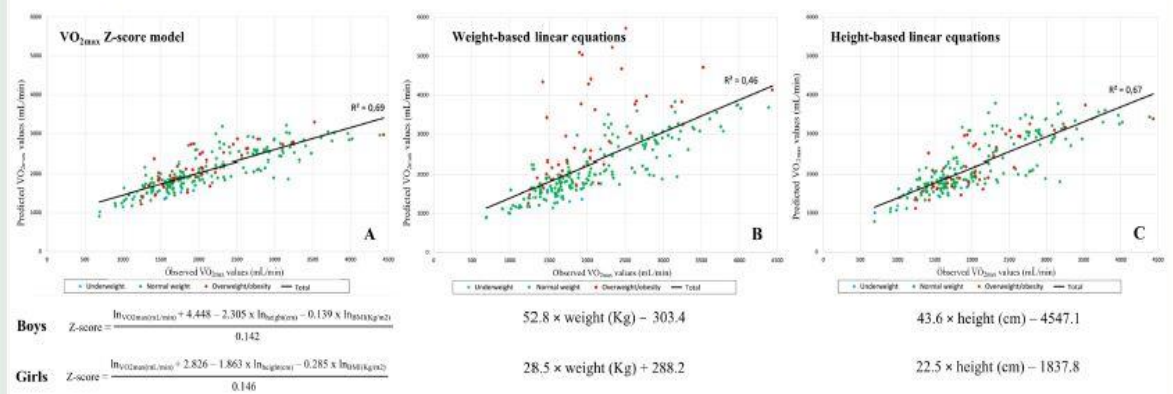
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### Structured Graphical Abstract

**Key Question:** The dissemination of CPET in paediatrics requires valid paediatric  $VO_{2max}$  reference values to define the upper and lower limits of the norm. Existing linear equations may not be appropriate for the contemporary paediatric population, especially for extreme weights.

**Key Finding:** For both genders, the mathematical model using natural logarithms of  $VO_{2max}$ , height, and BMI was the best fit for the data. This Z-score model could be applied to normal and extreme weights and was more reliable than linear equations.

**Take-home Message:** Providing Z-scores to assess aerobic fitness in the paediatric population should be useful in the follow-up of children with chronic diseases.



Legend: the “underweight” group was represented by blue points, the “normal weight” group by green points, and “overweight/obese” group by red points. The figure panels A, B and C represent the correlation between predicted and measured  $VO_{2max}$  values (in mL/min) using the Z-score model, the weight-based linear equations, and the height-based linear equations, respectively.

# Abstract

## **Aims:**

There has been a growing interest in the use of markers of aerobic physical fitness ( $VO_{2max}$  assessed by cardiopulmonary exercise test (CPET)) in the follow-up of paediatric chronic diseases. The dissemination of CPET in paediatrics requires valid paediatric  $VO_{2max}$  reference values to define the upper and lower normal limits. This study aimed to establish  $VO_{2max}$  reference Z-score values, from a large cohort of children representative of the contemporary paediatric population, including those with extreme weights.

## **Methods and results:**

In this cross-sectional study, 909 children aged 5 to 18 years old from the general French population (development cohort) and 232 children from the general German and US populations (validation cohort) underwent a CPET, following the guidelines on high-quality CPET assessment. Linear, quadratic, and polynomial mathematical regression equations were applied to identify the best  $VO_{2max}$  Z-score model. Predicted and observed  $VO_{2max}$  values using the  $VO_{2max}$  Z-score model, and the existing linear equations were compared, in both development and validation cohorts. For both sexes, the mathematical model using natural logarithms of  $VO_{2max}$ , height, and BMI was the best fit for the data. This Z-score model could be applied to normal and extreme weights and was more reliable than the existing linear equations, in both internal and external validity analyses (<https://play.google.com/store/apps/details?id=com.d2l.zscore>).

## **Conclusion:**

This study established reference Z-score values for paediatric cycloergometer  $VO_{2max}$  using a logarithmic function of  $VO_{2max}$ , height, and BMI, applicable to normal and extreme weights. Providing Z-scores to assess aerobic fitness in the paediatric population should be useful in the follow-up of children with chronic diseases.

## **Clinical trial registration:**

ClinicalTrials.gov [NCT04876209](https://clinicaltrials.gov/ct2/show/study/NCT04876209).

# Introduction

Tremendous progress in various paediatric chronic diseases has significantly improved the overall prognosis and transferred the mortality from childhood to adulthood in the most severe conditions.<sup>1</sup> Therefore, the question is currently more about ‘living well’ rather than ‘surviving’ with chronic illness in childhood. Among all determinants of quality of life in children, there has been a growing interest in assessing aerobic physical fitness, assessed by cardiopulmonary exercise test (CPET), in the follow-up of paediatric chronic diseases, such as congenital heart disease,<sup>2,3</sup> cystic fibrosis,<sup>4</sup> or chronic renal failure.<sup>5</sup> Indeed, in the general population, the maximum oxygen uptake ( $VO_{2max}$ ) assessed by CPET is a strong surrogate of physical capacity and an independent predictor of cardiovascular risk.<sup>6</sup> Interestingly, in 1980, the World Health Organization stated that exercise functional tests better reflected health-related quality of life than most examinations at rest.<sup>7</sup> Therefore, in the current context of sedentary lifestyle and physical deconditioning in healthy and chronically ill children,<sup>8</sup> CPET stands as a key examination in cardiovascular rehabilitation in this young population.<sup>9</sup>

Nevertheless, as recently stated by Takken *et al.*, ‘there is still a lot of progress to be made’ in validating reference equations in paediatric CPET.<sup>10</sup> Indeed, the  $VO_{2max}$  reference values defined by Cooper *et al.* in 1984 are based on linear equations according to body weight or height, from a small cohort of 109 American healthy children with normal weight.<sup>11,12</sup> Yet, the prevalence of obesity in the contemporary paediatric population needs to be considered when studying aerobic physical fitness in children nowadays.<sup>13</sup> Moreover, current research on nomograms in paediatrics supports the use of non-linear models,<sup>14</sup> using multiple anthropometric parameters,<sup>15</sup> in order to establish Z-scores from large representative cohorts.<sup>16</sup>

Therefore, the dissemination of CPET in children requires contemporary and valid paediatric reference values for  $VO_{2max}$  to define the upper and lower normal limits. In this study, we aimed to establish  $VO_{2max}$  reference Z-score values, from a large cohort of children representative of the contemporary paediatric population, including extreme weights.

