Medicine & Science IN Sports & Exercise
The Official Journal of the American College of Sports Medicine
www.acsm-msse.org

. . . Published ahead of Print

Scaling the Oxygen Uptake Efficiency Slope for Body Size in Cystic Fibrosis

Owen William Tomlinson[1,2], Alan Robert Barker[1], Patrick John Oades[2], and Craig Anthony Williams[1,2]

[1]Children's Health and Exercise Research Centre, Sport and Health Sciences, University of Exeter, Exeter, United Kingdom; [2]Royal Devon and Exeter NHS Foundation Trust Hospital, Exeter, United Kingdom

Accepted for Publication: 1 May 2017

Medicine & Science in Sports & Exercise, Publish Ahead of Print
DOI: 10.1249/MSS.0000000000001314

Scaling the Oxygen Uptake Efficiency Slope for Body Size in Cystic Fibrosis

Owen William Tomlinson[1, 2], Alan Robert Barker[1],

Patrick John Oades[2], and Craig Anthony Williams[1, 2]

[1]Children's Health and Exercise Research Centre, Sport and Health Sciences, University of Exeter, Exeter, United Kingdom; [2]Royal Devon and Exeter NHS Foundation Trust Hospital, Exeter, United Kingdom.

Corresponding author: Professor Craig A. Williams, Children's Health and Exercise Research Centre, Sport and Health Sciences, College of Life and Environmental Sciences, University of Exeter, St Luke's Campus, Exeter, EX1 2LU, UNITED KINGDOM

Tel: 44 (0)1392 724890

Email: c.a.williams@exeter.ac.uk

We declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. Funding was provided by the Royal Devon and Exeter NHS Foundation Trust, Exeter. Results of the present study do not constitute endorsement of the American College of Sports Medicine, and there are no conflicts of interest to declare.

Running Title: Scaling oxygen uptake efficiency in children

ABSTRACT

Purpose: The aim of this study was to describe the relationship between body size and the oxygen uptake efficiency slope (OUES) in paediatric patients with cystic fibrosis (CF) and healthy controls (CON), in order to identify appropriate scaling procedures to adjust the influence of body size upon OUES. **Methods:** The OUES was derived using maximal and submaximal points from cardiopulmonary exercise testing in 72 children (36 CF and 36 CON). OUES was subsequently scaled for stature, body mass (BM) and body surface area (BSA) using ratio-standard (Y/X) and allometric (Y/X^b) methods. Pearson's correlation coefficients were utilised to determine the relationship between body size and the OUES. **Results:** When scaled using the ratio-standard method, OUES had a significant positive relationship with stature (r = 0.54, $P < 0.001$) and BSA (r = 0.25, P = 0.031) and significant negative relationship with BM (r = -0.38, P = 0.016) in the CF group. Combined allometric exponents (b) for CF and CON were: stature 3.00, BM 0.86, BSA 1.40. A significant negative correlation was found between OUES and stature in the CF group when scaled allometrically (r = -0.37, P = 0.027). Non-significant ($P > 0.05$) correlations for the whole group were found between OUES and allometrically scaled BM (CF: r = -0.25, CON: r = 0.15) and BSA (CF r = -0.27, CON r = 0.13). **Conclusions:** Only allometric scaling of either BM or BSA, and not ratio-standard scaling, successfully eliminates the influence of body size upon OUES. Therefore this enables a more direct comparison of the oxygen uptake slope between patients with CF and healthy controls.

Keywords: exercise capacity, modelling, adolescence, respiratory, pulmonary disease

INTRODUCTION

It has been established that a high cardiopulmonary fitness (as represented by maximal oxygen uptake [$\dot{V}O_{2max}$]) is of benefit to young patients with cystic fibrosis (CF), being associated with an increased quality of life (22) and reduced risk of hospitalisation (27) and mortality (28). As such, regular, maximal, exercise testing is recommended to provide clinically relevant prognostic information for clinicians and patients (14), with cardiopulmonary exercise testing (CPET) endorsed as method of choice by the European Cystic Fibrosis Society and European Respiratory Society (21). However, measuring $\dot{V}O_{2max}$, by definition, requires a maximal effort and some patients may be unable or unwilling to reach a volitional maximum. Therefore, the oxygen uptake efficiency slope (OUES) (4), a reliable (31) and effort-independent measure of ventilatory efficiency, may be a viable submaximal alternative to $\dot{V}O_{2max}$ in this patient group (18).

