Normative Values for Cardiopulmonary Exercise Stress Testing Using Ramp Cycle Ergometry in Children and Adolescents

Danielle S. Burstein, MD[1], Michael G. McBride, PhD[1], Jungwon Min, PhD[2], Alexander A. Paridon, MD[3], Sarah Perelman, BS[4], Erika M. Huffman, MS[1], Shannon O'Malley, MS[1], Julia Del Grosso, MS[1], Herman Groepenhoff, PhD[5], Stephen M. Paridon, MD[1], and Julie A. Brothers, MD[1]

Objectives To provide sex, age, and race specific reference values for ramp cycle ergometer cardiopulmonary exercise test (CPET) in children in the US.

Study design Retrospective review was conducted of all cardiopulmonary CPET data from our Exercise Physiology Laboratory on healthy children and adolescents (6-18 years) with body mass index between the 5th and 95th percentiles and structurally normal hearts who performed a ramp cycle ergometry stress test between 1999 and 2015. Twenty-eight exercise variables were included: peak oxygen consumption, oxygen consumption at ventilatory anaerobic threshold, peak work rate, resting and peak heart rate and blood pressure, resting pulmonary function testing, and ventilatory responses to progressive exercise using breath-by-breath gas exchange. Owing to the nonlinear association between CPET results and age, fractional polynomials were used in the mixed-effects regression models to describe the sex- and age-specific normative values with 95% CIs, after adjusting for race and body mass index.

Results We analyzed data on 1829 children (average age, 13.6 ± 2.6 years; 52% male). After 12 years of age, males generally had higher peak values for aerobic capacity and work rate. There were progressive increases with age for both sexes in resting pulmonary function and ventilatory response to exercise, peak aerobic and work rate, and oxygen pulse. Notably, there was an age-related decrease in ventilatory equivalents of oxygen and carbon dioxide at the ventilatory anaerobic threshold.

Conclusions Future research using prospective, inclusive, and statistically planned cohorts with standardized laboratory approaches and confirmed interoperability should be considered as a focus for validating normative pediatric CPET values in the future. *(J Pediatr 2021;229:61-9)*.

A cardiopulmonary exercise test (CPET) is an objective measurement of evaluating physical fitness through assessment of the cardiovascular, respiratory, muscular, and metabolic systems and can help to elucidate the etiology of exercise-related symptoms.[1,2] CPET also provides valuable diagnostic and prognostic information in children with congenital and acquired heart disease and helps to determine prognosis for future events, need for therapies or interventions, and/or guidance for safe exercise participation.[3-7] Additionally, normative values are necessary when considering the use of exercise outcomes in clinical trials.

To accurately interpret the results of a CPET, age-specific normative values for exercise performance must be referenced owing to the significant changes in oxygen carrying capacity and oxygen consumption (VO_2) that occur from childhood, through adolescence and into adulthood. These changes are driven by maturation, changes in lean mass, growth related changes in the ratio of stroke volume and heart rate (HR) contributing to cardiac output and VO_2 in the exercising muscle. Adjusting for age to account for these significant changes in exercise physiology during childhood is required for appropriate comparisons of exercise performance between children of different ages.

BMI	Body mass index	VE	Minute ventilation
BP	Blood pressure	VO_2	Oxygen consumption
CPET	Cardiopulmonary exercise test	V_T	Tidal volume
HR	Heart rate	V_D/V_T	Dead space
MVV	Maximum voluntary ventilation	VE/VO_2	Ventilatory equivalents of oxygen
O_2 pulse	Oxygen pulse		
RER	Respiratory exchange ratio	VE/VCO_2	Ventilatory equivalents of carbon dioxide
VAT	Ventilatory anaerobic threshold		
VD/VT	Physiologic dead space to VT ratio		

From the [1]Division of Cardiology, Exercise Physiology laboratory, and [2]Healthcare Analytics Unit, Center for Pediatric Clinical Effectiveness and Policy Lab, Children's Hospital of Philadelphia, Philadelphia, PA; [3]Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI; [4]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; and [5]Vyaire Medical, Bettawa, IL

Supported in part by the Cardiac Center Clinical Research Core at the Children's Hospital of Philadelphia. Support for validation of formulae was provided by Keith Kwiatkowski from Vyaire Medical, Bettawa, IL. The authors declare no conflicts of interest.

0022-3476/$ - see front matter. © 2020 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.jpeds.2020.09.018

The most commonly referenced normative values for CPET in children come from small cohorts of healthy school age children from homogenous populations in the 1980s.[8,9] Additionally, data on ventilatory mechanics during exercise in preadolescent children have not been previously reported and are usually extrapolated from adult data. Our study aims to develop normative values for 28 key aerobic and ventilatory variables measured during a peak CPET.

Methods

The study was approved by the Institutional Review Board of the Children's Hospital of Philadelphia. Written informed consent was waived owing to the retrospective nature of the study.

Participants were included in our study if they were between the ages of 6 and 18 years and underwent peak ramp cycle exercise stress testing at The Children's Hospital of Philadelphia between January 1999 and December 2015 (with the exception of 2008 owing to technical limitations with gas-exchange metabolic data from that year). Patients with extreme body mass index (BMI) defined as less than the 5th percentile or greater than the 95th percentile based on the 2000 Centers for Disease Control and Prevention Growth Charts were excluded based on sensitivity analyses that demonstrated exclusion of extreme BMI resulted in more precise estimates.[10] All participants were identified through the Exercise Physiology Laboratory database, had structurally and functionally normal hearts, and had undergone a single peak CPET with normal aerobic and ventilatory variables as interpreted by our laboratory's exercise physiologists in comparison with previously established values.[8] A peak test was defined as achieving a peak respiratory exchange ratio (RER) of 1.10 or greater, using a ramp cycle ergometer protocol. Each participant's medical record was reviewed for documentation of normal cardiac structure and normal cardiopulmonary function based on physical examination, electrocardiogram, and/or echocardiogram reports. Participants were included if they met the criteria as noted and underwent the CPET for functional chest pain, presyncope, syncope, palpitations, family history of congenital cardiac anomaly, or family history of sudden death. Participants were excluded if they were under 6 years or older than 18 years of age, diagnosed with any cardiac abnormality or lung disease or arrhythmia, were taking cardiovascular medication, performed more than one exercise stress test or echocardiogram at our institution, or underwent treadmill exercise stress tests. Participants were also excluded if they did not perform a peak exercise stress test based on an RER of less than 1.10.

All CPET variables are shown in Table I. Each participant's height and weight were measured before

Table I. Exercise stress test variables

Variables	Variable definition	Variable units
FVC rest	Forced vital capacity at rest	Liter
FEV_1 rest	Forced expiratory volume in 1 second at rest	Liter
MVV rest	Maximal voluntary ventilation at rest	Liter/minute
VD/VT rest	Dead space to tidal volume ratio at rest	Percent
VD/VT peak	Dead space to tidal volume ratio at peak exercise	Percent
VE peak	Minute ventilation at peak exercise	Liter/minute
RR peak	Respiratory rate at peak exercise	Breath/minute
VT peak	Tidal volume at peak exercise	Liter
Breathing reserve actual	Breathing reserve (measured) at peak exercise	Percent
Breathing reserve estimate	Breathing reserve from estimated MVV (40 × FEV_1) at peak exercise	Percent
$PETO_2$ peak	Partial pressure of end-tidal oxygen at peak exercise	mm Hg
$PETCO_2$ peak	Partial pressure of end-tidal carbon dioxide at peak exercise	mm Hg
VE/VO_2 at VAT	Ventilatory equivalents of oxygen at ventilatory anaerobic threshold	None
VE/VCO_2 at VAT	Ventilatory equivalents of carbon dioxide at ventilatory anaerobic threshold	None
VE/VCO_2 slope	Slope of minute ventilation vs carbon dioxide production below terminal hyperventilation	None
Peak VO_2	Oxygen consumption at peak exercise	Milliliter/minute
VO_2 at VAT	Oxygen consumption at ventilatory anaerobic threshold	Milliliter/minute
VO_2 at VAT/Peak VO_2	Percentage of peak oxygen consumption when ventilatory anaerobic threshold occurs	Percent
Peak WR	Peak work rate	Watt
RER	Respiratory Exchange Ratio	None
O_2 Pulse rest	Oxygen pulse at rest	Milliliter/beat
O_2 Pulse peak	Oxygen pulse at peak exercise	Milliliter/beat
SBP rest	Systolic blood pressure at rest	mm Hg
SBP peak	Systolic blood pressure at peak exercise	mm Hg
DBP rest	Diastolic blood pressure at rest	mm Hg
DBP peak	Diastolic blood pressure at peak exercise	mm Hg
HR rest	Heart rate at rest	Beat/minute
HR peak	Heart rate at peak exercise	Beat/minute

the exercise stress test. Height was measured to the nearest millimeter in bare stocking feet with the participant standing upright against a wall-mounted stadiometer. Weight was measured to the nearest tenth of a kilogram, without shoes and in light clothes (t-shirt, underwear, shorts or pants, and socks), using a portable digital scale.