## Methods

### Study design and population

To elaborate  $VO_{2max}$  reference values for the *princeps* study (e.g. the development cohort), we used a French paediatric CPET database, initially generated by pooling all subjects aged <18 years enrolled in previous prospective controlled studies carried out in two paediatric CPET laboratories (Centre 1: M3C Regional Paediatric Cardiology Centre, Montpellier University Hospital, France; Centre 2: Paediatric Cardiology and Rehabilitation Centre, Saint-Pierre Institute, Palavas-Les-Flots, France).<sup>3,9,17–22</sup> We identified all subjects who underwent a complete CPET with a high quality score ( $\geq 10$  points) according to the American Thoracic Society/American College of Chest Physicians (ATS/ACCP) statement,<sup>23</sup> over a period of 10 years (from November 2010 to March 2020).

Children referred for CPET with the following clinical criteria were selected: non-severe functional symptom at rest (murmur, palpitation) or during exercise (chest pain or dyspnoea) and completely normal cardiological check-up, including physical examination, electrocardiogram, and echocardiography. Children with overweight or obesity referred to the CPET laboratory for physical fitness checkup were also eligible for the study. However, children with any other chronic disease, medical condition (cardiac, neurological, respiratory, muscular, or renal), or medical treatment and those requiring any further specialized medical consultation were not eligible.

Anthropometric parameters were collected (sex, age, weight, and height), and body mass index (BMI) percentiles were used to define patient groups: underweight (BMI < 5th percentile), normal weight (BMI between 5th and 84th percentiles), and overweight or obesity (BMI  $\geq$  85<sup>th</sup> percentile).<sup>24</sup>

To perform the external validity study, we used a US paediatric CPET database (Department of Cardiology, Children's Hospital, Boston, USA) and a German paediatric CPET database (Department of Paediatric Cardiology, German Heart Centre, Munich, Germany). All subjects enrolled in the external validity study were selected using the same clinical criteria as for the *princeps* study.

### **CPET procedures**

As previously reported, CPET procedures for children enrolled in the development cohort were harmonized and similar in both laboratories.<sup>3,18–20</sup> We used a single CPET paediatric cycle ergometer protocol adapted to children<sup>25</sup> to obtain a homogeneous incremental overall duration between 8 to 12 min including (i) 1-min baseline; (ii) 3-min warm-up (10 or 20 W), (iii) fixed increments of 10, 15, or 20 W each minute; (iv) pedalling rate of 60 to 80 revolutions per minute, (v) 3-min active recovery (20 W); (vi) 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  $VO_2$  value was collected, as usual in paediatrics.<sup>26,27</sup>

In terms of pulmonary function tests, spirometry was performed before the exercise test, with a flow volume curve, and measurement of the forced expiratory volume in 1 s (FEV1), the forced vital capacity (FVC), and the FEV1/FVC ratio (FEV1/FVC%). The results were expressed as Z-scores from the spirometry reference equations.<sup>16</sup> 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 electrocardiogram (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 devices: calibrated gas analyser (Quark CPET, Cosmed Srl, Pavana 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).

## Formal aspects

The study was conducted in compliance with the Good Clinical Practices and Declaration of Helsinki principles and registered on ClinicalTrials.gov (NCT04876209).

All previous prospective studies used to generate the CPET database were approved by an ethics committee and registered on an international clinical trial registry.<sup>3,18–20</sup> Informed consent was obtained from all parents or legal guardians. The use of the CPET database was approved by the institutional review board of each institution in France, the USA, and Germany.

## Statistics

The study population was described using means and standard deviations (SD) for quantitative variables and with frequencies for qualitative variables. Quantitative variables were compared using Student's *t*-test when the distribution was Gaussian and using the Mann–Whitney U-test otherwise. For qualitative variables, groups were compared using the chi-squared test or the Fisher's exact test.

To identify the best model for the Z-score construction, the  $VO_{2max}$  values were modelled according to the main anthropometric predictors: sex, age, height, weight, BMI, and body surface area (BSA). Three different mathematical regression models were successively applied: a linear model, a quadratic model, and a polynomial model of degree 2.<sup>28</sup> Models with several potential predictors were also evaluated. The models maximizing the Pearson's coefficient of determination (*R*<sup>2</sup>) were identified. To generate a model respecting the condition of homoscedasticity required for the construction of a Z-score, we also evaluated all linear, quadratic, polynomial models with log–log relationships [e.g. modelling the natural logarithm of  $VO_{2max}$  by the natural logarithm of the predictor(s)]. For each sex, we finally selected the model with the highest *R*<sup>2</sup> (e.g. best fit to the data) and the lowest heteroscedasticity in the residuals.<sup>29</sup> The Z-score distribution was described using median, 5th, and 95th percentiles. Under the condition of a standard normal distribution, the expected values of Z-score are 0, –1.64, and 1.64, respectively.

