Peak oxygen uptake cut-points to identify children at increased cardiometabolic risk – The PANIC Study

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We aimed to develop cut-points for directly measured peak oxygen uptake (VO₂peak) to identify boys and girls at increased cardiometabolic risk using different scaling methods to control for body size and composition. Altogether 352 children (186 boys, 166 girls) aged 9-11 years were included in the analyses. We measured VO₂peak directly during a maximal cycle ergometer exercise test and lean body mass (LM) by bioelectrical impedance. We computed a sex- and age-specific cardiometabolic risk score (CRS) by summing important cardiometabolic risk factors and defined increased cardiometabolic risk as >1 standard deviation above the mean of CRS. Receiver operating characteristics curves were used to detect VO₂peak cut-points for increased cardiometabolic risk. Boys with VO₂peak <45.8 mL kg body mass (BM)⁻¹ min⁻¹ (95% confidence interval [CI] = 45.1 to 54.6, area under the curve [AUC] = 0.86, P < 0.001) and <63.2 mL kg LM⁻¹ min⁻¹ (95% CI =52.4 to 67.5, AUC = 0.65, P = 0.006) had an increased CRS. Girls with VO₂peak <44.1 mL kg BM⁻¹ min⁻¹ (95% CI = 44.0 to 58.6, AUC = 0.67, P = 0.013) had an increased CRS. VO₂peak scaled by BM⁻⁰.⁴⁹ and LM⁻⁰.⁷⁷ derived from log-linear allometric modeling poorly predicted increased cardiometabolic risk in boys and girls. In conclusion, directly measured VO₂peak <45.8 mL kg BM⁻¹ min⁻¹ among boys and <44.1 mL kg BM⁻¹ min⁻¹ among girls were cut-points to identify those at increased cardiometabolic risk. Appropriately controlling for body size and composition reduced the ability of cardiorespiratory fitness to identify children at increased cardiometabolic risk.

KEYWORDS
adiposity, aerobic fitness, allometric scaling, children, maximal exercise, metabolic health
INTRODUCTION

An increased cardiometabolic risk in childhood has been associated with an elevated risk of metabolic syndrome and type 2 diabetes, increased arterial stiffness, endothelial dysfunction, and preclinical carotid atherosclerosis in adulthood. Therefore, the early identification of children with increased cardiometabolic risk is important to prevent cardiometabolic diseases in adulthood. Decreased cardiorespiratory fitness (CRF), independent of the levels of physical activity, has been considered a strong determinant of increased cardiometabolic risk in children and adolescents. However, only a few studies have investigated cut-points for CRF to identify children at increased cardiometabolic risk.

Previous studies have suggested that peak oxygen uptake (VO$_2$peak) lower than 44.4 mL kg body mass (BM)$^{-1}$ min$^{-1}$ in boys and lower than 39.5 mL kg BM$^{-1}$ min$^{-1}$ in girls are indicative of increased cardiometabolic risk. Furthermore, the most recent FITNESSGRAM guidelines suggest that boys with VO$_2$peak 37.3 to 41.2 mL kg BM$^{-1}$ min$^{-1}$ and girls with VO$_2$peak 35.3 to 37.3 mL kg BM$^{-1}$ min$^{-1}$ depending on their age have an increased risk of metabolic syndrome. However, these studies have measured workload or heart rate during a submaximal treadmill or cycle ergometer exercise test, a stage reached during a 20-m shuttle run test, or other types of exercise tests and converted these measures of performance into an estimate of VO$_2$peak instead of measuring VO$_2$peak directly during a maximal exercise test continued until exhaustion. Estimated VO$_2$peak obtained from these types of exercise tests is problematic in that it has, at best, 50% agreement with directly measured VO$_2$peak. Furthermore, VO$_2$peak thresholds obtained from these studies are based on VO$_2$peak divided by BM that is confounded by body fat content and may invalidate VO$_2$peak as a measure of CRF in children with increased body mass and particularly adiposity.

Allometric scaling of VO$_2$peak by measures of body size and composition using log-linear regression can partly overcome the problems related to scaling of VO$_2$peak by BM using the ratio standard method. Nonetheless, allometrically scaled VO$_2$peak for lean body mass (LM) is regarded superior to allometrically scaled VO$_2$peak for BM in order to account for variance in body fat content in the expression of VO$_2$peak among children and adolescents. Thus, allometrically scaled VO$_2$peak by LM has been recommended as the best approach in expressing VO$_2$peak among children and adolescents. However, there are few studies on the associations of CRF with cardiometabolic risk having appropriately controlled for body size and composition using the allometric methods or the ratio standard methods. Using these approaches has attenuated the associations of CRF with cardiometabolic risk, suggesting that CRF expressed in these manners has inferior predictive power compared with CRF scaled by BM.

METHODS

2.1 Study design and study population

The Physical Activity and Nutrition in Children (PANIC) Study is an ongoing physical activity and dietary intervention study (ClinicalTrials.gov NCT01803776) in a population sample of primary school children living in the city of Kuopio, Finland. Altogether 736 children 6-9 years of age who had been registered for the first grade in one of the 16 public schools of the city of Kuopio were invited for baseline examinations in 2007-2009.

