Oxygen Uptake Efficiency Slope in South American Healthy Adults COMPREHENSIVE REFERENCE VALUES AND INTERNATIONAL COMPARISONS

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The oxygen uptake efficiency slope (OUES) is an index of functional cardiopulmonary reserve derived from submaximal values of oxygen uptake (VO_2) measured during cardiopulmonary exercise testing (CPX). The OUES was first described by Baba et al.[1] and involves plotting VO_2 against the logarithm of minute ventilation (VE) at submaximal work rates according to the equation: $VO_2 = a \times \log VE + b$, in which "a" is the OUES value. A higher "a" value indicates a steeper slope, which corresponds to greater oxygen uptake during exercise, indicating better efficiency.

The interest in submaximal VO_2 values emerged in patients with heart disease due to restrictions in achieving maximum effort levels, especially in more severe cases, for which the prognostic value of peak variables is lower[2]. As the calculation of OUES does not depend on maximum effort, factors that would affect the reliability of the measure (e.g., protocol used, patient motivation, and tester's subjective choice of test end point) are minimized[1-5], consequently increasing measurement reproducibility[2,5-7].Regarding risk stratification, the prognostic value of OUES has already been documented in apparently healthy males[8], and in a variety of cardiovascular conditions, such as heart failure[3,9,10], coronary artery diseases[11,12] and congenital heart diseases[13]. In the study by Davies et al.[3], for example, OUES was the only CPX variable capable of predicting mortality events in a multivariate analysis. Another clinical use of the variable is to assess improvements after interventions such as cardiovascular rehabilitation[11,14,15].

For clinical application, calculated OUES is compared to reference values obtained in healthy populations[2,16-19]. However, the reference sample does not always have the same demographic characteristics and phenotype, which can generate considerable heterogeneity among studies. Moreover, some authors presented OUES values normalized by body surface area (OUES/BSA)[17], body mass (OUES/kg)[13], or the division of reference values by body mass index (BMI) subgroups[17], increasing variability in the available data.

Five reference value studies are currently available in the scientific literature[2,16-19]. Hollenberg et al.[2] was the only study developed for treadmill CPX, while the other studies were performed for cycling CPX[16-18] or both ergometers[19]. Hollenberg et al.[2] however described a OUES predictive equation rather than providing reference value tables with a North American sample aged 53 - 89 yr. Sun et al.[19] described predictive equations in a sample aged 17 - 78 yr including both a treadmill and cycle ergometer and reported higher OUES values on the former. Buys et al.[18] described absolute and BSA-normalized OUES stratified by sex and age group in a European sample (Belgium and the Netherlands) aged 20 to 60 yr. Barron et al.[17] described the absolute OUES in a German sample aged 25 to 84 and distributed according to BMI. More recently, Ashikaga et al.[16] described absolute OUES values in a Japanese sample aged 20 - 78 yr.

Similar to peak VO_2[20-24], the OUES can be highly influenced by anthropometric variables, with lower values for females[2,8,16-19]. Likewise, the OUES is potentially influenced by the sample characteristics, as significant peak oxygen uptake (VO_{2peak}) heterogeneity is found among countries[21,25,26], which underscores the importance of using appropriate OUES reference values for properly assessing patient characteristics and ensuring the adequate clinical application of the index.

To the best of our knowledge, however, the OUES has not yet been previously described in a South American adult population and no comparisons across nationalities have been performed. Therefore, the aim of the present study was to provide comprehensive OUES reference values for treadmill CPX in healthy Brazilian adults stratified by sex and age group. The information is provided in all previously described formats, including absolute (OUES) and normalized (OUES/kg and OUES/BSA) values as well as predictive equations. The secondary objective was to compare all previously published OUES reference value tables from different nationalities to the Brazilian data using the pooling method approach.

METHODS

PARTICIPANTS

A retrospective cross-sectional study was conducted with 7,843 treadmill CPX assessments performed at an experienced laboratory in Brasilia (city in the Midwest region of Brazil) between January 2011 to March 2020. This city received intense migration from several regions of the country in the mid-1960s due to the relocation of the capital. Thus, the study sample may represent a casual pooled data of the different regions of Brazil[21]. All exams were performed and interpreted by the same experienced physician following established guidelines[27,28].