As part of a complete CPET, our laboratory performs baseline pulmonary function testing to evaluate for underlying pulmonary abnormalities that may contribute to abnormal exercise performance. Before exercise testing all participants performed spirometry consisting of inspiratory and expiratory flow volume loops to estimate forced vital capacity, forced expiratory volume at 1 second, and maximum voluntary ventilation (MVV). MVV was directly measured over a 10-second interval and multiplied by 6 to provide the MVV over 1 minute. The measured MVV was used to calculate the breathing reserve at peak exercise using a standard formula.[11] Owing to potential error in measuring MVV in pediatric patients owing to poor technical effort, an alternative estimate of MVV is also calculated using the formulate forced expiratory volume at 1 second $\times$ 40 to provide an estimated breathing reserve.

Participants were included if they exercised to the limit of their tolerance using an electronically braked cycle ergometer (SensorMedics VIAsprint 150P, Yorba Linda, California). A peak test was defined as achieving a peak RER of greater than or equal to 1.10. The protocol consisted of 3 minutes of pedaling in an unloaded state (0 watts), followed by a ramp increase in work rate (WR) to peak exercise capacity and peak WR.[8] The slope of the ramp protocol was designed to achieve a peak WR of 3 watts/kg in females and preadolescent males and 3.5 watts/kg in adolescent males in 10-12 minutes of cycling time, with the ramp slope increase ranging from 10 to 25 watt per minute based on participant weight. Participants were encouraged to maintain a pedaling cadence (revolutions per minute) between 60 and 90 revolutions per minute throughout the study with an average of 60-70 revolutions per minute maintained until the last minute of exercise, where participants were encouraged to increase their peddling speed to achieve peak WR. This range was within the specified limits of the cycle ergometer to maintain an accurate WR. The children were able to view their cadence on a meter located in the center of the cycle handlebars. Clinical exercise physiologists trained at either a Masters or PhD level were present during the exercise stress testing and encouraged participants to exercise to their maximal volition. However, no attempt was made to standardize encouragement techniques used, because standardized approaches for providing encouragement during CPET do not exist.

A 12-lead electrocardiogram (Marquette Case-8000, Milwaukee, Wisconsin) was obtained at rest in the supine, sitting, and standing positions; during hyperventilation; during each minute of exercise; and during the 10 minutes of recovery. The cardiac rhythm was monitored continuously throughout the study. Blood pressure (BP) was measured in the left arm by auscultation at rest and every 3 minutes during exercise and recovery.

Breath-by-breath metabolic data measuring VO_2 and carbon dioxide production during exercise and the first 10 minutes of exercise recovery were obtained throughout the exercise study using a commercially available metabolic cart (SensorMedics V29 Encore). Measured variables are described in Table I and included minute VO_2 at peak exercise and at ventilatory anaerobic threshold (VAT), oxygen pulse (O_2 pulse) at rest and at peak exercise, minute ventilation (VE) at peak exercise, tidal volume (VT) at peak exercise, partial pressure of end-tidal oxygen and end-tidal carbon dioxide at peak exercise, respiratory rate at peak exercise, ventilatory equivalents of oxygen (VE/VO_2) and ventilatory equivalents of carbon dioxide (VE/VCO_2) at the VAT, VE/VCO_2 slope measured below the onset of terminal hyperventilation (when both the VE/VO_2 and carbon dioxide rise resulting in a fall in $PaCO_2$), RER at peak exercise, physical working capacity at peak exercise (WR, in watts), HR, and BP at rest and peak exercise. VAT was measured manually by both the exercise physiologist and the supervising cardiologist using the V-slope and ventilatory equivalents methods.[12] Estimated physiologic dead space to VT ratio (VD/VT) and breathing reserve were calculated at rest and peak exercise using standard methods.[11] All data were averaged over 10-second intervals for measurements at VAT and peak exercise.

Descriptive statistics for participant demographics were computed using traditional measures of central tendency and variability. To examine sex- and age-specific normative curves in CPET results, extreme or biologically implausible values defined as over mean $\pm$ 5 SDs were excluded in the analysis (17 participants were excluded based on these criteria). Testing for year effect was performed and did not demonstrate a significant year difference on CPET variables. Owing to the observed nonlinear association between CPET and age, we used mixed-effects regression models with fractional polynomial functions to describe its curvilinear fit across age. The fractional polynomial functions have been widely used to describe pediatric trajectory in various clinical outcomes. And it describes fructuated trajectories better for a long-term period with a more parsimonious model than other methods.[13-15] Fractional polynomial of degree m for age with powers $p_1, \ldots, p_m$ is given by $FPm(age) = \beta 1 \cdot age^{P1} + \ldots + \beta m \cdot age^{pm}$, where Powers $p_1, \ldots, p_m$ are taken from a fixed set of 8 candidate values $\{-2, -1, -0.5, \log, 0.5, 1, 2, 3\}$.[16]

A total of 164 models with the dimension of the fractional polynomial up to 3 (m = 3, chosen by the plotted

Table III. The age and sex-specific normative values for cardiopulmonary exercise stress test variables using fractional polynomial models in regression analysis after adjusting for race and BMI