Previous research in healthy adults has shown that OUES is strongly related to body size variables including stature, body mass (BM) and body surface area (BSA) (12), and has subsequently been applied to clinical settings including cardiac (36), neurological (23) and respiratory (6) populations, including a single study of adults with CF (18). This strong dependency on body size confounds interpretation of OUES and requires the use of scaling techniques to ensure appropriate interpretation within and between groups. However, scaling procedures have been performed by most (6, 12, 18, 36) but not all (23) studies to date.

The strong positive relationship between OUES and body size has further been observed in paediatric studies using stature (25), BM (11) and BSA (1). Whilst such paediatric studies have attempted to control for body size (1, 9, 10, 16), it has been assumed that the ratio standard scaling method (OUES/body size [Y/X]) is an effective approach at removing the influence of

body size. However, there are validity concerns associated with the ratio-scaling procedure that have been utilised to date (26). This issue may have greater implications in children (3), whose body size is rapidly changing with age, and furthermore in children with CF, who are characterised by malnutrition and inadequate growth (13).

Previous research has identified allometric scaling (Y/X^b, where b represents a power function to which X is raised) as a superior technique to the ratio-standard methods for controlling for body size when assessing $\dot{V}O_{2max}$ in both adults (7) and children (17). However, its applicability for scaling OUES in contrast to the currently employed ratio standard method remains unknown

Although the use of OUES in children with CF has been proposed (9), there are currently no studies that critically examine the validity of scaling methods to adjust for body size. Furthermore, the one previous study to have examined the role of OUES in children with CF (9) scaled for BSA using a ratio-standard approach. However, the utility of other body size variables that are frequently collected by clinical teams (stature, body mass) were not systematically considered.

Therefore the aim of this study was twofold: Firstly to characterise the relationship between body size and OUES in children with CF; and secondly, to identify the most appropriate procedure (ratio standard or allometric) for scaling OUES against different body size variables (stature, BM and BSA) in paediatric patients with CF and a matched control (CON) group. It is hypothesised that the allometric scaling procedure will remove the residual effects of body size on OUES compared to ratio standard procedures.

METHODS

Study Participants. Data were extracted from existing databases of valid CPET data, with 45 children and adolescents with CF being considered for inclusion in the current analysis. A total of 9 participants were excluded due to inadequate data (insufficient, or missing data, n = 7; insufficient test length, n = 2), resulting in a final sample of 36 children and adolescents with CF. Data were then age- and gender-matched against existing CON CPETs, resulting in a total sample of 72 participants (36 CF, 36 CON; mean age 13.3 ± 2.8 years).

For original data collection, ethics approval was granted by institutional and NHS Research Ethics committees. Written informed consent and assent were obtained from parents/guardians and children respectively.

Experimental Measures. Stature was measured to the nearest 0.01 m using a wall-mounted stadiometer (Holtain Ltd., Crymych, UK) and BM to the nearest 0.01 kg using a digital scale (Seca, Birmingham, UK). Body surface area (BSA) was estimated using the Haycock equation (20). Pulmonary function was assessed using a hand-held spirometer, with values for forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) being determined.

Experimental Protocol. All participants undertook an incremental CPET to volitional exhaustion on an electronically braked cycle ergometer (Lode, Groningen, the Netherlands). Breath-by-breath gas exchange data were collected using an online Cortex gas analysis system (Cranlea, Birmingham, UK) and exported in 10-second averages. Within the sample, 33 children (20 CF, 13 CON) undertook an additional supramaximal verification bout to determine $\dot{V}O_{2max}$

(5, 30). However, as not all children undertook the verification bout the highest $\dot{V}O_2$ observed is described as peak $\dot{V}O_2$.

Peak $\dot{V}O_2$ was obtained from the highest 10-second average from either the ramp or supramaximal bout (where applicable) and the gas exchange threshold (GET) was identified using the V-slope method (8) and confirmed through visual inspection of ventilatory equivalents for $\dot{V}O_2$ and $\dot{V}CO_2$. OUES was ascertained at three different intensities (100%, 75% and 50% of peak $\dot{V}O_2$), using data from the whole test up to, and including, the intensity of interest, in line with previous research (9). Simple, linear regressions between $\dot{V}O_2$ ($mL \cdot min^{-1}$) and $\log V_E$ were calculated in the form using GraphPad Prism (GraphPad Software, Inc., San Diego, CA, USA):

$$\dot{V}O_2 = a\,(\log V_E) + b \qquad \textit{Equation 1}$$

where the constant *a* the slope is defined as the OUES, and *b* the intercept with the *y*-axis (4). Regression constants were subsequently produced, as per Figure 1, to allow comparisons between groups.