The internal validity of the  $VO_{2max}$  Z-score model was assessed using data of the derivation sample in comparisons with Cooper's weight-based linear equations ( $VO_{2max} = [52.8 \times \text{weight (kg)} - 303.4]$  in boys;  $VO_{2max} = [28.5 \times \text{weight (kg)} + 288.2]$  in girls),<sup>11</sup> and Cooper's height-based linear equations ( $VO_{2max} = [43.6 \times \text{height (cm)} - 4547.1]$  in boys;  $VO_{2max} = [22.5 \times \text{height (cm)} - 1837.8]$  in girls).<sup>12</sup> We estimated the percentage of  $VO_{2max}$  variance (without log transformation) explained by the predicted value of each one of the three models ( $VO_{2max}$  Z-score model, weight-based linear equations, and height based linear equations), using Pearson's *R*<sup>2</sup> coefficient of determination. Differences between predicted and observed  $VO_{2max}$  values using the three models were then calculated and compared using a Student's *t*-test, for each sex and BMI group.

The external validity of the  $VO_{2max}$  Z-score model was assessed using observed  $VO_{2max}$  values from the US and German paediatric CPET databases (validation samples). The predicted values were calculated using the  $VO_{2max}$  Z-score model and Cooper's weight-based and height-based equations. We then used the same method as for the internal validation to compare predicted and  $VO_{2max}$  observed values.

$VO_{2max} < 80\%$  of predicted values, using Cooper's equations,<sup>18</sup> and  $VO_{2max} < -2$  Z-score, using the  $VO_{2max}$  Z-score model, were used as cutoff values to define impaired aerobic fitness.

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

## Results

### Population

#### Development cohort (derivation sample)

During the 10-year study period, a total of 909 children (mean age 11.4 +/- 2.7 years, 477 boys and 432 girls), following the eligibility criteria, were selected from our CPET database and included in the development cohort study to elaborate  $VO_{2max}$  reference values. The number of patients per age groups were  $N = 142$  [5–8 years],  $N = 333$  [9–11 years],  $N = 317$  [12–14 years], and  $N = 117$  [15–18 years]. This study fulfilled 11 of the 14 criteria from the ATS/ACCP statement on highquality CPET assessment ([Appendix 1](#)). The main anthropometric and CPET data of the development cohort are reported in [Table 1](#).

After stratification on BMI, we identified 38 underweight children, 639 children with normal weight, and 232 children with overweight or obesity (81 children with overweight  $\geq 85$ th percentile and 151 children with obesity  $\geq 95$ th percentile). The three BMI groups were similar in terms of age, height, and sex but significantly different in terms of  $VO_{2max}$  in mL/kg/min (underweight > normal weight > overweight/ obesity). These data are summarized in [Supplementary material online, Table S1](#).

No significant differences were observed between the recruiting centres and the technical devices in terms of main demographic and CPET data (after excluding subjects with overweight/obesity, as they were mostly recruited in Centre 1). These data are summarized in [Supplementary material online, Table S2](#).

#### Validation cohort (external validation sample)

A total of 232 children (129 in Germany and 103 in the USA) were included in the validation cohort, of which 111 are girls and 121 boys (mean age 13.9 • } 2.5 years). The subjects from the validation cohort (US and German population) were not significantly different from those from the development cohort, in terms of BMI, sex ratio, peak heart rate, and proportion of children with impaired  $VO_{2max}$  according to Cooper's weight-based equations ([Table 1](#)).