	Males	Females
Variables	Equation	Equation
FVC rest	$1.188628 - 0.0412131*age^3 + 0.0299612*age^3*ln(age) - 0.0054125*age^3*\{ln(age)\}^2 + 0.1234873*BMI - 0.5752623*black - 0.2031294*other$	$-0.8467293 + 0.0337128*age^2 - 0.0013808*age^3 + 0.0697378*BMI - 0.4566358*black - 0.1070514*other$
FEV_1 rest	$1.620875 - 0.0405234*age^3 + 0.0292996*age^3*ln(age) - 0.0052719*age^3*\{ln(age)\}^2 + 0.0837035*BMI - 0.4510965*black - 0.1513882*other$	$-0.0371021 + 0.0047576*age^3 - 0.0015234*age^3*ln(age) + 0.049804*BMI - 0.4011955*black - 0.1349187*other$
MVV rest	$54.79148 - 1.30032*age^3 + 0.9421805*age^3*ln(age) - 0.1696263*age^3*\{ln(age)\}^2 + 2.609113*BMI - 5.527065*black - 3.832014*other$	$12.81973 + 0.14482*age^3 - 0.0458817*age^3*ln(age) + 1.010064*BMI - 5.58469*black - 5.345177*other$
VD/VT rest	$60.95255 - 0.5116132*age - 0.7986126*BMI + 1.898956*black - 0.0053195*other$	$52.84662 - 0.3234297*age - 0.4548131*BMI + 4.238533*black + 3.238546*other$
VD/VT peak	$42.1705 - 0.0335475*age^3 + 0.0105605*age^3*ln(age) - 0.4620014*BMI + 2.946075*black + 0.1740549*other$	$41.56646 - 0.8954817*age - 0.4049347*BMI - 2.037338*black + 0.9183626*other$
VE peak	$35.61497 - 0.7963335*age^3 + 0.5905864*age^3*ln(age) - 0.1084876*age^3*\{ln(age)\}^2 + 2.500312*BMI - 9.351512*black - 6.143172*other$	$12.80688 + 2.957673*age + 1.172315*BMI - 4.161862*black - 1.543097*other$
RR peak	$75.68001 - 1.034606*age - 0.1765659*BMI + 4.451166*black - 1.207478*other$	$76.8412 - 0.7851545*age - 0.4819193*BMI + 5.389339*black - 2.059039*other$
VT peak	$0.3903699 - 0.0180986*age^3 + 0.013292*age^3*ln(age) - 0.0024191*age^3*\{ln(age)\}^2 + 0.0584863*BMI - 0.31064*black - 0.1018861*other$	$-0.2962193 + 0.0125602*age^2 - 0.0004855*age^3 + 0.0332004*BMI - 0.2396221*black - 0.0548401*other$
Breathing reserve actual	$2.888027 + 1.584844*age - 0.1818336*BMI + 0.9909358*black + 4.017748*other$	$11.4302 + 0.9651506*age - 0.1224104*BMI - 0.1903562*black - 0.8655168*other$
Breathing reserve estimate	$8.603027 + 1.445277*age - 0.0775038*BMI - 2.413392*black + 2.809061*other$	$28.44566 - 762.975/age^2 + 0.4004237*BMI - 6.707933*black - 1.460394*other$
$PETO_2$ peak	$116.5765 + 0.4310834*age - 0.1346674*BMI - 1.396031*black - 0.3503552*other$	$115.3876 + 0.290326*age - 0.0306626*BMI + 1.266142*black + 0.5359092*other$
$PETCO_2$ peak	$30.02187 + 0.1697649*age + 0.1115669*BMI + 1.34506*black + 0.6638981*other$	$30.17401 - 0.0166946*age + 0.1946096*BMI + 0.0728073*black + 0.3160021*other$
VE/VO_2 at VAT	$38.92668 - 0.5131084*age - 0.1161358*BMI + 0.2021061*black + 0.8229737*other$	$38.79297 - 0.190835*age - 0.2439275*BMI + 0.8691763*black + 1.412078*other$
VE/VCO_2 at VAT	$40.42918 - 0.01925*age^3 + 0.0060597*age^3*ln(age) - 0.1050647*BMI + 0.4832499*black + 0.0283904*other$	$41.47711 - 0.3277488*age - 0.2538881*BMI + 1.347517*black + 0.4198313*other$
VE/VCO_2 slope	$38.14903 - 0.5265288*age - 0.0917258*BMI + 0.1841037*black - 0.0323037*other$	$39.77808 - 0.3862257*age - 0.2373968*BMI + 0.2418698*black + 0.3277799*other$
Peak VO_2	$663.4761 - 109.0507*age^2 + 25.73226*age^3 - 6.791189*age^3*ln(age) + 96.15952*BMI - 187.1794*black - 94.15266*other$	$-738.0738 + 43.88493*age^2 - 13.26705*age^2*ln(age) + 45.71032*BMI - 200.6486*black - 74.13314*other$
VO_2 at VAT	$-2137.568 + 944.0926*ln(age) + 54.46946*BMI - 42.9567*black - 29.65506*other$	$587.442 - 28707.97/age^2 + 32.30628*BMI - 63.75956*black - 15.8611*other$
VO_2 at VAT/Peak VO_2	$110.5754 - 1538.825/age^2 - 0.5160478*age^2 + 0.0203701*age^3 - 0.0872369*BMI + 2.431914*black + 1.654535*other$	$66.2173 - 0.9623668*age + 0.2650668*BMI + 2.484744*black + 0.6463145*other$
Peak WR	$51.84456 - 2.295074*age^3 + 1.680791*age^3*ln(age) - 0.3056368*age^3*\{ln(age)\}^2 + 6.090936*BMI - 14.64468*black - 9.79048*other$	$-33.95983 + 1.495278*age^2 - 0.060288*age^3 + 2.985883*BMI - 19.39153*black - 4.967908*other$
RER	$1.067902 + 0.0125143*age - 0.000479*BMI - 0.0089041*black - 0.0120737*other$	$1.112898 + 0.011415*age - 0.0019272*BMI + 0.014646*black - 0.0205098*other$
O_2 Pulse rest	$-2.46314 + 0.2030271*age + 0.1464214*BMI + 0.0240332*black + 0.0421795*other$	$0.2083499 + 0.0730463*age + 0.0601541*BMI - 0.3141794*black - 0.1277118*other$
O_2 Pulse peak	$4.662809 - 0.651031*age^2 + 0.1498974*age^3 - 0.0393463*age^3*ln(age) + 0.5137186*BMI - 0.8859415*black - 0.6901005*other$	$-2.079577 + 0.0881097*age^2 - 0.0035572*age^3 + 0.2232603*BMI - 0.8522631*black - 0.356455*other$
SBP rest	$80.20814 + 2.261817*age + 0.1820885*BMI - 0.9589029*black + 1.903403*other$	$112.5847 - 675.5525/age^2 + 0.0056156*BMI + 0.5568862*black + 0.8939835*other$
SBP peak	$136.2253 - 0.8050038*age^3 + 0.5781798*age^3*ln(age) - 0.1033753*age^3*\{ln(age)\}^2 + 1.409337*BMI + 5.934252*black + 2.934223*other$	$155.4187 - 2017.648/age^2 + 0.2404293*BMI - 0.7604079*black - 0.092367*other$
DBP rest	$63.13579 + 0.5911718*age - 0.0063525*BMI + 1.854784*black - 0.7529992*other$	$63.57368 + 0.4393776*age + 0.0639073*BMI + 1.109765*black + 1.62713*other$
DBP peak	$63.52522 + 0.3808509*age - 0.2397426*BMI - 0.1078364*black + 1.539684*other$	$59.58667 + 0.3172016*age + 0.0473747*BMI + 2.654897*black + 1.723606*other$
HR rest	$104.2178 - 1.866549*age - 0.0547699*BMI - 1.601633*black + 2.514374*other$	$103.7705 - 1.477848*age - 0.042755*BMI + 0.7677255*black + 7.45018*other$
HR peak	$156.1962 + 97.36768*ln(age) - 58.13099*sqrt(age) - 0.067071*BMI - 2.066766*black + 0.3762757*other$	$60.13304 + 56.41577*sqrt(age) - 0.1413061*age^3 + 0.042915*age^3*ln(age) + 0.1223133*BMI - 3.225899*black - 0.3435899*other$

DBP, Diastolic blood pressure; *FEV$_1$*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *PETCO$_2$*, partial pressure of end-tidal carbon dioxide; *PETO$_2$*, partial pressure of end-tidal oxygen; *RR*, respiratory rate; *SBP*, systolic blood pressure.
Race was entered into formula as a value of 1 for respective category. For example, if a participant was white, “0” was entered for black and other. If the participant was black, “1” was entered for black and “0” for other. If the participant was other race (non-white and non-black), “0” was entered for black and “1” for other.

data and sensitivity analysis up to 4 dimension) were tested for each CPET outcome and the parsimonious polynomial models were determined by the function selection procedure in STATA (StataCorp, College Station, Texas), that is, selecting the simpler model with the lowest Bayesian information criterion, which indicated a better fit than other models.[17,18] The expected normative values of CPET were presented as regression models and plotted by age and sex for children 6 and 18 years of age after adjusting for race and BMI. Although our laboratory follows the National Institutes of Health definitions of race and ethnicity when entering demographic data for participants, owing to limited numbers of participants of American Indian or Alaska Native, Asian, Hispanic or Latino, Native Hawaiian or other Pacific Islander race and ethnicity, for the purposes of this project, race was defined as white, black, or other. Race was entered into formula as a value of 1 for respective category. Analyses were conducted using SAS 9.3 (SAS Institute, Cary, North Carolina) and STATA 15.

Normative data regression models for all 28 variables were then validated in a separate cohort of children who underwent CPET from 2018 to 2019 who met the same study inclusion and exclusion criteria as the initial study cohort who had undergone testing from 1999 to 2015. Model validation for the 28 variables was assessed by comparing the actual metabolic measurement from the healthy validation cohort to the predicted value $\pm$ 10%.