Altogether 512 children (248 girls, 264 boys), who accounted for 70% of those invited, participated in the baseline examinations in 2007-2009. The participants did not differ in sex distribution, age, or body mass index standard deviation score (BMI-SDS) from all children who started the first grade in the city of Kuopio in 2007-2009 based on data from the standard school health examinations performed for all Finnish children before the first grade. The present analyses are based on the 2-year follow-up data. We had complete data on variables needed in the analyses for 352 children (186 boys, 166 girls) 9-11 years of age. Of these children, 99.1% are Caucasians.

The PANIC Study protocol was approved by the Research Ethics Committee of the Hospital District of Northern Savo. A written informed consent was acquired from the parent or caregiver of each child and every child provided assent to participation.

2.2 Assessment of cardiorespiratory fitness

We assessed CRF by a maximal exercise test using the Ergoselect 200 K® electromagnetic cycle ergometer coupled with a pediatric saddle module (Ergoline, Bitz, Germany), as explained in detail earlier. The children and their parents and caregivers were informed about the exercise test in the invitation letter. A research nurse and a research physician gave the children instructions on how to perform the exercise test. The children were familiarized with the exercise test protocol two years earlier during baseline examination. They were also allowed to practice cycling with the ergometer and using the pediatric mask 10 minutes before the exercise test. The exercise test protocol, supervised by the research physician and assisted by the research nurse, included a 2.5-minute anticipatory period with the child sitting on the ergometer; a 3-minute warm-up period with a workload of 5 watts; a...
1-minute steady-state period with a workload of 20 watts; an exercise period with an increase in the workload of 1 watt per 6 seconds until exhaustion, and a 4-minute recovery period with a workload of 5 watts.

The children were asked to keep the cadence stable and within 70-80 revolutions per minute (rpm). The children were verbally encouraged to exercise until voluntary exhaustion. Heart rate was measured continuously throughout the exercise test using a 12-lead electrocardiogram (ECG) registered by the Cardiostoff® V6.5 Diagnostic System (GE Healthcare Medical Systems, Freiburg, Germany). The exercise test was considered maximal if the peak heart rate was at least 185 beats per minute and the respiratory exchange ratio was at least 1.0. However, the research physician also adjudged the exercise test maximal among 21 (6%) children with a peak heart rate of 179-184 beats per minute, because the cadence dropped below 65 rpm although the children still had the motivation to continue and the reason for terminating the test suggested a maximal effort had been provided. The peak workload was defined as the workload at the end of the exercise test.

The respiratory gas analysis was performed during the exercise test from the beginning of the 2.5-minute anticipatory period before the exercise test to the end of the 4-minute recovery period after the exercise test using the Oxycon Pro® respiratory gas analyzer (Jaeger, Hoechberg, Germany) and the Hans-Rudolph® pediatric mask (Shawnee, Kansas, USA). \( \dot{V}O_2 \) was measured using the breath-by-breath method and was averaged over consecutive 15-second periods. \( \dot{V}O_2 \) and the respiratory exchange ratio were defined as the highest 15-seconds average values recorded during the last minute of the exercise test.

### 2.3 Assessment of cardiometabolic risk factors

Cardiometabolic risk factors were assessed in the morning for two children, first of them arriving at 08:00, and second at 09:15. The research nurse measured body height, body weight, and waist circumference using standard protocols. Body mass index (BMI) was calculated by dividing body weight with body height squared and BMI-SDS using national references. The prevalence of overweight and obesity was defined using age- and sex-specific cut-points. Total body fat mass, body fat percentage (BF%), and LM were measured twice; the children having fasted for 12 hours, voided the bladder; and standing in light underwear, using the InBody® 720 bioelectrical impedance device (Biospace, Seoul, South Korea). We have found a good agreement between BF% and LM measured with bioelectrical impedance and those derived from dual-energy x-ray absorptiometry. The research nurse measured blood pressure manually from the right arm by a calibrated Heine 130 Gamma G7® aneroid sphygmomanometer (Heine Optotechnik, Herrsching, Germany). The measurement protocol included a 5-minute rest and thereafter three measurements in a sitting position at 2-minute intervals. The mean of all three values was used as the systolic and diastolic blood pressure. The research nurse took venous blood samples using a standard protocol after a 12-hour fast and the children having seated for 10 minutes. The assessment of serum insulin and plasma glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, have been explained in detail earlier.

### 2.4 Assessment of puberty

The research physician assessed pubertal status using a 5-stage scale described by Tanner. Boys were defined having entered clinical puberty if their testicular volume assessed by an orchidometer was ≥4 mL. (Tanner stage ≥2). Girls were defined having entered clinical puberty if their breast development had started (Tanner stage ≥2).

### 2.5 Calculation of cardiometabolic risk score

We calculated a continuous cardiometabolic risk score using population-specific and age- and sex-standardized Z-scores for waist circumference, insulin, glucose, HDL cholesterol, triglycerides, and the average of systolic and diastolic blood pressure by a formula: waist circumference +insulin + glucose − HDL cholesterol +triglycerides + the average of systolic and diastolic blood pressure. We defined elevated cardiometabolic risk as ≥1 standard deviation above the mean of the cardiometabolic risk score in the present study population. The rationale for using this approach is the existing evidence on the ability of a continuous cardiometabolic risk score in children to predict cardiometabolic diseases in adulthood. The clustering of risk factors may also provide a more sensitive and clinically more relevant evaluation of increased cardiometabolic risk than using individual risk factors, and may compensate for day-to-day fluctuations observed in the levels of individual risk factors.