**Table 1** Main anthropometric and CPET data of development and validation cohorts

Sex	Cohort Characteristics	Development cohort		Validation cohort					
		All	All	P <sup>a</sup>	German group	P <sup>b</sup>	US group	P <sup>c</sup>	
All	N	909	232	—	129	—	103	—	
	Age (years)	11.4 ± 2.7	13.9 ± 2.5	<b>&lt;0.01</b>	13.7 ± 2.7	<b>&lt;0.01</b>	14.2 ± 2.2	<b>&lt;0.01</b>	
	Height (cm)	151.2 ± 15.5	162.1 ± 14.1	<b>&lt;0.01</b>	161.3 ± 15.6	<b>&lt;0.01</b>	163.2 ± 11.8	<b>&lt;0.01</b>	
	Weight (Kg)	47.9 ± 21.1	55.4 ± 17.0	<b>&lt;0.01</b>	52.4 ± 15.9	<b>0.02</b>	59.0 ± 17.7	<b>&lt;0.01</b>	
	BMI (Kg/m <sup>2</sup> )	20.3 ± 6.2	20.7 ± 4.5	0.36	19.7 ± 3.3	0.28	21.9 ± 5.5	<b>0.01</b>	
	BMI (percentile)	56.6 ± 30.8	54.8 ± 28.8	0.44	48.2 ± 27.8	<b>&lt;0.01</b>	63.2 ± 28.0	<b>0.04</b>	
	Sex ratio (male/female)	1.1	1.1	0.99	1.1	0.98	1.1	1	
	Peak heart rate (beats per minute)	188.1 ± 8.9	186.8 ± 9.9	0.05	187.4 ± 10.1	0.42	186.0 ± 9.7	<b>0.02</b>	
	Percentage of predicted peak heart rate (%)	90.2 ± 4.4	90.7 ± 4.8	0.18	90.9 ± 4.9	0.12	90.4 ± 4.7	0.69	
	VO <sub>2max</sub> (mL/Kg/min)	40.0 ± 9.4	38.4 ± 9.4	<b>0.02</b>	40.8 ± 8.9	0.36	35.4 ± 9.2	<b>&lt;0.01</b>	
	VO <sub>2max</sub> predicts using weight-based linear equations (%)	99.3 ± 21.7	94.4 ± 20.9	<b>&lt;0.01</b>	100.2 ± 19.0	0.68	87.2 ± 21.1	<b>&lt;0.01</b>	
	VO <sub>2max</sub> <80% using weight-based linear equations (n%)	154 (16.9)	50 (21.6)	0.12	20 (15.5)	0.16	30 (29.1)	<b>&lt;0.01</b>	
	VO <sub>2max</sub> predicts using height-based linear equations (%)	101.2 ± 19.5	94.4 ± 18.1	<b>&lt;0.01</b>	97.5 ± 17.9	<b>0.03</b>	90.4 ± 17.6	<b>&lt;0.01</b>	
	VO <sub>2max</sub> <80% using height-based linear equations (n%)	95 (10.5)	49 (21.1)	<b>&lt;0.01</b>	20 (15.5)	0.12	29 (28.2)	<b>&lt;0.01</b>	
	Girls	N	432	111	—	62	—	49	—
Age (years)		11.5 ± 2.7	13.9 ± 2.6	<b>&lt;0.01</b>	13.6 ± 2.7	<b>&lt;0.01</b>	14.3 ± 2.3	<b>&lt;0.01</b>	
Height (cm)		151.2 ± 14.2	158.9 ± 11.9	<b>&lt;0.01</b>	157.9 ± 13.8	<b>&lt;0.01</b>	160.1 ± 9.1	<b>&lt;0.01</b>	
Weight (Kg)		48.3 ± 19.8	52.8 ± 15.4	<b>0.03</b>	49.9 ± 14.0	0.54	56.4 ± 16.4	<b>&lt;0.01</b>	
BMI (Kg/m <sup>2</sup> )		20.6 ± 6.2	20.6 ± 4.3	0.95	19.6 ± 3.1	0.22	21.7 ± 5.3	0.21	
BMI (percentile)		57.9 ± 30.3	54.8 ± 28.9	0.34	48.7 ± 29.2	<b>0.03</b>	62.6 ± 26.8	0.29	
Peak heart rate (beats per minute)		188.1 ± 8.9	186.6 ± 9.8	0.13	187.3 ± 9.9	0.54	185.7 ± 9.8	0.08	
Percentage of predicted peak heart rate (%)		90.3 ± 4.4	90.6 ± 4.6	0.55	90.8 ± 4.6	0.39	90.3 ± 4.6	0.99	
VO <sub>2max</sub> (mL/Kg/min)		36.1 ± 7.9	34.0 ± 7.5	<b>0.01</b>	35.9 ± 7.3	0.84	31.6 ± 7.2	<b>&lt;0.01</b>	
VO <sub>2max</sub> predicts using weight-based linear equations (%)		101.8 ± 19.1	98.6 ± 21.0	0.12	103.3 ± 21.0	0.55	92.6 ± 19.7	<b>&lt;0.01</b>	
VO <sub>2max</sub> <80% using weight-based linear equations (n%)		55 (12.7)	20 (18.0)	0.20	8 (12.9)	1	12 (24.5)	<b>0.04</b>	
VO <sub>2max</sub> predicts using height-based linear equations (%)		104.4 ± 17.4	99.1 ± 19.2	<b>&lt;0.01</b>	101.1 ± 18.5	0.18	96.6 ± 19.9	<b>&lt;0.01</b>	
VO <sub>2max</sub> <80% using height-based linear equations (n%)		19 (4.4)	17 (15.3)	<b>&lt;0.01</b>	7 (11.3)	0.04	10 (20.4)	<b>&lt;0.01</b>	
Boys		N	477	121	—	67	—	54	—
		Age (years)	11.2 ± 2.6	13.9 ± 2.5	<b>&lt;0.01</b>	13.8 ± 2.7	<b>&lt;0.01</b>	14.1 ± 2.2	<b>&lt;0.01</b>
	Height (cm)	151.3 ± 16.6	165.1 ± 15.2	<b>&lt;0.01</b>	164.4 ± 16.7	<b>&lt;0.01</b>	165.9 ± 13.2	<b>&lt;0.01</b>	
	Weight (Kg)	47.5 ± 22.3	57.8 ± 18.2	<b>&lt;0.01</b>	54.8 ± 17.3	<b>0.01</b>	61.4 ± 18.7	<b>&lt;0.01</b>	
	BMI (Kg/m <sup>2</sup> )	20.0 ± 6.2	20.8 ± 4.7	0.19	19.7 ± 3.4	0.74	22.1 ± 5.7	<b>0.02</b>	
	BMI (percentiles)	55.4 ± 31.2	54.9 ± 28.9	0.87	47.8 ± 26.7	0.06	63.6 ± 29.4	0.06	
	Peak heart rate (beats per minute)	188.2 ± 8.8	187.0 ± 10.0	0.19	187.6 ± 10.3	0.59	186.2 ± 9.7	0.13	
	Percentage of predicted peak heart rate (%)	90.1 ± 4.5	90.7 ± 5.0	0.20	91.0 ± 5.2	0.19	90.5 ± 4.8	0.58	
	VO <sub>2max</sub> (mL/Kg/min)	43.5 ± 9.3	42.4 ± 9.2	0.26	45.3 ± 7.9	0.13	38.8 ± 9.6	<b>&lt;0.01</b>	
	VO <sub>2max</sub> predicts using weight-based linear equations (%)	97.1 ± 23.6	90.6 ± 20.2	<b>&lt;0.01</b>	97.2 ± 16.6	0.97	82.4 ± 21.3	<b>&lt;0.01</b>	
	VO <sub>2max</sub> <80% using weight-based linear equations (n%)	99 (20.8)	30 (24.8)	0.40	12 (17.9)	0.70	18 (33.3)	0.05	
	VO <sub>2max</sub> predicts using height-based linear equations (%)	98.3 ± 20.8	90.0 ± 16.0	<b>&lt;0.01</b>	94.3 ± 16.9	0.08	84.8 ± 13.1	<b>&lt;0.01</b>	
	VO <sub>2max</sub> <80% using height-based linear equations (n%)	76 (15.9)	32 (26.4)	<b>0.01</b>	13 (19.4)	0.59	19 (35.2)	<b>&lt;0.01</b>	

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

BMI, body mass index; CPET, cardiopulmonary exercise test.