Results

Of the 2111 participants screened, a total of 1829 met the study inclusion criteria based on the normal BMI criteria. The average age was 13.6 $\pm$ 2.6 years, 52% were male, with an average BMI of 20.4 $\pm$ 2.9 kg/m_2 and BMI percentile of 62 $\pm$ 23% (**Table II**; available at www.jpeds.com). The racial distribution was 77% white, 13% black, and 10% other. Best-fit regression models stratified by sex for each variable are shown in **Table III**. Assessment of the results by race showed significant differences between black participants and other racial groups for most data. For this reason, regression formulas included an adjustment for race. As stated elsewhere in this article, race was defined as white, black, or other and was entered into the formula as a value of 1 for the respective categories. For example, if a participant was white, "0" was entered for black and other. If the participant was black, "1" was entered for black and "0" for other. If the participant was other race (non-white and non-black), "0" was entered for black and "1" for other. An example calculation of a predictive value for peak VO_2 is shown at the bottom of **Table IV** (available at www.jpeds.com).

Resting Pulmonary Function Testing

Figure 1 (available at www.jped.com) shows the curves by age and sex for resting pulmonary function testing including forced vital capacity, forced expiratory volume at 1 second, MVV, and VD/VT. Males had greater peak values across all pulmonary function variables than females. There was a positive correlation between age and pulmonary function values until approximately age 14 years for females and 16 years for males, after which point the values generally plateaued as shown by the slopes illustrated in **Figure 1**. There was improved ventilatory efficiency with age with a negative correlation between age and estimated ratio of physiologic VD/VT.

Ventilatory Response to Exercise

Figures 2 and **3** (available at www.jpeds.com) show the values for respiratory function at peak exercise. With age, VE increased (males greater than females) driven by increased VT as evidenced by the decrease in peak respiratory rate with age. Partial pressure of end-tidal oxygen and partial pressure of end-tidal carbon dioxide at peak exercise increased gradually with age, although there was not a significant difference by sex. There was improved ventilatory efficiency with age with a negative correlation between age and the ventilatory equivalents of CO_2 (VE/VCO_2) measured at the VAT, the slope of VE/VCO_2 measured below the onset of terminal hyperventilation, and estimated VD/VT at rest and peak exercise. At the VAT, in children older than 11 years, females had higher VE/VO_2 and VE/VCO_2, although both values decreased with age as shown by the slope illustrated in **Figure 4** (available at www.jpeds.com). Notably, below age 12 years, VE/VO_2 and VE/VCO_2 at VAT were above 30. The VE/VCO_2 slope (**Figure 2**) decreased with age across both sexes. Breathing reserve increased with age and was greater for females than males for the estimated breathing reserve, although this finding was not seen in the measured breathing reserve.

Aerobic and Physical Working Capacity

Figure 5 shows the value curves by age and sex for unindexed peak VO_2 and WR. Again, males had greater values than females across all age groups that widen at 12 years old based on the slope shown in **Figure 5**. There was a positive correlation between age and values for peak VO_2 and WR until age 16 years, after which point both curves plateaued. Although VO_2 at VAT increased by age across both sexes, the proportion of peak VO_2 when VO_2 at VAT occurred (VO_2 at VAT/Peak VO_2) decreased with age for both sexes from 65% at 8 years old to 55% at 18 years old. The RER at peak exercise also increased with

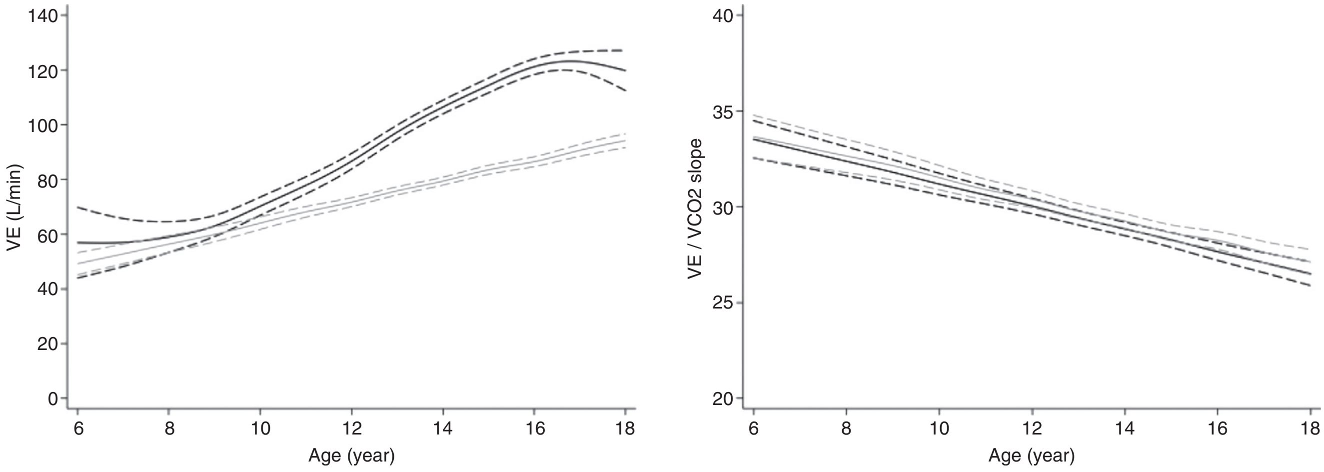

Figure 2. Age- and sex-specific curves for VE on right and slope of minute ventilation vs carbon dioxide production below terminal hyperventilation (VE/VCO_2 slope) on left. Males shown in *black*, females in *gray*. *Solid line* represents mean value and *dashed lines* represent 95% CIs.

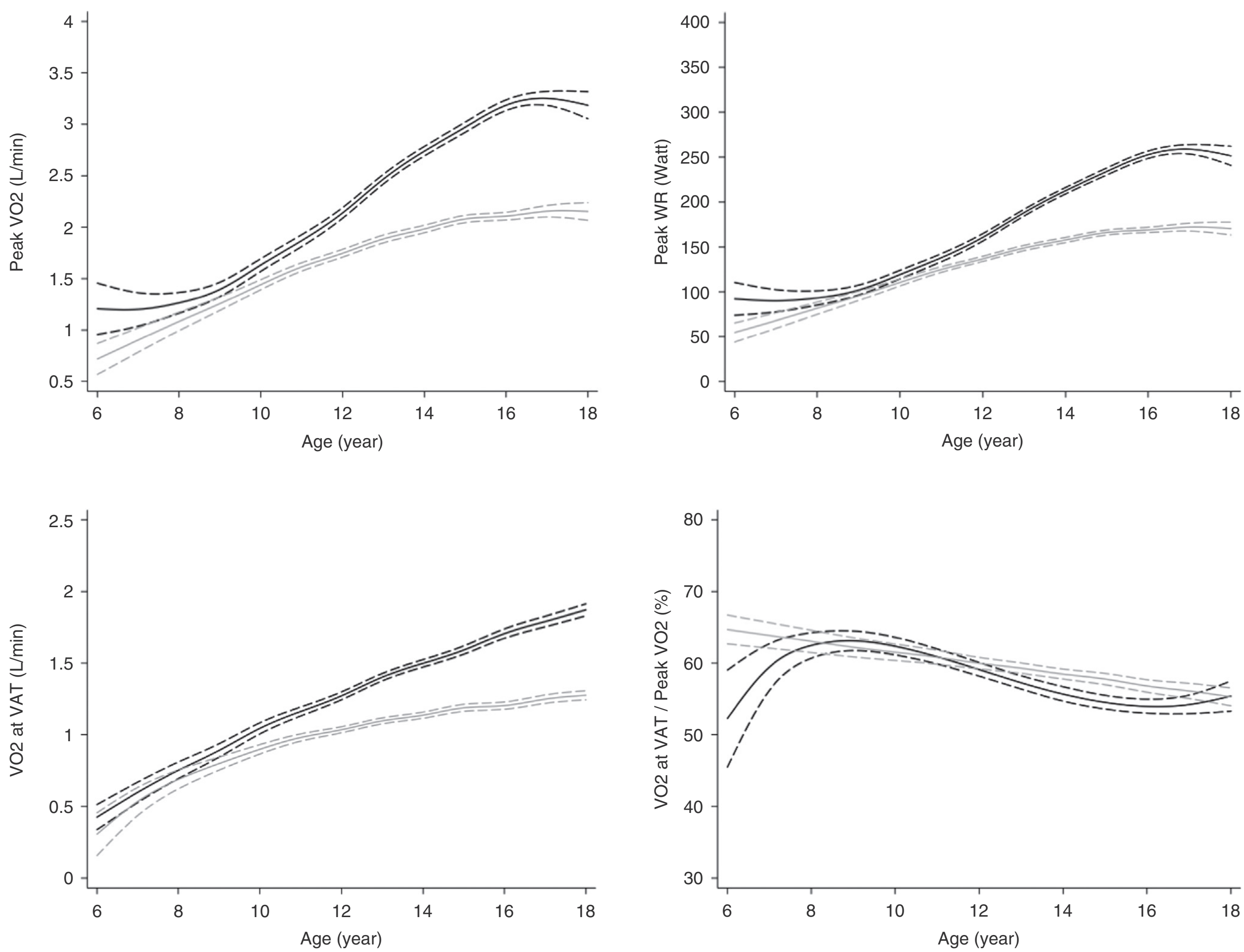

Figure 5. Age- and sex-specific curves for peak VO_2 on upper right, peak work rate (peak WR) on upper left, VO_2 at VAT on lower left, percent of peak VO_2 when ventilator anaerobic threshold occurs (VO_2 at VAT/Peak VO_2) on lower right. Males shown in *black*, females in *gray*. *Solid line* represents mean value and *dashed lines* represent 95% CIs.