### 2.6 Allometric scaling of peak oxygen uptake

Allometric scaling of \( \dot{V}O_2 \) was performed by the log-linear regression model with sex and BM or LM as independent variables and \( \dot{V}O_2 \) as a dependent variable. The scaling exponent (b) was identified in the allometric equation \( \dot{V}O_2 = YX^b \), where X is the anthropometric scaling variable (BM or LM). \( \dot{V}O_2 \) and X were log transformed, and least squares regression with the equation \( \ln(\dot{V}O_2) = \ln(Y/b) \ln(X) \) was used to obtain the scaling exponent b. We found that the scaling exponent b for BM was 0.49 (95% confidence interval [CI] = 0.43 to 0.55) and that for LM was 0.77 (95% CI = 0.70 to 0.85). To test if the slopes of the association of \( \dot{V}O_2 \) with BM and LM were similar in boys
and girls, we added the interaction term to the model. The interactions of sex with BM \( (P = 0.362) \) and LM \( (P = 0.932) \) were not statistically significant. These allometric models were able to remove the associations of VO_2peak with BM \( (r = -0.072, P = 0.328) \) and LM \( (r = 0.022, P = 0.939) \), indicating their validity in scaling CRF.

### 2.7 Statistical methods

Student’s \( t \)-test, Mann-Whitney \( U \) test, and Chi-square test were used to compare basic characteristics between boys and girls. The associations of measures of CRF with the cardiometabolic risk score were studied using linear regression analyses. The associations were adjusted for age and study group and additionally for puberty. Receiver operating characteristics (ROC) curves were used to investigate VO_2peak cut-points associated with increased cardiometabolic risk. We decided not to provide cut-points for allometrically scaled VO_2peak because they would depend on the scaling exponent \( b \) that is specific to our study population. Moreover, a recent review has highlighted that no general scaling exponent \( b \) is available.\(^{29}\) The area under the curve (AUC) was used as a measure of the effectiveness of the predictor variable to identify correctly children having a cardiometabolic risk score \( \geq +1 \) SD (sensitivity) and to identify correctly children having a cardiometabolic risk score \(< 1\) SD (specificity). An AUC of 1.0 represents the ability to identify perfectly children having a cardiometabolic risk score \( \geq +1 \) SD from other children, whereas an AUC of 0.5 indicates no greater predictive ability than chance. We also compared the cardiometabolic risk score in the categories of VO_2peak scaled by BM and LM among boys and girls combined using analysis of covariance with Sidak correction adjusted for age and the study group. V_{O2peak} was associated with increased cardiometabolic risk. Allometrically scaled VO_2peak variances (very low \(< 2.5\%\), low \([2.5\%\text{-}15.9\%]\), medium \([16\%\text{-}83.9\%]\), high \([84\%\text{-}97.5\%]\), and very high \([>97.5\%]\)) as defined in our earlier study in the same pediatric population.\(^{30}\) We combined children in the two highest categories because of the small number of children in the highest category to increase statistical power in these analyses. Student’s \( t \)-tests, Mann-Whitney \( U \) tests, Chi-square tests, and linear regression analyses were conducted using the SPSS statistics software, version 23.0 (IBM Corp, Armonk, NY, USA). ROC curve analyses were performed using the MedCalc\(^{®}\) statistical software, version 16.1 (MedCalc\(^{®}\) Software bvba, Ostend, Belgium). Our power calculation provided a sample size of 352 children. In this calculation, we determined the effect size that corresponds to the power of 0.8 at 0.05 alpha to test differences in the associations of CRF within sex-specific categories and cardiometabolic risk. Cohen’s \( d \) effect size for \( F \)-test \( (d = 0.177) \) was derived using the G*Power statistical software, version 3.1.9.2. Cohen’s \( d \) effect size for \( F \)-test is interpreted as small for \( d = 0.1 \), medium for \( d = 0.25 \), and large for \( d = 0.4 \).

### 3 RESULTS

#### 3.1 Characteristics of children

Boys had more LM, less fat mass, a lower BF%, a higher waist circumference, lower insulin, higher glucose, higher HDL cholesterol, and higher VO_2peak scaled by BM and LM compared with girls (Table 1).

#### 3.2 Associations of peak oxygen uptake with cardiometabolic risk

Absolute VO_2peak expressed in mL/min was directly associated with cardiometabolic risk in boys and girls adjusted for age and the study group (Table 2). VO_2peak scaled by BM and LM were inversely related to cardiometabolic risk in boys and girls after these adjustments. Allometrically scaled VO_2peak expressed in mL kg BM\(^{-0.49}\) min\(^{-1}\) and mL kg LM\(^{-0.77}\) min\(^{-1}\) were also inversely associated with cardiometabolic risk in boys. Moreover, allometrically scaled VO_2peak expressed in mL kg LM\(^{-0.77}\) min\(^{-1}\), but not allometrically scaled VO_2peak expressed in mL kg BM\(^{-0.49}\) min\(^{-1}\), was associated with cardiometabolic risk among girls. These relationships in boys and girls were unaltered after additional adjustment for puberty (data not shown).