<sup>a</sup>Comparison between the 'development cohort' and 'validation cohort' (German and US groups).

<sup>b</sup>Comparison between the 'development cohort' and 'German group'.

<sup>c</sup>Comparison between the 'development cohort' and 'US group'.

## VO<sub>2</sub>max Z-score model generated from the development cohort

For both sexes, the mathematical model using natural logarithms of VO<sub>2</sub>max, height, and BMI was the best fit for the data.

In female subjects, the equation was:

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

This equation determined 69% of the variability of the VO<sub>2</sub>max logarithm ( $R^2 = 0.69$ ). The median, 5th, and 95th Z-score percentiles were  $-0.05$ ,  $-1.65$ , and  $1.73$ , respectively.

In male subjects, the equation was:

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

This equation determined 78% of the variability of the VO<sub>2</sub>max logarithm ( $R^2 = 0.78$ ). The median, 5th, and 95th Z-score percentiles were  $0.01$ ,  $-1.73$ , and  $1.72$ , respectively.

The distribution of VO<sub>2</sub>max Z-score percentiles according to sex and BMI groups is reported in [Table 2](#).

## Comparison of the Z-score model to Cooper's equations

### *Development cohort (derivation sample)*

In the development cohort, the predicted values using the VO<sub>2</sub>max Z-score model explained 65% ( $R^2 = 0.65$ ) of the variability of the observed VO<sub>2</sub>max values in girls and 75% ( $R^2 = 0.75$ ) of the variability in boys. Cooper's weight-based linear equations explained 47% ( $R^2 = 0.47$ ) of the variability in girls, and 44% ( $R^2 = 0.44$ ) in boys. Cooper's height-based linear equations explained 57% ( $R^2 = 0.57$ ) of the variability in girls and 73% ( $R^2 = 0.73$ ) in boys.

Absolute differences between predicted and measured VO<sub>2</sub>max values were systematically lower using the Z-score model than using Cooper's weight-based equations, except for the subgroup of boys with normal weight for which no significant difference was observed between the two models. Absolute differences between predicted and measured VO<sub>2</sub>max values were lower using the Z-score model than those when using Cooper's height-based equations, except for the subgroup of girls with normal weight for which no significant difference was observed between the two models ([Table 3](#)).

The distribution of  $\text{VO}_{2\text{max}}$  values using the Z-score model was centred around zero Z-score for all weight ranges (*Figure 1, panel A*), whereas the distribution of  $\text{VO}_{2\text{max}}$  values using Cooper's weight-based equations was not centred around 100% of the predicted  $\text{VO}_{2\text{max}}$  for extreme weights (*Figure 1, panel B*), and the distribution of  $\text{VO}_{2\text{max}}$  values using Cooper's height-based equations tended to be above 100% of the predicted  $\text{VO}_{2\text{max}}$  for subjects with normal weights and overweight or obesity (*Figure 1, panel C*).

### **Validation cohort (external validation sample)**

In the validation cohort (German and US groups), the predicted values  $\text{VO}_{2\text{max}}$  Z-score model explained 50% ( $R^2 = 0.50$ ) of the variability of the observed  $\text{VO}_{2\text{max}}$  values in girls and 65% ( $R^2 = 0.65$ ) in boys, whereas Cooper's weight-based equations explained 34% ( $R^2 = 0.34$ ) of the variability in girls and 34% ( $R^2 = 0.34$ ) in boys, and Cooper's height-based equations explained 51% ( $R^2 = 0.51$ ) of the variability in girls and 65% ( $R^2 = 0.65$ ) in boys.

Absolute differences between predicted and measured  $\text{VO}_{2\text{max}}$  values were systematically lower using the Z-score model than using Cooper's weight-based equations, except for subgroup of boys with normal weight, the difference between predicted and measured  $\text{VO}_{2\text{max}}$  values being lower using Cooper's weight-based equations than that when using the Z-score model. However, the mean difference between the two models (<15 mL/min) was not clinically relevant. Absolute differences between predicted and measured  $\text{VO}_{2\text{max}}$  values were lower using the Z-score model than using Cooper's height-based equations for boys, higher for girls with overweight or obesity, and similar for girls with normal weight (non-clinically relevant difference of 3 mL/min) (*Table 4*).

The correlation between predicted and observed  $\text{VO}_{2\text{max}}$  was better using the Z-score model ( $R^2 = 0.69$ ) (*Figure 2, panel A*) than that when using Cooper's weight-based equations ( $R^2=0.46$ ) (*Figure 2, panel B*), but nearly equivalent to Cooper's height-based equations ( $R^2=0.67$ ) (*Figure 2, panel C*).

## **Discussion**

From a development cohort of 909 healthy children aged 5 to 18 years who underwent a cycloergometer CPET, this study defined paediatric reference Z-score values of  $\text{VO}_{2\text{max}}$ . The most suitable which can be applied to normal and extreme weights, and was validated by a validation cohort including 232 German and American healthy children.