age regardless of sex (**Figure 3**). **Figure 6** (available at www.jpeds.com) profiles resting and peak O_2 pulse, which is defined by stroke volume multiplied by arterial-mixed venous O_2 difference and therefore acts as a surrogate for stroke volume, with values for males being greater than females after 10 years old. For both sexes, resting and peak O_2 pulse increased with age.

BP and HR Response to Exercise

Figure 7 (available at www.jpeds.com) shows the resting and peak BP and HR responses during CPET. Systolic BP was higher for males both at rest and peak exercise, with a greater difference seen above age 12 years old based on the slope of the curve in **Figure 7**. In contrast, diastolic BP was similar across sexes both at rest and peak exercise, although there was a greater decrease in the diastolic BP at peak exercise in males than females. The HRs at rest and peak exercise were similar across sexes; with age, there was a gradual decrease in resting HR, but no change in peak HR.

Data Validation

The normative data regression models for all 28 variables were then validated in a second cohort of 50 healthy participants from our laboratory that underwent CPET from 2018 to 2019. The models consistently predicted accurate values, defined as the actual measurement falling between 90% and 110% of the predicted value, in the healthy validation cohort for the 28 variables. **Table IV** provides a comparison between the predicted values for peak VO_2 in our normative data values compared with previously used normative values from Cooper et al.[8] Within the same age and sex population, our dataset provides different predicted peak VO_2 values when BMI and race are incorporated, whereas previously used normative values have only 1 predicted value for peak VO_2 for a given age and sex. For example, based on previously used normative values an 11-year-old boy has a predicted peak VO_2 of 42 mL/kg/minute, whereas our normative data provide a predicted peak VO_2 that ranges from 37 to 46 mL/kg/minute based on their race and BMI.

Discussion

Historically, the most commonly cited normative values for ramp cycle ergometry CPET in children came from a small cohort study of healthy school-age children in 1984.[8] Data were obtained from 109 school-aged children who voluntarily participated after being recruited from local schools, community organizations, and hospital staff. Children were excluded if they were obese, had chronic medical conditions, or were not allowed to participate in normal physical education. Additionally, 86% of the cohort was Caucasian and most were from the middle socioeconomic status. More recently, a study of Canadian school-aged healthy volunteers who performed peak CPET using a ramp protocol developed normative values for several exercise variables; however, this study had a smaller sample size of 228 children.[19] In contrast, our study included data on more than 1800 children from a diverse suburban and urban population that has previously been shown to be reflective of the general pediatric population in the US.[20] However, owing to the underrepresentation of Hispanic or Latino, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander participants in our study, there may be a role for developing regionally specific normative values for CPET in the future for further refinement.

Previous work on ventilation in children have demonstrated a high correlation between ventilation and age as well as lean body mass.[21-24] However, data on normative values of ventilation during exercise in children (including VE, respiratory rate, VT, partial pressure of end-tidal oxygen, partial pressure of end-tidal carbon dioxide, and breathing reserve) had not been previously reported and were often extrapolated from adult data.

Another issue is the concept of appropriate mode of scaling when interpreting aerobic fitness in children of various sizes.[10,25] For more than 30 years, ratio scaling, or indexing peak VO_2 to BMI, had been used in an attempt to standardize pediatric values for aerobic fitness across age and body size. Although the goal of ratio scaling was to provide a simple method to compare aerobic fitness testing among different age individuals, it failed to take into account all the factors that influence aerobic capacity and fitness. Such factors included not only weight, but also height, age, race, sex, and genetics. Similarly, methods, such as allometric scaling, which aims to incorporate the biological mechanisms that link body size to metabolic function, also shared these same limitations by not incorporating multiple variables that influence aerobic fitness.[26] As a consequence, there was no simple scaling mechanism to accurately compare aerobic fitness across age populations. The advantage of our normative data is that they take into account age, BMI, race, and sex in each variable's formula calculation. This factor makes our data generalizable across the pediatric and adolescent populations. Although the use of a fractional polynomial regression model made the calculation of CIs significantly more complex, this issue was readily addressable using the programing abilities of the current generation of commercially available metabolic carts. This approach allows the normative values to be much more specific for the individual participant based on their age, sex, BMI, and race.

There were several potential limitations in the present study. Participants were enrolled after referral to a pediatric cardiologist, raising potential that this may not be a healthy cohort. However, study participants had a detailed cardiac evaluation to rule out evidence of cardiac disease based on a pediatric cardiologist's assessment using a history and physical examination and review of an electrocardiogram and echocardiogram, as well as asymptomatic performance during CPET. The study requirement to exclude those who underwent subsequent cardiac evaluation or testing also helps to mitigate this concern.

Additionally, owing to the lack of standardized approaches for providing encouragement to achieve peak exercise as well as the interoperability across CPET laboratories, there may be some limitation to how our data compare with other laboratories. Because this analysis was a retrospective chart review, some potentially useful data were unavailable. Some examples include lack of data on lean body mass, pubertal status, and physical activity level, which were not available at the time of CPET. However, previous data have shown that physical activity participation accounts for little of the variation in peak VO_2.[27,28] Additionally, the limited number Hispanic or Latino, American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander participants may limit the generalizability of this CPET data to these populations and require future study for further refinement across these subpopulations.

Owing to improved study power in a more contemporary cohort, these data offer improved normative exercise values. Prospective, multi-institutional efforts to continually update and validate normative CPET values in an evolving pediatric population should be an area of ongoing research. ■

Submitted for publication Jun 9, 2020; last revision received Sep 4, 2020; accepted Sep 9, 2020.

Reprint requests: Danielle S. Burstein, MD, 3401 Civic Center Blvd, Cardiology, 8NW64, Philadelphia, PA, 19104. E-mail: bursteind@email.chop.edu