The inclusion criteria were subjects aged > 20 yr and respiratory exchange ratio (RER) ≥ 1.0 at peak exercise. The exclusion criteria were (1) history or symptoms of cardiovascular, pulmonary, oncologic, rheumatic, and severe orthopaedic disease; (2) presence of cardiovascular risk factors (e.g., hypertension, diabetes mellitus, current smoking, and obesity); (3) cardiac abnormalities during CPX (myocardial ischemia or non-analysable effort electrocardiogram); and (4) missing data.

This study received approval from the Human Research Ethics Committee of the University of Brasilia (CAAE: 35706720.4.0000.8093). Due the retrospective nature of the study, informed consent was waived.

CLINICAL ASSESSMENT

Before performing CPX, the subjects underwent a standardized clinical assessment, with the collection of demographic and anthropometric variables as well as clinical information regarding cardiovascular risk factors and previous diseases. The demographic

and anthropometric variables were age (yr), sex, weight (kg), height (m), BMI ($kg.m^{-2}$), and BSA (m^2) calculated using the DuBois equation[29].

CARDIOPULMONARY EXERCISE TESTING

The CPX was performed using a treadmill (Centurium 200, Micromed) with a breath-by-breath gas analysis system (Cortex Metalyser 3B) and 12-lead electrocardiographic monitoring (Ergopc Elite, Micromed). Symptom-limited maximal exercise testing was performed with an individualized ramp protocol. Treadmill speed started at 2 to 4 $km.h^{-1}$ with 0% inclination. The load increase rate was linear and adjusted according to age and sex, with a steeper speed increase in males and younger subjects and the use of a steeper inclination rate for older subjects. This load adjustment in the ramp protocol was individualized to yield a fatigue-limited exercise test with an expected duration of eight to 12 minutes[30,31]. The system was calibrated according to the manufacturer's recommendations to ensure reliable measures.

The following CPX variables were evaluated: clinical signs and symptoms, electrocardiographic response, peak heart rate (HR, beats per minute), relative VO_{2peak} ($mL.kg^{-1}.min^{-1}$), peak loads, peak RER, and OUES. The VO_{2peak} was expressed as the highest 30-second averaged sample obtained from the final minute of the test. The values considered for peak loads, RER and HR were the highest achieved at peak effort. In this study, the OUES was presented in all previously published forms (absolute and normalized by both body weight [kg] and BSA).

POOLED DATA AND INTERNATIONAL COMPARISONS

To perform comparisons between OUES databases derived from other population samples, we searched for published studies that described the OUES as a reference value

table in at least one of the expected forms (absolute or normalized) stratified by sex and age group and with descriptive data (sample size, mean and standard deviation).

STATISTICAL ANALYSIS

Data were described as mean and SD for sex and age group (in ten-yr intervals). OUES variables were also described as percentiles (P5, P10, P25, P50, P75, P90, and P95). Normality was assessed using the Kolmogorov-Smirnov test. The Kruskal-Wallis test with a multiple-comparisons post-test (Benjamini-Hochberg method) was used for OUES comparisons among different age groups because data had a non-normal distribution. The Mann-Whitney test was used to investigate differences between the sexes.

Predictive equations for OUES, OUES/kg, and OUES/BSA in males and females were calculated using age to predict the variables. Anthropometric variables were not used in these predictive models, since weight and BSA were used to normalise OUES. As a non-linear peak VO_2 age relationship has been documented for a sample of the population from different regions of Brazil[21], the equations were calculated using second-order polynomial regression to predict the OUES by age for both sexes. In addition to age-predicted equations, multiple linear regression was also calculated for absolute OUES using age (including age squared) and anthropometric variables for both sexes.

To perform international comparisons, regression analyses using second-order polynomial regression to predict the OUES by age were performed for both sexes in each of the selected studies, using "x" as the intermediate value for age within each ten-yr subgroup and OUES values extracted from the published articles. These data were pooled and converted into tables and graphs.