In this study, the population from the development cohort was representative of the general contemporary paediatric population, with a balanced sex ratio and a 25% proportion of overweight or obese children, which is in line with the 30% prevalence of overweight or obesity in the European epidemiological data.<sup>13</sup> Similarly, the population from the validation cohort was also representative of the general contemporary paediatric population. The BMI was higher in the US group, with a 27% proportion of obesity, which reflects the current US epidemiological data.<sup>30</sup> The German group was similar to the development cohort in terms of BMI, as expected in a paediatric European population. From a general perspective, the increasing prevalence of overweight in children with chronic diseases, as observed for example in congenital heart disease, made it crucial to better assess aerobic fitness in this population.<sup>31</sup> However, aerobic fitness in obese vs. non-obese children has been scarcely

reported, as addressed by the literature review from Hansen *et al.*, which concluded that cardiopulmonary anomalies during maximal exercise test in obese adolescents remain uncertain.<sup>32</sup> At the opposite, many children with chronic diseases are affected by growth retardation, which may negatively impact their exercise capacity. Therefore, this study will enable, for the first time, interpretation of aerobic physical fitness in children with chronic illness and low or high BMI, using  $VO_{2max}$  reference values adapted for extreme weight paediatric subjects.

**Table 2**  $VO_{2max}$  Z-score distribution in terms of sex and BMI (development cohort)

Cohorts	Sex	BMI group	N	5th percentile	25th percentile	Median	75th percentile	95th percentile
Development cohort	Girls	All	432	-1.65	-0.63	-0.05	0.59	1.73
		Underweight	17	-2.07	-0.65	-0.07	0.30	0.67
		Normal weight	299	-1.45	-0.60	-0.03	0.66	1.81
		Overweight/obesity	116	-1.67	-0.65	-0.10	0.40	1.67
	Boys	All	477	-1.73	-0.68	0.01	0.71	1.72
		Underweight	21	-1.49	-1.35	-0.60	-0.24	0.76
		Normal weight	340	-1.56	-0.49	0.13	0.67	1.57
		Overweight/obesity	116	-1.62	-0.78	-0.12	0.68	1.68

BMI, body mass index.

**Table 3** Difference comparisons between observed and predicted  $VO_{2max}$  values in the development cohort

Sex	BMI group	N	$VO_{2max}$ difference (mL/min) using the Z-score model	$VO_{2max}$ difference (mL/min) using Cooper's weight-based linear equations	$P^a$	$VO_{2max}$ difference (mL/min) using Cooper's height-based linear equations	$P^b$
Girls	All	432	-20.2 ± 253.9	26.1 ± 410.8	<b>&lt;0.01</b>	-75.7 ± 278.8	<b>&lt;0.01</b>
	Underweight	17	42.0 ± 144.5	-175.6 ± 175.4	<b>&lt;0.01</b>	127.2 ± 139.1	<b>&lt;0.01</b>
	Normal weight	299	-34.1 ± 253.9	-111.2 ± 245.0	<b>&lt;0.01</b>	-37.9 ± 271.3	0.30
	Overweight/obesity	116	7.8 ± 264.0	409.5 ± 519.1	<b>&lt;0.01</b>	-202.5 ± 268.2	<b>&lt;0.01</b>
Boys	All	477	-22.9 ± 311.3	272.1 ± 895.6	<b>&lt;0.01</b>	116.1 ± 371.9	<b>&lt;0.01</b>
	Underweight	21	130.6 ± 189.0	-222.0 ± 195.6	<b>&lt;0.01</b>	261.9 ± 321.6	<b>&lt;0.01</b>
	Normal weight	340	-43.5 ± 301.3	-34.8 ± 303.6	0.21	120.3 ± 362.1	<b>&lt;0.01</b>
	Overweight/obesity	116	9.5 ± 347.4	1260.9 ± 1316.3	<b>&lt;0.01</b>	77.7 ± 403.1	<b>&lt;0.01</b>

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

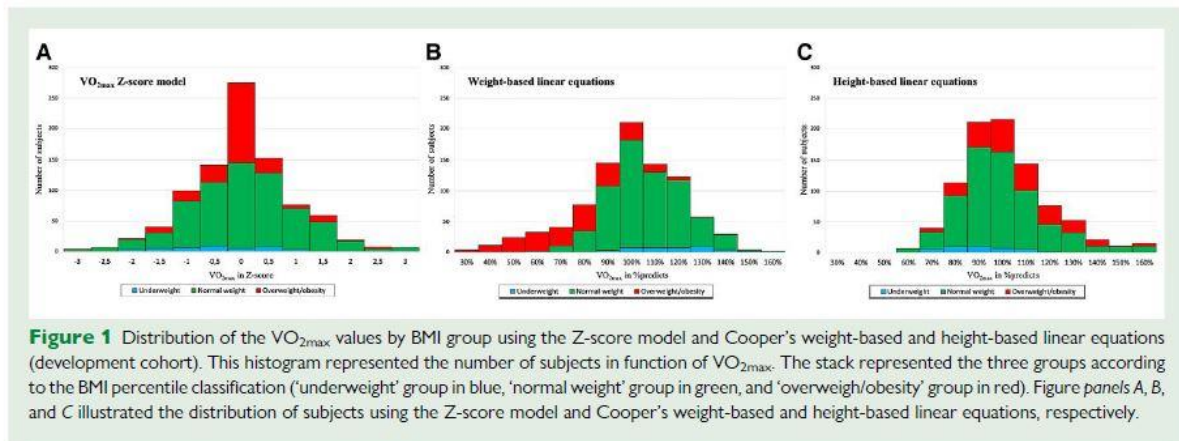
BMI, body mass index.

<sup>a</sup>Comparison between the Z-score model and Cooper's weight-based linear equations using signed rank test.

<sup>b</sup>Comparison between the Z-score model and Cooper's height-based linear equations using signed rank test.