#### 3.3 Peak oxygen uptake in identifying children with increased cardiometabolic risk

In boys, VO_2peak less than 45.8 mL kg BM\(^{-1}\) min\(^{-1}\) and VO_2peak less than 63.2 mL kg LM\(^{-1}\) min\(^{-1}\) were associated with increased cardiometabolic risk. Allometrically scaled VO_2peak expressed in mL kg BM\(^{-0.49}\) min\(^{-1}\) and in mL kg LM\(^{-0.77}\) min\(^{-1}\) also differentiated boys with increased cardiometabolic risk (Table 3).

In girls, VO_2peak less than 44.1 mL kg BM\(^{-1}\) min\(^{-1}\) was associated with increased cardiometabolic risk. However, neither VO_2peak scaled by LM nor allometrically scaled VO_2peak for BM or LM was able to differentiate girls with increased cardiometabolic risk.

#### 3.4 Cardiometabolic risk among children in categories of peak oxygen uptake

Cardiometabolic risk decreased in a dose-dependent manner with increasing categories of VO_2peak expressed in mL kg BM\(^{-1}\) min\(^{-1}\) among children \( (P < 0.001 \) for linear trend) (Figure 1). Moreover, children in the highest category of VO_2peak expressed in mL kg LM\(^{-1}\) min\(^{-1}\) also had a lower cardiometabolic risk than children in other categories of VO_2peak (Figure 1).
DISCUSSION

We found a strong inverse association between directly measured \( \dot{V}_{\text{O}} \cdot \text{O}_2 \text{peak} \) scaled by BM and cardiometabolic risk among boys and girls. \( \dot{V}_{\text{O}} \cdot \text{O}_2 \text{peak} \) less than 45.8 mL kg BM\(^{-1}\) min\(^{-1}\) in boys and 44.1 mL kg BM\(^{-1}\) min\(^{-1}\) in girls was associated with increased cardiometabolic risk with moderate sensitivity and specificity. However, the inverse associations of \( \dot{V}_{\text{O}} \cdot \text{O}_2 \text{peak} \) scaled by LM or \( \dot{V}_{\text{O}} \cdot \text{O}_2 \text{peak} \) scaled by BM\(^{-0.49}\) and LM\(^{-0.77}\) derived from log-linear allometric modeling with cardiometabolic risk were markedly weaker. \( \dot{V}_{\text{O}} \cdot \text{O}_2 \text{peak} \) less than 63.2 mL kg LM\(^{-1}\) min\(^{-1}\) was linked to increased cardiometabolic risk in boys, although sensitivity was poor. Furthermore, \( \dot{V}_{\text{O}} \cdot \text{O}_2 \text{peak} \) scaled by allometric methods was able to differentiate boys at increased cardiometabolic risk with adequate sensitivity but poor specificity. Neither \( \dot{V}_{\text{O}} \cdot \text{O}_2 \text{peak} \) scaled by LM nor allometrically scaled \( \dot{V}_{\text{O}} \cdot \text{O}_2 \text{peak} \) for BM or LM was able to differentiate girls with increased cardiometabolic risk.

Our results are in agreement with previous findings that CRF measured in exercise test laboratories or using field tests and scaled by BM using the ratio standard method had a strong inverse association with cardiometabolic risk in children.\(^{10-12}\) However, the inverse relationship between CRF scaled by BM and cardiometabolic risk is partly confounded by adiposity, because CRF divided by BM is a measure of both CRF and body fat content. We observed that using \( \dot{V}_{\text{O}} \cdot \text{O}_2 \text{peak} \) scaled by LM or allometric scaling of \( \dot{V}_{\text{O}} \cdot \text{O}_2 \text{peak} \) for BM or LM instead of \( \dot{V}_{\text{O}} \cdot \text{O}_2 \text{peak} \) scaled by BM attenuated the magnitude of the inverse association between CRF and cardiometabolic risk by 50%-75%. These results are in consonance with the observation that estimated \( \dot{V}_{\text{O}} \cdot \text{O}_2 \text{peak} \) scaled by BM provided spurious associations with cardiometabolic risk among children.