Anthropometric variables were analysed using ordinary one-way analysis of variance (ANOVA) with multiple comparisons (Benjamini-Hochberg) or the unpaired t-test stratified

by sex to compare the sample characteristics of the study. Factorial ANOVA (two-way) with multiple comparisons (Benjamini-Hochberg) or the unpaired t-test was used to analyse differences in OUES values among the nations for each sex and age group.

All statistical analyses were performed using GraphPad Prism 9 or IBM-SPSS 27.0 for Windows. All tests with $P < .05$ were considered statistically significant.

RESULTS

SAMPLE

A total of 7,843 CPXs were performed during the study period and screened for eligibility. After the application of the inclusion and exclusion criteria, 3,544 assessments of healthy subjects were included for analysis (Figure 1). Mean age was 40.5 ± 10.7 yr for females (n = 1,574) and 40.3 ± 10.0 yr for males (n = 1,970), with no significant difference. Regarding anthropometric variables, males were heavier, taller, had a lower BMI, and had higher BSA than females ($P < .001$). We found a small difference in both peak HR (median difference: - 2 bpm; 95% CI: - 3 to - 1) and peak RER (median difference: - 0.01; 95% CI: - 0.02 to -0.01), with lower values in females. Additionally, males exhibited significantly higher VO_{2peak} (median difference: 9.6 $mL.kg^{-1}.min^{-1}$; 95% CI: 9.2 - 10.1) ($P < .001$) (Table 1).

OUES REFERENCE VALUES

We created a comprehensive OUES reference table (absolute and normalized by weight and BSA) stratified by sex and age group (in ten-yr intervals from 20 - 80 yr). The data were expressed in subgroups as mean, standard deviation, and percentile (P5, P10, P25, P50, P75, P90 and P95). We were unable to define P5 and P95 values for males in the last decade due to the small sample size (n = 7) (Table 2, Figure 2) (Figure 1, Supplemental

Digital Content, which illustrate percentile distribution). We also provided the OUES data in age subgroups of five-yr intervals (see Table 1 and 2, and Figure 2, Supplemental Digital Content, which show data in five-yr intervals).

Overall, comparisons between the sexes revealed lower OUES, OUES/kg, and OUES/BSA values in females ($P < .001$). Considering differences in age groups, none of the OUES values (absolute or normalized) were significantly different between 20-29 and 30-39 yr or between 60-69 and 70-80 yr for either females or males (Figure 2). A gradual decline in absolute and normalized OUES values was found in the last four decades (40 - 80 yr) for males. The decline in OUES/kg was similar for females, but the decline in absolute OUES and OUES/BSA initiated a decade later (50 - 80 yr). Despite the lower OUES values in the last decade compared to the previous age subgroup, the difference was not statistically significant in either sex.

OUES PREDICTIVE EQUATIONS FOR THE ADULT POPULATION

Predictive equations for OUES, OUES/kg, and OUES/BSA were calculated for females and males with age (yr) as the predictor:

Females

$$OUES = 1{,}436 + (38.02 \times Age) - (0.5565 \times Age^2);\ r^2 = 0.079$$

$$OUES/kg = 26.11 + (0.4690 \times Age) - (0.007472 \times Age^2);\ r^2 = 0.079$$

$$OUES/BSA = 895.2 + (20.58 \times Age) - (0.3043 \times Age^2);\ r^2 = 0.077$$

Males

$$OUES = 2{,}682 + (45.47 \times Age) - (0.7658 \times Age^2);\ r^2 = 0.104$$

$$OUES/kg = 38.60 + (0.2968 \times Age) - (0.005726 \times Age^2);\ r^2 = 0.060$$

$$OUES/BSA = 1{,}450 + (17.47 \times Age) - (0.3011 \times Age^2);\ r^2 = 0.079$$

The second-order polynomial regression analysis performed to predict the OUES by age revealed a non-linear characteristic for absolute and normalized values, with a concave curve indicating smaller reductions in the OUES among younger ages and a steeper decline among older ages (Figure 3) (see Figure 2, Supplemental Digital Content, which also show data regression curves).