References

1. Nassis GP, Sidossis LS. Methods for assessing body composition, cardiovascular and metabolic function in children and adolescents: implications for exercise studies. Curr Opin Clin Nutr Metab Care 2006;9:560-7.
2. Reybrouck T, Mertens L. Physical performance and physical activity in grown-up congenital heart disease. Eur J Cardiovasc Prev Rehabil 2005;125:498-502.
3. Edelson JEB, Burnstein DS, Paridon SM, Stephens P Jr. Exercise stress testing: A valuable tool to predice risk and prognosis. Prog Pediatr Cardiol 2019;54.
4. Van Hare GF, Ackerman MJ, Evangelista JAK, Kovacs RJ, Myerburg RJ, Shafer KM, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 4: Congenital Heart Disease: a scientific statement from the American Heart Association and American College of Cardiology. Circulation 2015;132:e281-91.
5. Takken T, Giardini A, Reybrouck T, Gewilllig M, Hövels-Gürich HH, Longmuir PE, et al. Recommendations for physical activity, recreation sport, and exercise training in paediatric patients with congenital heart disease: a report from the Exercise, Basic & Translational Research Section of the European Association of Cardiovascular Prevention and Rehabilitation, the European Congenital Heart and Lung Exercise Group, and the Association for European Paediatric Cardiology. Eur J Prev Cardiol 2012;19:1034-65.
6. Paridon SM, Alpert BS, Boas SR, Cabrera ME, Caldarera LL, Daniels SR, et al. Clinical stress testing in the pediatric age group: a statement from the American Heart Association Council on Cardiovascular Disease in the Young, Committee on Atherosclerosis, Hypertension, and Obesity in Youth. Circulation 2006;11315:1905-20.
7. Washington RL, Bricker JT, Alpert BS, Daniels SR, Deckelbaum RJ, Fisher EA, et al. Guidelines for exercise testing in the pediatric age group. From the Committee on Atherosclerosis and Hypertension in Children, Council on Cardiovascular Disease in the Young, the American Heart Association. Circulation 1994;90:2166-79.
8. Cooper DM, Weiler-Ravell D, Whipp BJ, Wasserman K. Aerobic parameters of exercise as a function of body size during growth in children. J Appl Physiol Respir Environ Exerc Physiol 1984;56:628-34.
9. Washington RL, van Gundy JC, Cohen C, Sondheimer HM, Wolfe RR. Normal aerobic and anaerobic exercise data for North American school-age children. J Pediatr 1988;112:223-33.
10. Welsman J, Armstrong N. Interpreting aerobic fitness in youth: the fallacy of ratio scaling. Pediatr Exerc Sci 2019;31:184-90.
11. Stephens P Jr, Paridon SM. Exercise testing in pediatrics. Pediatr Clin North Am 2004;51:1569-87.
12. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986;60:2020-7.
13. Min J, Wen X, Xue H, Wang Y. Ethnic disparities in childhood BMI trajectories and obesity and potential causes among 29,250 US children: findings from the Early Childhood Longitudinal Study-Birth and Kindergarten Cohorts. Int J Obes (Lond) 2018;42:1661-70.
14. Wen X, Kleinman K, Gillman MW, Rifas-Shiman SL, Taveras EM. Childhood body mass index trajectories: modeling, characterizing, pairwise correlations and socio-demographic predictors of trajectory characteristics. BMC Med Res Methodol 2012;12:38.
15. Ryoo JH, Long JD, Welch GW, Reynolds A, Swearer SM. Fitting the fractional polynomial model to non-Gaussian longitudinal data. Front Psychol 2017;8:431.
16. Stata.com. Fractional polynomial regression syntax menu. www.stata.com/manuals13/rfp.pdf. Accessed November 9, 2018.
17. Stata.com. Fp postestimation-Postestimation tools for fp. www.stata.com/manuals13/rfp.pdf. Accessed November 9, 2018.
18. Royston P. Model selection for univariable fractional polynomials. Stata J 2017;17:619-29.
19. Blanchard J, Blais S, Chetaille P, Bisson M, Counil FP, Huard-Girard T, et al. New reference values for cardiopulmonary exercise testing in children. Med Sci Sports Exerc 2018;50:1125-33.
20. Brothers J, McBride M, Paridon A, Zhang X, Paridon S. Fatness is not a factor of fitness: analysis of cardiorespiratory data from healthy children over an 8-year period. Cardiol Young 2013;23:47-53.
21. Cooper DM, Leu SY, Galassetti P, Radom-Aizik S. Dynamic interactions of gas exchange, body mass, and progressive exercise in children. Med Sci Sports Exerc 2014;46:877-86.
22. Cooper DM, Kaplan MR, Baumgarten L, Weiler-Ravell D, Whipp BJ, Wasserman K. Coupling of ventilation and CO2 production during exercise in children. Pediatr Res 1987;21:568-72.
23. Giardini A, Odendaal D, Khambadkone S, Derrick G. Physiologic decrease of ventilatory response to exercise in the second decade of life in healthy children. Am Heart J 2011;161:1214-9.
24. Nagano Y, Baba R, Kuraishi K, Yasuda T, Ikoma M, Nishibata K, et al. Ventilatory control during exercise in normal children. Pediatr Res 1998;43:704-7.
25. Welsman JR, Armstrong N. Interpreting cardiorespiratory fitness in young clinical populations-folklore and fallacy. JAMA Pediatr 2019 [Epub ahead of print].
26. 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 (1985) 2006;100:1851-6.

27. Dencker M, Thorsson O, Karlsson MK, Lindén C, Eiberg S, Wollmer P, et al. Gender differences and determinants of aerobic fitness in children aged 8-11 years. Eur J Appl Physiol 2007;99:19-26.

28. Dencker M, Bugge A, Hermansen B, Anderson LB. Objectively measured daily physical activity related to aerobic fitness in young children. J Sports Sci 2010;28:139-45.

50 Years Ago in *The Journal of Pediatrics*

Hepatopulmonary Syndrome: Transplantation Is the Big Difference

Kravath RE, Scarpelli EM, Bernstein J. Hepatogenic cyanosis: arteriovenous shunts in chronic active hepatitis. J Pediatr 1971;78:238-45.

Fifty years ago, Kravath et al presented a girl with chronic hepatitis, portal hypertension, cyanosis, spider nevi, exertional dyspnea, and clubbing. From the onset of symptoms at the age of 10 years until she died 6 years later, she had several hospital admissions. With advancing liver disease, she had lower oxygen saturation in blood, lower arterial PaO_2 in, and a low single-breath carbon monoxide diffusing capacity. Postmortem examination revealed pulmonary arteriovenous anastomoses and dilated vascular channels.

Hepatopulmonary syndrome is characterized by impaired arterial oxygenation induced by intrapulmonary vascular dilatation in the setting of liver disease, portal hypertension, or congenital portosystemic shunts. In 1884, a woman with liver cirrhosis and cyanosis was described, and arteriovenous fistulas and dilatation of pulmonary vessels were found in 1956 thus in 1977 the term hepatopulmonary syndrome was suggested.[1-3]

Hepatopulmonary syndrome evolves insidiously in some children with chronic liver disease and is accompanied by complications and higher mortality. In severe cases, oxygen therapy may be required. Even though intrapulmonary vascular dilation could be subclinical without hypoxemia, pulse oximetry may be useful for screening. The mechanisms of hepatopulmonary syndrome are likely to involve endogenous vasodilators and pulmonary vascular remodeling.[4]

Fifty years ago, the severe liver disease progressed slowly despite a thorough workup and this patient eventually developed a coma and died. Hepatopulmonary syndrome often resolves after liver transplantation and the availability of transplantation is the major difference from the situation 50 years ago.

Runar Almaas, MD, PhD
Department of Pediatric Research
Oslo University Hospital
Oslo, Norway

Ola Didrik Saugstad, MD, PhD
Department of Pediatric Research
University of Oslo
Oslo, Norway

Ann and Robert H. Lurie Children's Hospital of Chicago
Northwestern University Feinberg School of Medicine
Chicago, Illinois

References

1. Fluckiger M. Vorkommen von trommelschagel formigen fingerendphalangen ohne chronische veranderungen an der lungen oder am herzen. Wien Med Wochenschr 1884;34:1457.
2. Rydell R, Hoffbauer FW. Multiple pulmonary arteriovenous fistulas in juvenile cirrhosis. Am J Med 1956;21:450-60.
3. Kennedy TC, Knudson RJ. Exercise-aggravated hypoxemia and orthodeoxia in cirrhosis. Chest 1977;72:305-9.
4. Warner S, McKiernan PJ, Hartley J, Ong E, van Mourik ID, Gupte G, et al. Hepatopulmonary syndrome in children: a 20-year review of presenting symptoms, clinical progression, and transplant outcome. Liver Transpl 2018;24:1271-9.

Table II. Patient demographics

Characteristics	n = 1829
Age, years	13.6 ± 2.6
Male sex	959 (52)
BMI, kg/m^2	20.4 ± 2.9
BMI %	61.6 ± 23.4
Race	
White	1410 (77)
Black	234 (13)
Other	185 (10)

Values are mean ± SD or number (%).