This study established reference Z-score equations for aerobic fitness in children, derived from a non-linear mathematical model using natural logarithms of  $VO_{2max}$ , height, and BMI. Indeed, 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>16</sup> or echocardiographic spline equations.<sup>14</sup> Similarly, allometry should be considered to define reference equations for aerobic fitness in children,<sup>15</sup> and during growth and pubertal stages, the relationship between  $VO_{2max}$  and its main factors, such as total mass, lean mass, and height, is not necessarily linear. As a result, in this study, the non-linear

$VO_{2max}$  Z-score model was clearly superior to Cooper's weight-based linear equations to define the normal limits, from both internal and external validity analyses. Moreover, the Z-score model also seemed more appropriate than Cooper's height-based equations, although its superiority in external validity was more moderate. This highlights the importance to consider height as a major anthropometric parameter of aerobic fitness in paediatrics.



This study intended to satisfy a high methodological quality level and fulfilled 11 of the 14 criteria from the ATS/ACCP statement on CPET,<sup>23</sup> which is better than previous reports.<sup>10</sup> Moreover, the use of an external validation cohort with US and European subjects avoided overfitting the model. From a cohort of 228 healthy children aged 12 to 17, Blanchard *et al.* reported Z-score values for aerobic fitness in children, but no external validation was performed.<sup>33</sup> In our study, a large number of children were enrolled, 909 subjects in the development cohort and 232 subjects in the validation cohort, covering a wide range of ages from 5 to 18 years old. Previous studies on  $VO_{2max}$  reference values in paediatrics included <300 subjects each, enrolled only normal weight children, and covered much more selective age groups.<sup>10</sup>

Providing Z-scores in exercise physiology for the paediatric population will be useful in clinical practice to determine the  $VO_{2max}$  lower normal limit, the pathological threshold defining impaired exercise capacity, and, most importantly, children eligible for rehabilitation programs.<sup>9</sup> The following open-source application can be used to calculate the  $VO_{2max}$  Z-score: <https://play.google.com/store/apps/details?id=com.d2l.zscore>.

### Study limitation

Several parameters influencing aerobic fitness were not collected in this study, such as lean mass, pubertal status, or the level of physical activity. Moreover, subjects enrolled in the study were not community based. We had initially considered drawing lots of schools to identify volunteers to perform a CPET, as in our previous paediatric studies on patient-reported outcomes.<sup>2,34</sup> However, we were concerned that a large proportion of child volunteers would be athletes.

The impact of ethnic variation on body fat and muscle mass has not been investigated because of restrictive French laws on the assessment of ethnicity in clinical research.

**Table 4** Difference comparisons between predicted and measured  $VO_{2max}$  values in the validation cohort

Sex	Validation cohort	BMI classification	N	$VO_{2max}$ difference (mL/min) using the Z-score model	$VO_{2max}$ difference (mL/min) using Cooper's weight-based linear equations	$P^a$	$VO_{2max}$ difference (mL/min) using Cooper's height-based linear equations	$P^b$
Girls	All	Underweight	7	13.9 ± 273.1	-190.7 ± 289.0	<b>&lt;0.01</b>	90.7 ± 259.9	<b>0.03</b>
		Normal weight	87	10.2 ± 366.8	-20.9 ± 371.5	<b>0.02</b>	-7.2 ± 374.2	<b>&lt;0.01</b>
		Overweight/obesity	17	134.9 ± 240.3	494.5 ± 447.5	<b>0.02</b>	-50.8 ± 229.9	<b>&lt;0.01</b>
	Germany	Underweight	6	-7.4 ± 292.7	-197.1 ± 316.0	<b>0.03</b>	58.3 ± 268.8	<b>0.06</b>
		Normal weight	50	-37.7 ± 355.7	-70.7 ± 384.5	<b>0.02</b>	-56.0 ± 349.4	<b>0.04</b>
		Overweight/obesity	6	23.8 ± 294.1	221.8 ± 352.8	0.03	-113.9 ± 301.2	0.03
	USA	Underweight	1	-141.5	-152.6	—	285.2	—
		Normal weight	37	74.9 ± 376.3	46.4 ± 346.8	0.09	58.8 ± 400.5	0.01
		Overweight/obesity	11	195.4 ± 194.2	643.2 ± 435	<b>&lt;0.01</b>	-16.43 ± 187.0	<b>&lt;0.01</b>
Boys	All	Underweight	1	357.8	126.7	—	604.1	—
		Normal weight	96	-102.0 ± 463.4	88.9 ± 396.1	<b>&lt;0.01</b>	241.2 ± 454.8	<b>&lt;0.01</b>
		Overweight/obesity	24	110.1 ± 500.2	1423.9 ± 1125.4	<b>&lt;0.01</b>	328.7 ± 474.4	<b>&lt;0.01</b>
	Germany	Underweight	0	—	—	—	—	—
		Normal weight	60	-172.4 ± 496.8	16.6 ± 389.0	<b>&lt;0.01</b>	157.3 ± 465.6	<b>&lt;0.01</b>
		Overweight/obesity	7	-206.4 ± 599.2	862.4 ± 1189.7	<b>0.02</b>	-20.4 ± 557.4	<b>0.21</b>
	USA	Underweight	1	357.8	126.7	—	604.1	—
		Normal weight	36	15.3 ± 379.6	209.3 ± 383.2	<b>&lt;0.01</b>	381.2 ± 404.6	<b>&lt;0.01</b>
		Overweight/obesity	17	240.5 ± 403.9	1655.1 ± 1046.5	<b>&lt;0.01</b>	472.5 ± 363.1	<b>&lt;0.01</b>