Predictive equations for absolute OUES were also calculated with multiple linear regression using age (yr), age squared, weight (kg), and height (m) as predictors. These equations revealed greater r^2 than the equations for absolute OUES using only age.

Females

OUES = - 1,738 + (34.18 x Age) - (0.4949 x Age^2) + (8.561 x Weight) + (1,650 x Height); $r^2 = 0.174$

Males

OUES = - 1,786 + (30.95 x Age) - (0.5389 x Age^2) + (14.12 x Weight) + (2,016 x Height); $r^2 = 0.239$

OUES INTERNATIONAL COMPARISONS

According to the required criteria to assess possible differences among countries, only the two studies – one European (n = 1,411) (Belgium and the Netherlands)[18] and one Japanese[16] (n = 529) – provided the required data and were considered in the descriptive tables of the pooled data (Table 3) (see Table 3, Supplemental Digital Content, which show samples' characteristics). and graphical comparisons (Figure 3). The European study performed with a German sample[17] could not be included due to a different age group standardisation and missing data on mean and standard deviation values. The Japanese study[16] described the OUES in absolute values with an age range from 20 to 78 yr, while the European study[18] reported both OUES and OUES/BSA ranging from 20 to 60 yr. In both

studies, CPX was performed on a cycle ergometer. The studies derived from the United States population[2,19] reported predictive OUES equations, but no reference value tables with age group division were provided, precluding these studies from being in the comparisons**.** Therefore, international comparisons were performed among samples from Brazil, Japan, and Europe (Belgium and the Netherlands).

The anthropometric variables revealed significant heterogeneity among these nations (see Table 3, Supplemental Digital Content, which show samples' characteristics). Japanese individuals were older and had lower weight, height, and BMI for both sexes. Contrarily, the European sample had higher weight and height for both sexes, while the Brazilian sample presented intermediate values for these variables. No difference in BMI was found between European and Brazilian females, whereas a small but significant difference was found for males. Brazilians had lower BSA than Europeans for both sexes; the Japanese study did not provide this variable.

The international comparisons of the pooled OUES revealed significant heterogeneity (Figure 3 and Table 3). Factorial ANOVA was performed in the first four decades of age (20 - 59 yr) for absolute OUES, since the European data above 60 yr were not described and Japanese values were not provided for OUES/BSA.

The analysis demonstrated a significant source of variation for both country and age group in the OUES values ($P < .0001$ for females and males). The interaction in the sources of variation was also significant for females ($P = .0004$), but only a trend for males ($P = .0537$), indicating that, in addition to the heterogeneity in the OUES values, the influence of age on OUES was not similar among countries.

In the pairwise comparisons, significantly higher OUES values were found in the European sample for both sex and age group (20 - 60 yr) compared to the Japanese sample. The difference between the European and Brazilian samples was statistically significant for

all sex and age groups, except for females aged 50-59 yr. The differences between the Japanese and Brazilian samples were statistically significant for all age groups, except females aged 20-29 and 50-59 yr and males more than 70 yr of age (Table 3).

The OUES/BSA values were only available in the Brazilian and European studies. In males, the normalized measure reduced the difference in the values and the significant difference was no longer found in the age groups 30-39 and 50-59 yr. A reduction in the difference in the variable was also found in females, but the difference remained statistically significant in all age groups, except 50-59 yr (Table 3 and Figure 3).

Age predictive equations were calculated and graphically displayed considering the second-order polynomial regression analysis (Figure 3). Japanese values revealed a more linear trend in females, while European and Brazilian values revealed a curvilinear behaviour, both with a concave curve. The three countries displayed a non-linear characteristic in males, but with different morphologies of the curvilinear behaviour. The European and Brazilian samples presented a concave curve and the Japanese sample presented a convex curve, indicating differences in the influence of age on the OUES. The predictive equations obtained for females and males with age (yr) as the predictor are described below:

Females

European: $OUES = 2{,}339 + (23.13 \times Age) - (0.5133 \times Age^2)$

European: $OUES/BSA = 1{,}477 + (4.844 \times Age) - (0.2028 \times Age^2)$

Japanese: $OUES = 2{,}128 - (4.826 \times Age) - (0.03292 \times Age^2)$

Males

European: $OUES = 2{,}857 + (47.21 \times Age) - (0.7669 \times Age^2)$

European: $OUES/BSA = 1{,}726 + (6.613 \times Age) - (0.1979 \times Age^2)$

Japanese: $OUES = 3{,}225 - (26.32 \times Age) + (0.1612 \times Age^2)$

DISCUSSION

The present study provided comprehensive OUES reference values for South American individuals based on a large sample. Comprehensive reference value tables for absolute and normalized (OUES/kg and OUES/BSA) values were provided stratified by sex and age group (Table 2, Figure 2, Supplemental Digital Content). Predictive equations (central tendency and lower 95% CI) were obtained for absolute and normalized OUES values. We also provided pooled data from four different countries and described possible differences among nationalities.

In the present sample, we found anthropometric differences between the sexes and higher VO_{2peak} in males. The differences between the sexes in peak HR and RER had a low magnitude and were not clinically relevant. Comparisons between the sexes showed lower OUES values in females, with a decline along the decades, which is similar to findings described in previous studies[2,8,16-19]. The age-associated decline in the OUES reflects expected physiological changes in multiple organ systems, such as the heart, lungs, blood vessels, skeletal muscles, and nervous system[2].

The sex and age differences observed between the South American and other samples[2,16-18] indicates that the use of a single OUES cut-off value for predicting outcomes should be reevaluated. Myers et al.[9] defined an OUES cut-off of 1,400 for risk stratification in patients with heart failure. According to our data (Table 2), this number would be classified below the 5th percentile for all age groups in healthy males. For females, surprisingly, the value would be within the 5th and 10th percentile for the 20-29-yr-old group, 10th and 25th for both the 40-49-yr-old and 50-59-yr-old groups, 25th and 50th percentile for 60-69-yr-old group, and between 50th and 75th percentile in our oldest age group (see Figure 3, Supplemental Digital Content, which illustrate the cut-off value among percentile

distribution). These findings raise significant concerns regarding the applicability of the aforementioned cut-off level[9] for female patients with heart failure in Brazil, as the results would be mainly classified as expected average values (5^{th} - 95^{th} percentile) based on our sample with healthy subjects, which may also happen in other nationalities.

Interestingly, we also found that the non-linear second-order polynomial regression was the best fitting curve model to explain the relation between the OUES and age in the Brazilian sample. This approach is not novel. Mylius et al.[32] demonstrated that a curvilinear trend as a second-order polynomial fitting model performed better than a linear fitting model to explain the reduction in VO_2 with age in a Dutch sample, which is similar to our finding using Brazilian data[21].

Although the original study by Buys et al.[18] presented the OUES-age relation as a linear trend, our regression analysis performed with the European data also revealed a concave curvilinear relationship for both absolute and BSA-normalized values, suggesting that the appropriateness of the fitting to a linear or a second-order regression behaviour should be addressed in future studies.

The low r^2 values found in the Brazilian sample (0.06 - 0.104 in males and 0.077 - 0.079 in females) are in agreement with values described in previous studies[17,18] that reported a low r^2 with age as a predictor. In the study by Barron et al.[17], the influence of age on the OUES revealed by linear regression identified r^2 values of 0.17 for males and 0.12 for females. This behaviour is clinically expected, as the regression predicts a central estimate of the OUES in relation to age and significant individual variations are a biological characteristic of VO_2-related variables, which can also be seen within the range of the values (Table 2, Figure 2, and Supplemental Digital Content).

Similar to previous studies regarding VO_{2peak}[21,25,26], the pooled analysis revealed significant OUES heterogeneity among the nationalities, presumably due to different

demographic and biopsychosocial characteristics, since the OUES is strongly influenced by anthropometric variables and exhibits significant inter-individual variation[33]. The present study found higher OUES values in the European sample in both sexes for all age groups compared to the Brazilian and Japanese data. Other demographic and biopsychosocial variables, such as physical activity level and ethnicity, may have influenced the results.