Table IV. Comparison of predicted peak VO_2 between Burstein et al (present study) and Cooper et al[10]

Example scenarios	Burstein et al Peak VO_2 (mL/kg/minute)	Cooper et al Peak VO_2 (mL/kg/minute)
An 11-year-old white male with BMI 15 and weight 32 kg*	46	42
An 11-year-old white male with BMI 20 and weight 48 kg	41	42
An 11-year-old black male with BMI 15 and weight 32 kg	41	42
An 11-year-old black male with BMI 20 and weight 48 kg	37	42
An 11-year-old white female with BMI 15 and weight 32 kg	44	38
An 11-year-old white female with BMI 20 and weight 48 kg	34	38
An 11-year-old black female with BMI 15 and weight 32 kg	38	38
An 11-year-old black female with BMI 20 and weight 48 kg	30	38
A 16-year-old white male with BMI 18 and weight 50 kg	55	50
A 16-year-old white male with BMI 24 and weight 77 kg	43	50
A 16-year-old black male with BMI 18 and weight 50 kg	51	50
A 16-year-old black male with BMI 24 and weight 77 kg	41	50
A 16-year-old white female with BMI 18 and weight 45 kg	42	34
A 16-year-old white female with BMI 25 and weight 70 kg	32	34
A 16-year-old black female with BMI 18 and weight 45 kg	38	34
A 16-year-old black female with BMI 25 and weight 70 kg	29	34

*Example of peak VO_2 formula for an 11-year-old black male with BMI 15 Peak VO_2 = 663.4761 − 109.0507*age^2 + 25.73226*age^3 − 6.791189*age^3*ln(age) + 96.15952*BMI − 187.1794*black − 94.15266*other Peak VO_2 = 663.4761 − 109.0507*11^2 + 25.73226*11^3 − 6.791189*11^3*ln(11) + 96.15952*15 − 187.1794.

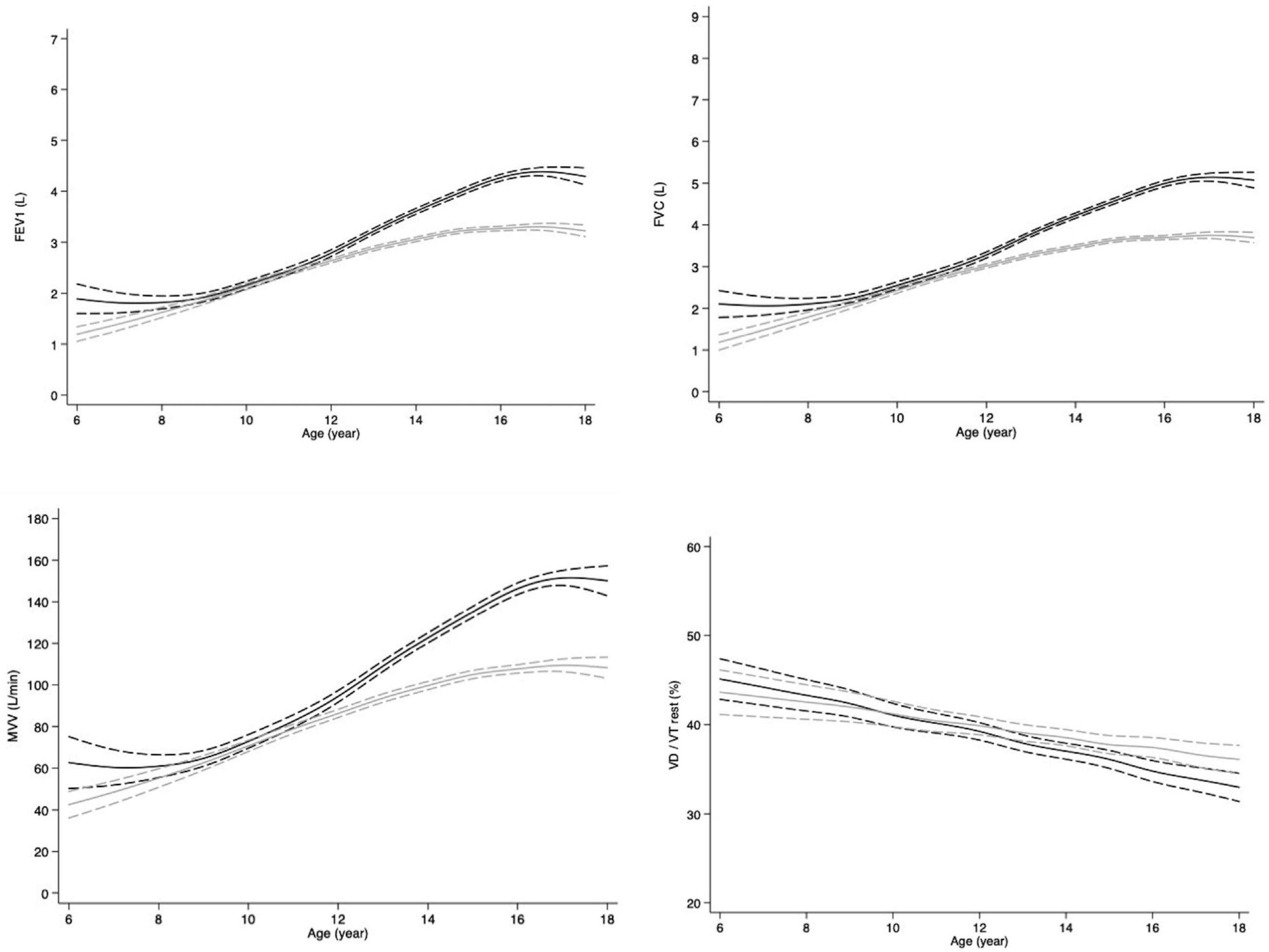

Figure 1. Age- and sex-specific curves for baseline pulmonary function testing (forced vital capacity [FVC], forced expiratory volume at 1 second [FEV_1], MVV, VD/VT) at rest. Males shown in *black*, females in *red*. *Solid line* represents mean value and *dashed lines* represent 95% CIs.

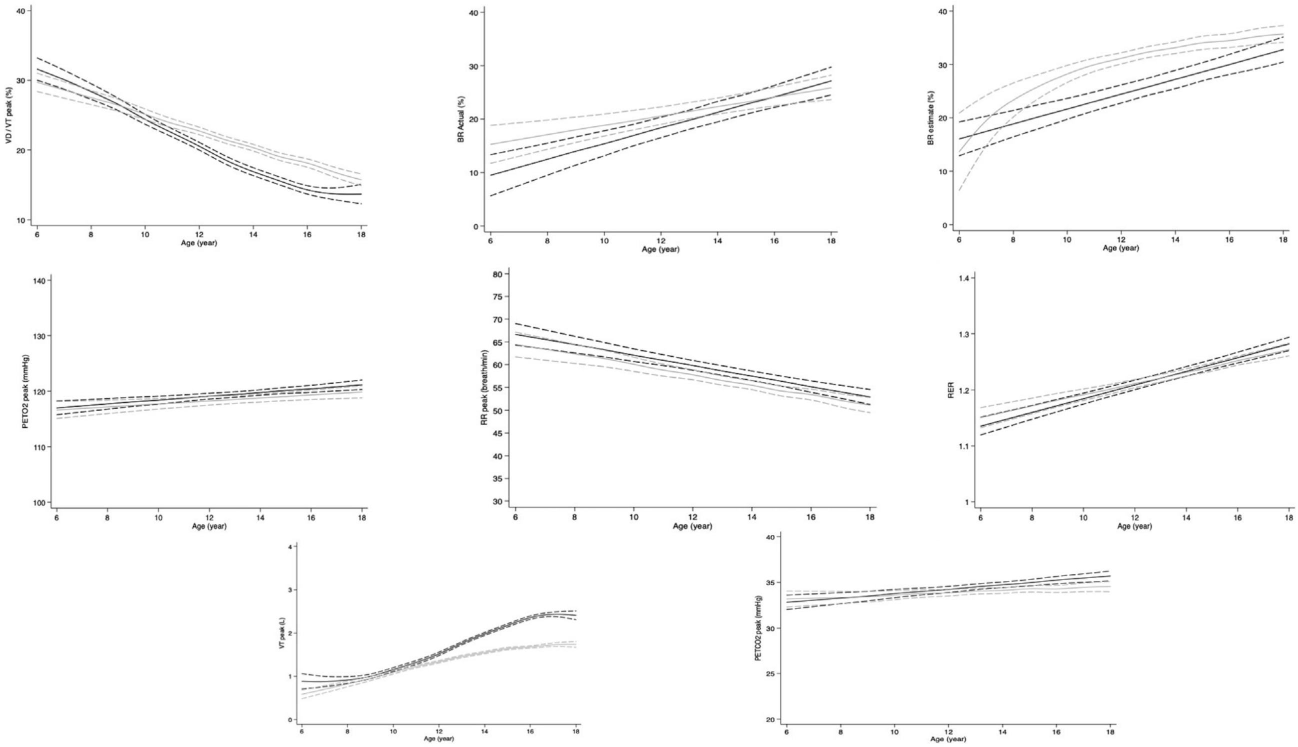

Figure 3. Age- and sex-specific curves for pulmonary function at peak exercise. Variables include VD/BT, breathing reserve actual and estimate, partial pressure of end-tidal oxygen ($PETO_2$), respiratory rate, RER, VT, partial pressure of end-tidal carbon dioxide ($PETCO_2$). Males shown in *black*, females in *red*. *Solid line* represents mean value and *dashed lines* represent 95% CIs.