### Table 1: Characteristics of 352 children

|                       | Boys (n = 186) | Girls (n = 166) | P for difference |
|-----------------------|---------------|-----------------|-----------------|
| Age (y)               | 9.8 (0.5)     | 9.8 (0.4)       | 0.696           |
| Body height (cm)      | 141.5 (6.0)   | 140.4 (6.6)     | 0.127           |
| Body weight (kg)      | 34.3 (9.7)*   | 33.1 (9.6)*     | 0.248           |
| Clinical puberty (%)\(^a\)  | 15.1   | 37.7            | <0.001          |
| Overweight and obesity (%) | 19.9   | 18.7             | 0.773           |
| Waist circumference (cm) | 61.7 (9.1)* | 59.4 (9.5)*     | 0.012           |
| Body fat mass (kg)    | 5.5 (5.6)*    | 6.1 (5.8)*      | 0.009           |
| Body fat percentage (%) | 15.9 (11.1)* | 18.3 (11.0)*    | <0.001          |
| Lean body mass (kg)   | 27.0 (3.6)    | 25.3 (3.5)      | <0.001          |
| Serum insulin (pmol/L)| 4.9 (3.9)*    | 6.1 (4.4)*      | <0.001          |
| Plasma glucose (mmol/L)| 5.0 (0.3)*   | 4.9 (0.4)*      | <0.001          |
| Plasma HDL cholesterol (mmol/L) | 1.7 (0.3) | 1.6 (0.3)     | 0.040           |
| Plasma triglycerides (mmol/L) | 0.6 (0.3)* | 0.5 (0.3)*     | 0.916           |
| Systolic blood pressure (mm Hg) | 100.0 (8.0) | 101.0 (7.0)      | 0.795           |
| Diastolic blood pressure (mm Hg) | 61.2 (7.5)  | 61.4 (7.7)      | 0.830           |
| Peak heart rate (beats/min) | 198.8 (8.7) | 200.1 (8.6)     | 0.167           |
| Peak respiratory exchange ratio | 1.1 (0.1)    | 1.1 (0.1)       | <0.001          |
| \( \dot{V}_{\text{O}} \cdot \text{O}_2 \text{peak} \) (mL kg BM\(^{-1}\) min\(^{-1}\)) | 52.0 (7.0) | 46.3 (6.9)       | <0.001          |
| \( \dot{V}_{\text{O}} \cdot \text{O}_2 \text{peak} \) (mL kg LM\(^{-1}\) min\(^{-1}\)) | 66.7 (6.5) | 61.9 (6.5)       | <0.001          |
| \( \dot{V}_{\text{O}} \cdot \text{O}_2 \text{peak} \) (mL kg BM\(^{-0.49}\) min\(^{-1}\)) | 314.0 (37.0) | 277.0 (33.0)   | <0.001          |
| \( \dot{V}_{\text{O}} \cdot \text{O}_2 \text{peak} \) (mL kg LM\(^{-0.77}\) min\(^{-1}\)) | 224.0 (21.0) | 207.0 (21.0)   | <0.001          |
| Cardiometabolic risk score | 0.18 (3.6) | 0.13 (3.5)     | 0.878           |

BM: body mass; HDL: high-density lipoprotein; LM: lean body mass; \( \dot{V}_{\text{O}} \cdot \text{O}_2 \text{peak} \): peak oxygen uptake.

The values are means (standard deviations) from the Student’s t-test for normally distributed variables, medians (interquartile ranges) from the Mann-Whitney U test for variables with skewed distributions\(^*\), or percentages from the Chi-square test for categorical variables.

\(^a\)Boys were defined having entered clinical puberty if their testicular volume assessed by an orchidometer was \( \geq 4 \) mL (Tanner stage \( \geq 2 \)).\(^{37}\) Girls were defined having entered clinical puberty if their breast development had started (Tanner stage \( \geq 2 \)).\(^{36}\)
and the view that \( V\cdot O_2\)peak scaled allometrically or by fat-free mass would be a better measure to estimate the magnitude of the association between CRF and cardiometabolic risk.\(^\text{22}\)

Notwithstanding, the measures of CRF scaled by LM may also be influenced by adiposity because individuals with higher fat mass also have higher LM.\(^\text{44}\) In the present cross-sectional study, adjusting for puberty had no effect on the relationships between \( V\cdot O_2\)peak and cardiometabolic risk in boys or girls. Therefore, longitudinal studies are needed to clarify the role of CRF in cardiometabolic health during growth and maturation. It is also important to note that CRF is strongly influenced by genetic factors\(^\text{45}\) and some genetic variants have been reported to modify the relationship between CRF and cardiometabolic risk factors, such as adiposity, insulin resistance, and elevated blood pressure.\(^\text{45}\)

In our study, genetics may play a role in the inverse association between CRF controlled for body fat and cardiometabolic risk.\(^\text{46}\)

The cut-point for \( V\cdot O_2\)peak of 45.8 mL kg BM\(^{-1}\) min\(^{-1}\) to identify girls aged 9-11 years at increased cardiometabolic risk in our study was notably higher than the cut-point for \( V\cdot O_2\)peak of 37.0 mL kg BM\(^{-1}\) min\(^{-1}\) observed among girls aged 9-10 years in a previous study.\(^\text{15}\)

The reason for a higher threshold for \( V\cdot O_2\)peak among girls in our study than in the earlier study may be that Finnish girls aged 9-11 years are more fit than girls of the same age in other pediatric populations.\(^\text{13}\) Welk and co-workers\(^\text{13}\) found that the cut-point for estimated \( V\cdot O_2\)peak to identify children aged 10-11 years at increased cardiometabolic risk was 40.2 mL kg BM\(^{-1}\) min\(^{-1}\) in both sexes. The diversity in cut-points may also be due to the different age ranges of children because most of the earlier studies have reported pooled data of various age groups.\(^\text{10,11,14}\) There is some evidence that the cut-point for \( V\cdot O_2\)peak decreases with increasing age in girls, whereas it remains relatively stable in boys.\(^\text{31}\) One explanation for this sex difference may be that body fat content increases more in girls than in boys during maturation that introduces more confounding by adiposity in the measurement of CRF in girls.\(^\text{47}\) Another reason for the array of cut-points for \( V\cdot O_2\)peak scaled by BM may be that the prevalence of overweight has varied among the study populations.\(^\text{13,23}\)