We also found that normalization of the OUES by BSA reduced the magnitude of the differences in the international comparison of the European and Brazilian data, suggesting that this value would be considered more appropriate for clinical purposes. Agostoni et al.[34] previously highlighted the importance of normalizing the OUES for a better understanding and applicability of the variable, since comparisons between subjects of different ages, sexes, ethnicities, heights, and weights are required for a proper evaluation. Thus, it is necessary to consider the use of weight-normalized or BSA-normalized values, as done by Hossri et al.[35], who proposed OUES reference values for children and adolescents with normalisation by weight and BSA.

According to the presented description of OUES reference values and documented heterogeneity among different nationalities, our study may have provided a better understanding regarding the OUES as a prognostic tool, including absolute and normalized values and differences among age groups and between the sexes.

Limitations

First, although including the largest sample in the current literature, the proposed standard reference values were provided from a single centre, which reduced the external validity of the findings. However, the single-centre characteristic of the study may indicate higher agreement in the results, since all CPXs were conducted by the same experienced professional.

Second, the CPX was performed in only one city in the Midwest region (Brasilia, capital of Brazil). However, this city received intense migration from several regions of the country in the mid-1960s due to the relocation of the capital. Thus, our sample may be a casual pooled data representation of the different regions of Brazil. This characteristic may be one of the factors explaining the observed intermediate values for VO_{2peak} in the Midwest region of Brazil compared to the Southeast and Northeast[21,25]. Thus, the OUES values observed in our study may reflect appropriate values not only for the Midwest region but for the entire Brazilian population.

Third, it is important to mention that our study focused only on treadmill values, with no inclusion of results from cycle ergometers. Moreover, the sample size in the oldest age group in our study (70-80 yr) was small, limiting the statistical analysis in this group. A significant limitation was the limited data available in the literature necessary for the international pooled analysis, as we only found two studies with complete data available for our study and the statistical analysis was performed with the available published data (mean, standard deviation, and sample size) rather than raw data.

Lastly, the regression model used limits the age range for the derived equation to the original characteristic of the sample data (20 - 80 yr). Thus, our equations are not appropriate for subjects < 20 yr and may not reflect the age reduction trend in subjects > 80 yr.

CONCLUSION

Our study provided comprehensive OUES reference values for a healthy adult population of both sexes stratified by age group divided in ten-yr intervals and generated new prediction equations. Pooled data and international comparisons among Brazilian, Japanese, and European (Belgium and the Netherlands) samples revealed heterogeneity, with differences in OUES values and age-related patterns. These differences were reduced in the

comparison of the Brazilian and European samples when BSA-normalized values were considered.

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LIST OF SUPPLEMENAL DIGITAL CONTENT