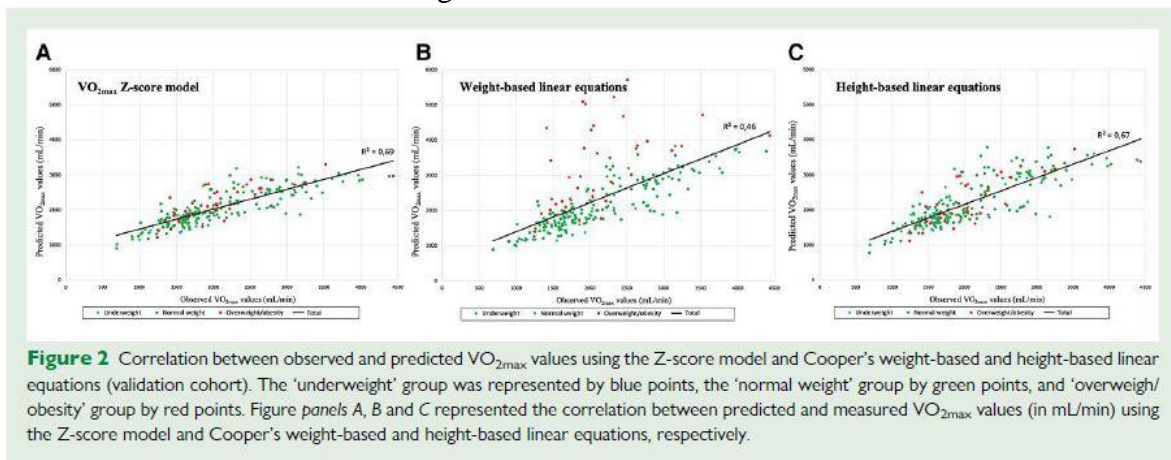
Values are mean ± standard deviation. Significant P-values are marked in bold.

BMI, body mass index.

<sup>a</sup>Comparison between the Z-score model and Cooper's weight-based linear equations using signed rank test.

<sup>b</sup>Comparison between the Z-score model and Cooper's height-based linear equations using signed rank test.

Defining aerobic fitness 'normality' for extreme weights remains difficult. Moreover, some clinical factors, such as hyperlipidaemia, hypertension, and insulin resistance, related to metabolic syndrome, may impair exercise capacity. Nevertheless, the existence of reference Z-score values for the overall paediatric population will help determine the impact of any additional chronic disease (congenital heart disease, asthma, renal failure, etc.) on aerobic fitness in children with extreme weights.



# Conclusion

This study defined paediatric reference Z-score values for  $VO_{2max}$ , e.g. the main aerobic fitness parameter. For both sexes, the most suitable mathematical model used a logarithmic function of height and BMI, which could be applied to normal and extreme weights. This study intended to satisfy a high methodological quality level, by enrolling a high number of subjects, covering wide age and weight ranges, undergoing external validation, and fulfilling most criteria on high-quality CPET assessment. Providing Z-scores to assess aerobic fitness in the paediatric population should be useful in the follow-up of children with various chronic diseases.

## Authors' contributions

A.G., S.M., and P.A. directed conceptualized and designed the study, enrolled patients, drafted the initial manuscript, and reviewed and revised the manuscript. S.G., G.D.L.V., A.N., A.H., J.R., S.M.Y., L.S., J.M. enrolled patients and reviewed and revised the manuscript. T.B., C.P., and H.H. 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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## In memoriam

This study is dedicated to Dr. Jonathan Rhodes, in memory of his extensive work on exercise physiology in children.

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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.

## Appendix 1 Criteria from the ATS/ACCP statement on high-quality CPET assessment

Criteria	Description	Current study
<i>Population characteristics</i>		
(1) Subjects are community based	The subjects studied preferably are community based rather than hospital based.	No
(2) Physical activity	Level of physical activity is reported.	No
(3) Racial groups	No exclusion of different racial groups	Yes
(4) Smokers	Exclusion of smokers in the sample studied	Yes
(5) Definition of confidence limits	No lack of definition of de confidence limits for individual or specified characteristics (including age, sex, and anthropomorphic considerations)	Yes
<i>Sample size</i>		
(6) Number of subjects tested	The number of subjects tested is sufficiently equal or larger than the appropriately powered sample size, with a uniform distribution of subjects for sex and groups.	Yes

*Continued*



**Continued**

<b>Criteria</b>	<b>Description</b>	<b>Current study</b>
<i>Randomization</i>		
(7) Randomization was applied	The study design includes a randomization process to avoid the potential bias seen when more physically active subjects volunteer for the study.	No
<i>Design:</i>		
(8) Prospective study	A prospective study design	Yes
<i>Quality assurance of equipment and methodologies</i>		
(9) Quality control was applied	Quality was achieved using recommendations contained in the ATS/ACCP guidelines and the CPET protocols in accordance with recommendations specified in the ATS/ACCP guidelines.	Yes
(10) Exercise testing protocol and procedures	Exercise testing protocol and procedures are described.	Yes
(11) Results are obtained by either breath-by-breath analysis	Results are obtained by either breath-by-breath analysis or mixing chamber treated in accordance with recommendation contained in the ATS/ACCP guidelines.	Yes
<i>Treatment of data</i>		
(12) CPET result in interval averaged and the peak value reported	CPET result in interval averaged, preferably every 30–60 s (to avoid the noise of shorter interval), and the peak value reported represents the mean of the last-completed stage or of all the data collected during the final stage, but preferably for no <30 s.	Yes
<i>Validation</i>		
(13) Reference equations are validated	Reference equations are validated in population other than those used to generate the existing data.	Yes
<i>Statistical treatment of data:</i>		
(14) The function that most accurately describes the distribution of the data is used.	The function that most accurately describes the distribution of the data is used. For example, curvilinear (power) functions may more accurately describe the distribution of the data. Furthermore, the precision of the individual and population predicted values are reported.	Yes

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