### TABLE 2

| Associations of peak oxygen uptake with cardiometabolic risk score in boys and girls |
|----------------------------------|------------------|------------------|
|                                  | Boys (n = 186) | Girls (n = 166) |
| \( V\cdot O_2\)peak (mL/min)    | 0.229 | 0.356 | <0.001 |
| \( V\cdot O_2\)peak (mL kg BM\(^{-1}\) min\(^{-1}\)) | -0.577 | -0.484 | <0.001 |
| \( V\cdot O_2\)peak (mL kg LM\(^{-1}\) min\(^{-1}\)) | -0.252 | -0.245 | 0.001 |
| \( V\cdot O_2\)peak (mL kg BM\(^{-0.49}\) min\(^{-1}\)) | -0.261 | -0.123 | 0.127 |
| \( V\cdot O_2\)peak (mL kg LM\(^{-0.77}\) min\(^{-1}\)) | -0.185 | -0.166 | 0.036 |

The values are standardized regression coefficients and \( p \)-values from linear regression models adjusted for age and the study group.

### TABLE 3

| Receiver operating characteristics curve analyses to predict increased cardiometabolic risk in boys and girls |
|---------------------------------------------------------------|------------------|------------------|
| Cut-points | Sensitivity | Specificity | AUC | 95% CI | \( p \)-value |
| Boys (n = 186) | | | | | |
| \( V\cdot O_2\)peak (mL kg BM\(^{-1}\) min\(^{-1}\)) | | | | | |
| <45.8 | 75.0 | 85.4 | 0.86 | 0.80-0.90 | <0.001 |
| \( V\cdot O_2\)peak (mL kg LM\(^{-1}\) min\(^{-1}\)) | | | | | |
| <63.2 | 50.0 | 76.6 | 0.65 | 0.58-0.72 | 0.006 |
| \( V\cdot O_2\)peak (mL kg BM\(^{-0.49}\) min\(^{-1}\)) | | | | | |
| a | 78.6 | 55.0 | 0.66 | 0.59-0.73 | 0.027 |
| \( V\cdot O_2\)peak (mL kg LM\(^{-0.77}\) min\(^{-1}\)) | | | | | |
| a | 75.0 | 46.8 | 0.61 | 0.54-0.68 | 0.047 |
| Girls (n = 166) | | | | | |
| \( V\cdot O_2\)peak (mL kg BM\(^{-1}\) min\(^{-1}\)) | 44.1 | 69.6 | 69.2 | 0.69 | 0.59-0.74 | 0.013 |
| \( V\cdot O_2\)peak (mL kg LM\(^{-1}\) min\(^{-1}\)) | b | | | 0.57 | 0.49-0.65 | 0.332 |
| \( V\cdot O_2\)peak (mL kg BM\(^{-0.49}\) min\(^{-1}\)) | b | | | 0.50 | 0.42-0.58 | 0.977 |
| \( V\cdot O_2\)peak (mL kg LM\(^{-0.77}\) min\(^{-1}\)) | b | | | 0.53 | 0.45-0.61 | 0.633 |

AUC: area under the curve; CI: confidence interval;

a Cut-points were not provided because they would depend on the scaling exponent that are specific to our study population.
b Scaled \( V\cdot O_2\)peak could not differentiate girls with cardiometabolic risk.
Moreover, different assessments of CRF and cardiometabolic risk factors and different definitions of increased risk may explain the incongruence in CRF cut-points among these studies.10-13,17 In consonance with earlier studies, 10,12,15 the prevalence of increased cardiometabolic risk defined by ≥+1 SD of the cardiometabolic risk score in our study was 25% among boys and 34% in girls.

We found moderate sensitivity and specificity of the measures of CRF in predicting increased cardiometabolic risk which corresponds to those of previous studies.10-12,15 Sensitivity for VO\textsubscript{2peak} scaled by BM was 75% in boys and 69% in girls. This sex difference may be due to a stronger inverse association between CRF and cardiometabolic risk in boys than in girls.13 Nonetheless, the false-positive rate would be too high for screening children with increased cardiometabolic risk using VO\textsubscript{2peak} scaled by BM. There is a trade-off between false-positive and false-negative rates. Classification accuracy may lead to the problem of fictitious interpretation when applying cut-points with a high false-positive rate than those with a high false-negative rate. Improving CRF may decrease cardiometabolic risk; however, a large number of false-positive cases would result in failure to correctly identify children at increased risk, in contrast to recommending increased physical activity to improve CRF in false-negative cases.10 It is important that children are not subject of the social stigma associated with being erroneously classified as being at increased cardiometabolic risk. In addition, it is better to err on the side of caution so that children who truly are at increased risk are not deprived of health care.10

Loftin and co-workers suggested that VO\textsubscript{2peak} should be allometrically scaled for LM due to the involvement of skeletal muscle in locomotion.29 We found that VO\textsubscript{2peak} scaled by LM had worse ability to differentiate boys with increased cardiometabolic risk than VO\textsubscript{2peak} scaled by BM. Neither VO\textsubscript{2peak} scaled allometrically nor VO\textsubscript{2peak} scaled by LM could differentiate girls with increased cardiometabolic risk. Appropriately scaled CRF resulted in a poor prediction of cardiometabolic risk; whereas, CRF scaled by BM using the ratio standard method, was a better predictor of cardiometabolic risk. The reason for this is that CRF scaled by BM combines the information from these two measures such that both decreased CRF and increased weight, and/or body fat content are associated with increased cardiometabolic risk. Proposing age-specific cut-points for CRF scaled by BM using the ratio standard method offers clear diagnostic utility in identifying children at increased cardiometabolic risk, which tracks well from childhood into adulthood.39 There was a linear decrease in cardiometabolic risk with increasing categories of VO\textsubscript{2peak} scaled by BM. Similarly, children in the highest category of VO\textsubscript{2peak} scaled by LM had reduced cardiometabolic risk compared with other children. However, the differences in cardiometabolic risk across the categories of VO\textsubscript{2peak} scaled by LM were markedly smaller than those of VO\textsubscript{2peak} scaled by BM.