Scaling Approaches. Each body size variable (stature, BM and BSA) was used to scale OUES at peak $\dot{V}O2$, and at the GET, using the ratio-standard (Y/X) and allometric (Y/X^b) scaling methods. Allometric scaling of OUES was performed using log-linear regression models (34) with disease status (CF or CON) and the anthropometric variable in question (stature, BM, BSA) entered as predictor variables. Age and gender were not entered into the model due to the prior matching of patients. The log-linear regression models produced scaling exponents (*b*) and associated 95% confidence intervals (CIs) that were used to scale the OUES using a power

function ratio (Y/X^b). All regression models assumptions (multicollinearity and independence, homoscedasticity, linearity and normal distribution of residuals) were checked and satisfied. The log-linear regression model was conducted for each group (CF and CON separately) and as a combined whole (CF and CON combined) for each OUES parameter (peak $\dot{V}O_2$, 75% peak $\dot{V}O_2$, 50% peak $\dot{V}O_2$).

Statistical Analyses. Statistical analyses were conducted using SPSS v.23 (IBM, Armonk, NY, USA). Independent *t*-tests identified mean differences in the anthropometric and CPET outcomes between CF and CON. Pearson's correlation coefficients were run to examine the relationship between each body size variable and the absolute, ratio-standard scaled and allometrically-scaled OUES to assess size dependence of OUES. Fisher's z-transformations identified group differences between correlations. The alpha level was set at 0.05 for all analyses.

RESULTS

All descriptive data are presented as mean and standard deviation. Differences between group means with regards to the anthropometric, pulmonary and CPET outcomes are presented in Table 1. No significant differences ($P > 0.05$) were observed between groups for anthropometric or CPET variables. A significantly ($P < 0.05$) lower FEV1 (% predicted) was observed in the CF group, but no other pulmonary variables.

Each body size variable was significantly ($P < 0.001$) and positively correlated with OUES (Figure 2; A1, B1, C1). This finding is consistent across CF, CON, and as a combined group (Table 2), with the magnitude of the correlation consistently lower in CF when compared against

CON. However, this was only statistically significant ($P < 0.05$) for absolute OUES when plotted against stature (Figure 2; A1).

When the ratio-standard scaling (Y/X) method was used, significant and positive correlations were present between the scaled maximal OUES and both stature and BSA for the combined group (Table 2) and CON group (Figure 2; A2, C2), but not the CF group. Whilst OUES scaled for BM did not retain a significant relationship with BM itself at the combined level (Table 2), it approached significance ($P = 0.073$). When split into sub-groups, a significant negative relationship was observed between scaled OUES and BM in CF (Figure 2; B2).

The output from the log-linear regression models is displayed in Table 3. Smaller b exponents were observed for the CF group, when compared to CON, for each anthropometric factor. The exponents for the combined group were as follows: at 50% peak $\dot{V}O_2$ (stature = 3.60, BM = 1.06, BSA = 1.72); at 75% peak $\dot{V}O_2$ (stature = 2.93, BM = 0.80, BSA = 1.31), and at 100% peak $\dot{V}O_2$ (stature = 2.59, BM = 0.77, BSA = 1.24). A greater difference was evident between the scaling exponents (Δb) of CF and CON groups for stature (1.39) relative to those for body mass (0.16) and BSA (0.36). When the exponents were averaged across groups and OUES parameters, the scaling factors were stature = 3.00, BM = 0.86, and BSA = 1.40.

When OUES was scaled allometrically (Y/X^b) using the averaged exponents from Table 3, no significant correlations were present against BM or BSA at either the group (Figure 2; B3, C3) or combined (Table 2) level. However, a significant ($P < 0.05$) negative relationship was evident within the CF group between allometrically-scaled OUES and stature (Figure 2; A3). Furthermore, allometric scaling of OUES at submaximal intensities (50% peak $\dot{V}O_2$ and 75%

peak $\dot{V}O_2$), using the exponents identified in Table 3 for BM and BSA produced non-significant correlations ($P > 0.05$; data not reported).