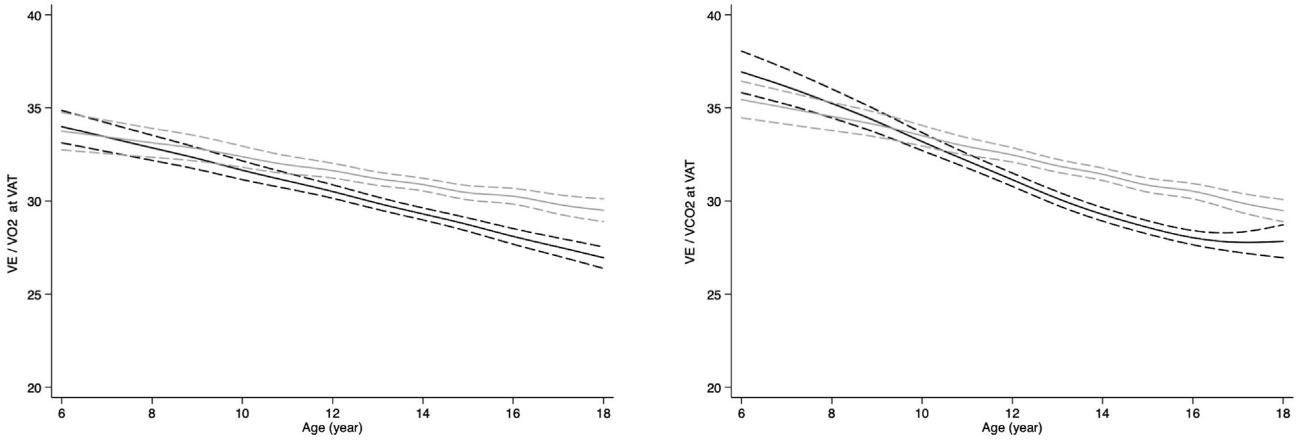

Figure 4. Age- and sex-specific curves for ventilatory equivalents at anaerobic threshold (VE/VO_2 at VAT and VE/VCO_2 at VAT). Males shown in *black*, females in *red*. *Solid line* represents mean value and *dashed lines* represent 95% CIs.

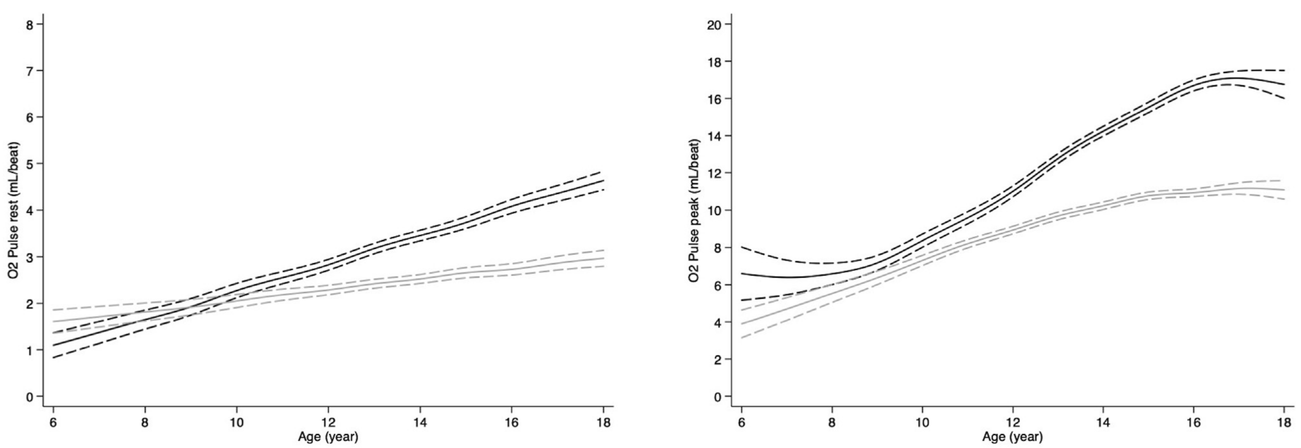

Figure 6. Age- and sex-specific curves for O_2 pulse at rest and peak exercise. Males shown in *black*, females in *red*. *Solid line* represents mean value and *dashed lines* represent 95% CIs.

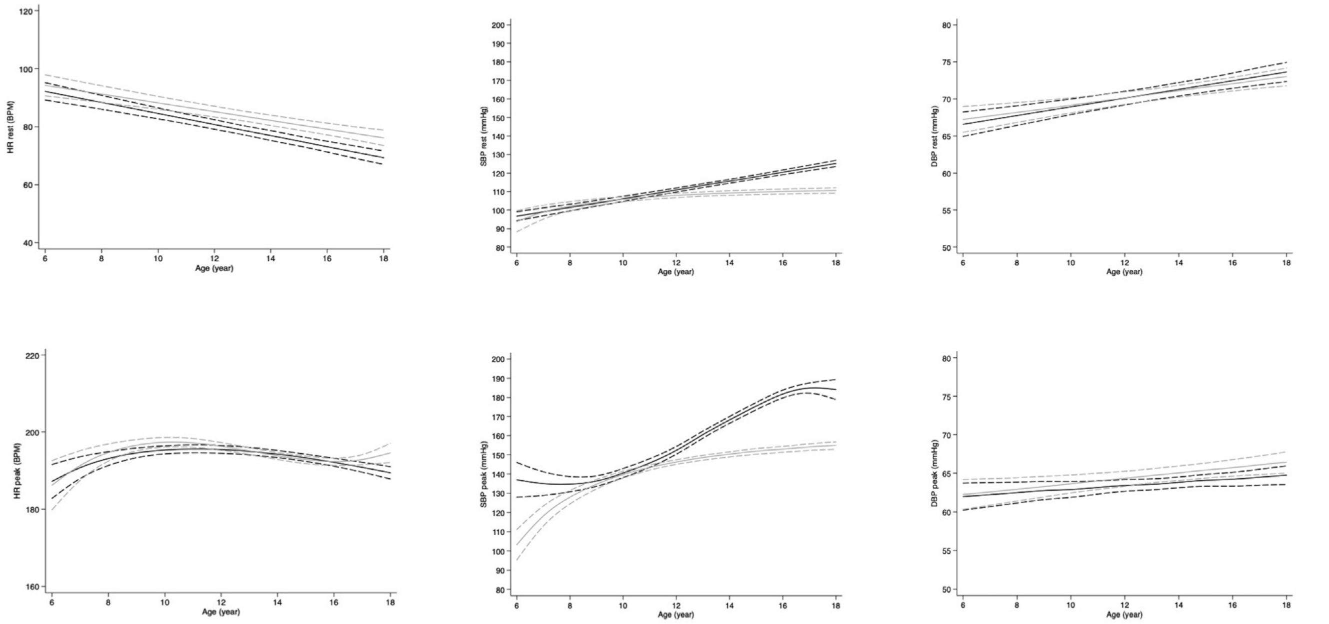

Figure 7. Age- and sex-specific curves for HR, systolic and diastolic BP at rest and at peak exercise. Males shown in *black*, females in *red*. *Solid line* represents mean value and *dashed lines* represent 95% CIs.