The strengths of this study include a large population sample of children 9-11 years of age, the direct assessment of VO\textsubscript{2peak}, and the use of VO\textsubscript{2peak} scaled allometrically for BM and LM. Our study provides a robust threshold for VO\textsubscript{2peak} scaled by BM in these children aged 9-11 years; however, we cannot extrapolate our findings to other age groups. Our study participants were Caucasian children, so the cut-points may not be generalized to children of different ethnic groups. A limitation of the study is its cross-sectional design that does not allow us to arrive at a conclusion regarding the causality of the association between CRF and cardiometabolic risk. Therefore, longitudinal studies are warranted in order to investigate whether a decrease in adiposity-independent measures of CRF is associated with an increase in cardiometabolic risk over time among children and adolescents. In addition, it would be important to provide evidence for the effects of growth and maturation on the cut-points for CRF using different methods to scale CRF for body size and composition.

In conclusion, we found that directly measured VO\textsubscript{2peak} less than 45.8 mL kg BM\textsuperscript{-1} min\textsuperscript{-1} in boys 9-11 years of age and less than 44.1 mL kg BM\textsuperscript{-1} min\textsuperscript{-1} in girls 9-11 years
of age was associated with increased cardiometabolic risk with moderate sensitivity and specificity. The association of CRF scaled by BM with cardiometabolic risk was markedly weaker than that of CRF scaled by LM because scaling by LM reduced the dependence of the measure of CRF on adiposity. Appropriately controlling for body size and composition reduced the ability of CRF to identify boys and girls at increased cardiometabolic risk.

5 | PERSPECTIVES

Cardiometabolic risk tracks from childhood into adulthood and the early identification of individuals at increased risk is essential in developing public health actions targeted at preventing cardiometabolic diseases. Our results showed that CRF scaled by BM, which is partly confounded by adiposity, had a strong inverse association with cardiometabolic risk among children. Appropriately controlling for body size and composition markedly attenuated the predictive ability of CRF. The strong inverse association between CRF scaled by BM and cardiometabolic risk suggests that CRF scaled by BM can be used in screening children at increased cardiometabolic risk. However, children may be erroneously classified as being at increased risk, which may subject them to social stigma. Hence, there should be cautious interpretation and utilization of CRF thresholds so that children who truly are at increased cardiometabolic risk are not deprived of appropriate intervention.

A markedly weakened relationship between CRF and increased cardiometabolic risk when adiposity was appropriately controlled for raises the question of whether there is an etiological link between CRF and cardiometabolic health in children. Hence, longitudinal research is needed to establish whether decreased CRF, using appropriate scaling methods to control for body size and composition, increases cardiometabolic risk among children.

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16. Mesa JL, Ruiz JR, Ortega FB, et al. Aerobic physical fitness in relation to blood lipids and fasting glycaemia in adolescents: influence of weight status. *Nutr Metab Cardiovasc Dis*. 2006;16(4):285-293.

17. Moreira C, Santos R, Ruiz JR, et al. Comparison of different VO2max equations in the ability to discriminate the metabolic risk in Portuguese adolescents. *J Sci Med Sport*. 2011;14(1):79-84.

18. Cureton KJ, Plowman SA, Mahar MT. FITNESSGRAM / ACTIVITYGRAM Reference Guide (4th Edition). 2013.

19. Ruiz JR, Silva G, Oliveira N, Ribeiro JC, Oliveira JF, Mota J. Criterion-related validity of the 20-m shuttle run test in youths aged 13–19 years. *J Sports Sci*. 2009;27(9):899-906.

20. Shaibi GQ, Cruz ML, Ball G, et al. Cardiovascular fitness and the metabolic syndrome in overweight latino youths. *Med Sci Sports Exerc*. 2005;37(6):922.

21. Ahn B, McMurray R, Harrell J. Scaling of VO2max and its relationship with insulin resistance in children. *Pediatr Exerc Sci*. 2013;25(1):43.

22. McMurray RG, Hosick PA, Bugge A. Importance of proper scaling of aerobic power when relating to cardiometabolic risk factors in children. *Ann Hum Biol*. 2011;38(5):647-654.

23. Loftin M, Sothern M, Trosclair L, O’Hanlon A, Miller J, Uddal J. Scaling VO(2) peak in obese and non-obese girls. *Obes Res*. 2001;9(5):290-296.

24. Dencker M, Wollmer P, Karlsson MK, Lindén C, Andersen LB, Thomsson O. Body fat, abdominal fat and body fat distribution related to VO2peak in young children. *Int J Pediatr Obes*. 2011;6(2-2):e597–e602.