Supplemental Digital Content.pdf

REFERENCES

1. Baba R, Nagashima M, Goto M, et al. Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *J Am Coll Cardiol*. 1996;28(6):1567-72.
2. Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. *J Am Coll Cardiol*. 2000;36(1):194-201.
3. Davies LC, Wensel R, Georgiadou P, et al. Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope. *Eur Heart J*. 2006;27(6):684-90.
4. Van Laethem C, Bartunek J, Goethals M, Nellens P, Andries E, Vanderheyden M. Oxygen uptake efficiency slope, a new submaximal parameter in evaluating exercise capacity in chronic heart failure patients. *Am Heart J*. 2005;149(1):175-80.
5. Van Laethem C, De Sutter J, Peersman W, Calders P. Intratest reliability and test-retest reproducibility of the oxygen uptake efficiency slope in healthy participants. *Eur J Cardiovasc Prev Rehabil*. 2009;16(4):493-8.
6. Baba R, Kubo N, Morotome Y, Iwagaki S. Reproducibility of the oxygen uptake efficiency slope in normal healthy subjects. *J Sports Med Phys Fitness*. 1999;39(3):202-6.
7. Coeckelberghs E, Buys R, Goetschalckx K, Pattyn N, Vanhees L, Cornelissen V. Test-Retest Reliability of Maximal and Submaximal Gas Exchange Variables in Patients With Coronary Artery Disease. *J Cardiopulm Rehabil Prev*. 2016;36(4):263-9.
8. Peterman JE, Novelli DS, Fleenor BS, Whaley MH, Kaminsky LA, Harber MP. Oxygen Uptake Efficiency Slope as a Predictor of Mortality Risk: THE BALL STATE ADULT FITNESS LONGITUDINAL LIFESTYLE STUDY (BALL ST). *J Cardiopulm Rehabil Prev*. 2022.
9. Myers J, Arena R, Dewey F, et al. A cardiopulmonary exercise testing score for predicting outcomes in patients with heart failure. *Am Heart J*. 2008;156(6):1177-83.
10. Ritt LE, Myers J, Stein R, et al. Additive prognostic value of a cardiopulmonary exercise test score in patients with heart failure and intermediate risk. *Int J Cardiol*. 2015;178:262-4.
11. Buys R, Coeckelberghs E, Cornelissen VA, Goetschalckx K, Vanhees L. Prognostic value of the post-training oxygen uptake efficiency slope in patients with coronary artery disease. *Eur J Prev Cardiol*. 2016;23(13):1363-71.
12. Coeckelberghs E, Buys R, Goetschalckx K, Cornelissen VA, Vanhees L. Prognostic value of the oxygen uptake efficiency slope and other exercise variables in patients with coronary artery disease. *Eur J Prev Cardiol*. 2016;23(3):237-44.
13. Tsai YJ, Li MH, Tsai WJ, Tuan SH, Liao TY, Lin KL. Oxygen uptake efficiency slope and peak oxygen consumption predict prognosis in children with tetralogy of Fallot. *Eur J Prev Cardiol*. 2016;23(10):1045-50.
14. Lima RM, Vainshelboim B, Ganatra R, Dalman R, Chan K, Myers J. Exercise Training Improves Ventilatory Efficiency in Patients With a Small Abdominal Aortic Aneurysm: A RANDOMIZED CONTROLLED STUDY. *J Cardiopulm Rehabil Prev*. 2018;38(4):239-245.
15. Popovic D, Kumar N, Chaudhry S, Bagai A, Arena R, Kumar N. Improvements in Key Cardiopulmonary Exercise Testing Variables Following Cardiac Rehabilitation in Patients With Coronary Artery Disease. *J Cardiopulm Rehabil Prev*. 2018;38(5):E5-E8.