25. Ondrak KS, McMurray RG, Bangdiwala SI, Harrell JS. Influence of aerobic power and percent body fat on cardiovascular disease risk in youth. *J Adolesc Heal*. 2007;41(2):146-152.

26. Neville AM, Bate S, Holder RL. Modeling physiological and anthropometric variables known to vary with body size and other confounding variables. *Am J Phys Anthropol*. 2005;48:141-153.

27. Neville AM, Ramsbottom R, Williams C. Scaling physiological measurements for individuals of different body size. *Eur J Appl Physiol Occup Physiol*. 1992;65(2):110-117.

28. Welsman JR, Armstrong N, Nevill AM, Winter EM, Kirby BJ. Scaling peak VO2 for differences in body size. *Med Sci Sports Exerc*. 1996;28(2):259-265.

29. Loftin M, Sothern M, Abe T, Bonis M. Expression of VO2peak in children and youth, with special reference to allometric scaling. *Sport Med*. 2016;46(10):1451-1460.

30. Lintu N, Viitasalo A, Tompuri T, et al. Cardiorespiratory fitness, respiratory function and hemodynamic responses to maximal cycle ergometer exercise test in girls and boys aged 9–11 years: the PANIC Study. *Eur J Appl Physiol*. 2015;115(2):235-243.

31. Armstrong N, Welsman JR. Assessment and interpretation of aerobic fitness in children and adolescents. *Exerc Sport Sci Rev*. 1994;22:435-476.

32. Väistö J, Eloranta A-M, Viitasalo A, et al. Physical activity and sedentary behaviour in relation to cardiometabolic risk in children: cross-sectional findings from the Physical Activity and Nutrition in Children (PANIC) Study. *Int J Behav Nutr Phys Act*. 2014;11(1):55.

33. Saari A, Sankilampi U, Hannila M-L, Kiviniemi V, Kesseli K, Dunkel L. New Finnish growth references for children and adolescents aged 0 to 20 years: length/height-for-age, weight-for-height, and body mass index-for-age. *Ann Med*. 2011;43(3):235-248.

34. Tompuri TT, Lakka TA, Hakulinen M, et al. Assessment of body composition by dual-energy X-ray absorptiometry, bioimpedance analysis and anthropometrics in children: the Physical Activity and Nutrition in Children study. *Clin Physiol Funct Imaging*. 2015;35(1):21-33.

35. Ågren J, Hallikainen M, Vidgren H, Miettinen TA, Gylling H. Postprandial lipemic response and lipoprotein composition in subjects with low or high cholesterol absorption efficiency. *Clin Chim Acta*. 2006;366(1):309-315.

36. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in girls. *Arch Dis Child*. 1969;44:291-303.

37. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child*. 1970;45(239):13-23.

38. Ekelund U, Anderssen SA, Froberg K, Sardinha LB, Andersen LB, Brage S. Independent associations of physical activity and cardiorespiratory fitness with metabolic risk factors in children: The European youth heart study. *Diabetologia*. 2007;50(9):1832-1840.

39. Koskinen J, Magnussen CG, Sinaiko A, et al. Childhood age and associations between childhood metabolic syndrome and adult risk for metabolic syndrome, type 2 diabetes mellitus and carotid intima media thickness: The international childhood cardiovascular cohort consortium. *J Am Heart Assoc*. 2017;6(8):e005632. https://doi.org/10.1161/JAHA.117.005632.

40. Andersen LB, Wedderkopp N, Hansen HS, Cooper AR, Froberg K. Biological cardiovascular risk factors cluster in Danish children and adolescents: the European youth heart study. *Prev Med (Baltim)*. 2003;37:363-367.

41. Resaland GK, Aadland E, Nilsen A, Bartholomew JB, Andersen LB, Anderssen SA. The effect of a two year school-based daily physical activity intervention on a clustered CVD risk factor score – the Sognsdal school-intervention study. *Scand J Med Sci Sports*. 2017;28(3):1027-1035.

42. Andersen LB, Sardinha L, Froberg K, Riddoch CJ, Page AS, Anderssen SA. Fitness, fatness and clustering of cardiovascular risk factors in children from Denmark, Estonia and Portugal: the European Youth Heart Study. *Int J Pediatr Obes*. 2008;3(suppl 1):58-66.

43. Tolfrey K, Barker A, Thom JM, Morse CI, Narici MV, Batterham AM. Scaling of maximal oxygen uptake by lower leg muscle volume in boys and men. *J Appl Physiol*. 2006;100(6):1851–1856.

44. Toth MJ, Goran MI, Ades PA, Howard DB, Poehlman ET. Examination of data normalization procedures for expressing peak VO2 data. *J Appl Physiol*. 1993;75(5):2288–2292.

45. Bray MS, Hagberg JM, Pérusse L, et al. The human gene map for performance and health-related fitness phenotypes: The 2006–2007 update. *Med Sci Sports Exerc*. 2009;41(1):34–72.

46. Maes H, Beunen GP, Vlietinck RF, et al. Inheritance of physical fitness in 10-yr-old twins and their parents. *Med Sci Sports Exerc*. 1996;28(12):1479–1491.

47. Armstrong N, Welsman JR, Nevill AM, Kirby BJ. Modeling growth and maturation changes in peak oxygen uptake in 11–13 yr olds. *J Appl Physiol*. 1999;87(6):2230–2236.

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