16. Ashikaga K, Itoh H, Maeda T, et al. Ventilatory efficiency during ramp exercise in relation to age and sex in a healthy Japanese population. *J Cardiol*. 2021;77(1):57-64.
17. Barron AJ, Dhutia NM, Glaser S, et al. Physiology of oxygen uptake kinetics: Insights from incremental cardiopulmonary exercise testing in the Study of Health in Pomerania. *IJC Metab Endocr*. 2015;7:3-9.
18. Buys R, Coeckelberghs E, Vanhees L, Cornelissen VA. The oxygen uptake efficiency slope in 1411 Caucasian healthy men and women aged 20-60 years: reference values. *Eur J Prev Cardiol*. 2015;22(3):356-63.
19. Sun XG, Hansen JE, Stringer WW. Oxygen uptake efficiency plateau: physiology and reference values. *Eur J Appl Physiol*. 2012;112(3):919-28.
20. Almeida AEMd, Santander IRMF, Campos MIM, et al. Classification System for Cardiorespiratory Fitness Based on a Sample of the Brazilian Population. *Int J Cardiovasc Sci*. 2019;32:343-354.
21. Milani M, Milani JGPO, Cipriano GFB, Castro I, Cipriano Junior G. Reference Standards for Cardiorespiratory Fitness in Brazil: A Pooled Analysis and Overview of Heterogeneity in National and International Studies. *J Cardiopulm Rehabil Prev*. 2022;42(5):366-372.
22. Kaminsky LA, Arena R, Myers J. Reference Standards for Cardiorespiratory Fitness Measured With Cardiopulmonary Exercise Testing: Data From the Fitness Registry and the Importance of Exercise National Database. *Mayo Clin Proc*. 2015;90(11):1515-23.
23. Kaminsky LA, Arena R, Myers J, et al. Updated Reference Standards for Cardiorespiratory Fitness Measured with Cardiopulmonary Exercise Testing: Data from the Fitness Registry and the Importance of Exercise National Database (FRIEND). *Mayo Clin Proc*. 2022;97(2):285-293.
24. Kaminsky LA, Imboden MT, Arena R, Myers J. Reference Standards for Cardiorespiratory Fitness Measured With Cardiopulmonary Exercise Testing Using Cycle Ergometry: Data From the Fitness Registry and the Importance of Exercise National Database (FRIEND) Registry. *Mayo Clin Proc*. 2017;92(2):228-233.
25. Milani M, Milani JGPO, Cipriano GFB, Cipriano Junior G. Heterogeneity of cardiorespiratory fitness among Brazilian regions and comparison with Norwegian values. *Eur Heart J*. 2021;42:2674.
26. Peterman JE, Arena R, Myers J, et al. Development of Global Reference Standards for Directly Measured Cardiorespiratory Fitness: A Report From the Fitness Registry and Importance of Exercise National Database (FRIEND). *Mayo Clin Proc*. 2020;95(2):255-264.
27. Meneghelo RS, Araújo CGS, Stein R, Mastrocolla LE, Albuquerque PF, Serra SM. III Diretrizes da Sociedade Brasileira de Cardiologia sobre Teste Ergométrico. *Arq Bras Cardiol*. 2010;95(5 Suppl 1):1-26.
28. American Thoracic S, American College of Chest P. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2003;167(2):211-77.
29. Redlarski G, Palkowski A, Krawczuk M. Body surface area formulae: an alarming ambiguity. *Sci Rep*. 2016;6:27966.
30. Herdy AH, Ritt LE, Stein R, et al. Cardiopulmonary Exercise Test: Background, Applicability and Interpretation. *Arq Bras Cardiol*. 2016;107(5):467-481.
31. Meneghelo RS, Araújo CGS, Stein R, Mastrocolla LE, Albuquerque PF, Serra SM. III Guidelines of Sociedade Brasileira de Cardiologia on the exercise test. *Arq Bras Cardiol*. 2010;95(5 Suppl 1):1-26.
32. Mylius CF, Krijnen WP, van der Schans CP, Takken T. Peak oxygen uptake reference values for cycle ergometry for the healthy Dutch population: data from the LowLands Fitness Registry. *ERJ Open Res*. 2019;5(2).

33. Akkerman M, van Brussel M, Hulzebos E, Vanhees L, Helders PJ, Takken T. The oxygen uptake efficiency slope: what do we know? *J Cardiopulm Rehabil Prev*. 2010;30(6):357-73.
34. Agostoni P, Gugliandolo P, Campodonico J. Inside OUES: fact or fiction? *Eur J Prev Cardiol*. 2019;26(2):174-176.
35. Hossri CA, Souza IPA, de Oliveira JS, Mastrocola LE. Assessment of oxygen-uptake efficiency slope in healthy children and children with heart disease: Generation of appropriate reference values for the OUES variable. *Eur J Prev Cardiol*. 2019;26(2):177-184.

FIGURE LEGENDS

Figure 1. Flowchart of exams assessed to provide OUES reference values.

Figure 2. Absolute and normalized oxygen uptake efficiency slope (OUES) values stratified by sex and age group.

Data expressed as median, IQR, 95% limits, and outliers.

Statistics: Kruskal-Wallis with multiple comparisons post-test (Benjamini-Hochberg method). All comparisons were statistically significant. Non-significant (ns) comparisons were reported.

BSA, body surface area; OUES, oxygen uptake efficiency slope.

Figure 3. International comparison of absolute oxygen and body surface area-normalized uptake efficiency slope (OUES) values.

Data expressed as median and SEM.

Tendency curves were calculated by second-order polynomial regression, using raw data in Brazil and available literature data (mean, SD, and sample size) in Belgium/Netherlands and Japan.