DISCUSSION

The aims of this study were to initially describe the relationship between OUES and body size in children with CF and to identify appropriate procedures for scaling OUES against different body size variables. The main results have shown both significant relationships between OUES and body size; and that ratio-standard scaling is ineffective in controlling for body size, whereas allometric scaling does remove residual influences.

The relationships between body size and OUES for the present study are shown in Table 2 and Figure 2. These analyses identified large correlations for the CON group, with the magnitude closely resembling previous OUES research in healthy 7-18 year olds (25). No previous study has detailed the magnitude of the relationship between OUES and body size in children with CF. The magnitude of the correlation in the CF group is lower than the CON group and reached statistical significance for the relationship between OUES and stature (Table 2, Figure 2). This could be due to the shorter stature typically observed in children with CF (15) – a consequence of the chronic malnutrition associated with the disease (13). However, the reported non-significant difference in body size, including stature, and OUES at peak exercise between CF and CON groups is similar to previous studies, despite decreased mean OUES values at peak exercise for both CF and CON groups in relation to previous research – a difference potentially accounted for by differences in aerobic fitness (9). This suggests additional body size independent factors affect the OUES in CF and therefore may account for the smaller correlation coefficients observed in the present study.

When ratio-standard scaling is utilised to adjust OUES, significant correlations exist against all the body size variables (Table 2, Figure 2; A2, B2, C2), with the magnitude, and significance, of coefficients being different for each body size variable and group. These significant positive coefficients result in biasing against individuals with a smaller stature or BSA. Whilst the combined correlation coefficient for BM is non-significant, it remains significant and negative within the CF group, thus biasing against heavier individuals, and removing its potential to be uniformly utilised across both groups. Furthermore, evidence against the use of the ratio-standard method to scale OUES is provided by the *b* values obtained in the log-linear regression. For the ratio-standard method to be effective, the *b* values would be required to equal, or at least be very close to, 1 (33). As is shown in Table 3, the obtained values do not equal 1, nor do the 95% CI, which represent the uncertainty of the point estimate, span 1 consistently across both groups. Therefore, the ratio-standard procedure does not uniformly control for size in children with, and without CF, for each body size variable.

Previous research has advocated scaling of OUES in children using a ratio-standard approach, controlling for fat-free mass (FFM) or BSA (1). However, the authors did not verify the assumption that this technique appropriately removes the influence of body size. As a result, subsequent studies have cited this study as reason for scaling OUES in such a manner when making comparisons between groups in paediatric populations with chronic disease (9, 10, 35). However, the results of the current study have shown the ratio standard approach to be invalid and is likely to result in incorrect conclusions in previous OUES research due to the inaccurate expression of data (9).

Upon utilising allometric scaling, non-significant relationships ($P > 0.05$) were found between the corrected OUES from peak exercise and both BM and BSA for CF and CON groups, as well as the combined group values. However, the magnitude of coefficient is between -0.25 and -0.30 for BM and BSA in the CF group, indicating that this method does not fully control for size, but remains an improvement on the ratio-standard method. Unlike BM and BSA, stature retained a significant relationship with allometrically corrected OUES within the CF group ($P < 0.05$; Figure 2; A3). A non-significant mean difference between CF and CON for stature was found, therefore suggesting it is not stature itself, but the interaction of the two (stature and OUES) that is different between groups. This difference in the relationship between stature and OUES is further evidenced by *b* values between groups (Table 3), with the Δb between CF and CON of 1.39 being over three times greater than that of BSA ($\Delta b = 0.36$). Therefore, our data suggest stature is an unsuitable variable for scaling OUES, regardless of which scaling procedure is used. In contrast, the more homogenous *b* values between CF and CON groups for both BM and BSA (Table 3) indicate these body size variables should be used for future allometric scaling of OUES, as the exponents can be uniformly applied to both groups. The same results were found for OUES at submaximal intensities (50% peak $\dot{V}O_2$ and 75% peak $\dot{V}O_2$), with allometric scaling proving to be the optimal methodology for removing residual effects of body size. This is a notable finding, as it highlights the importance of scaling, even for submaximal parameters of exercise, given that many patients may be unable, or unwilling, to perform maximal exercise.

The results shown above indicate that either BM or BSA is an appropriate body size variable against which to scale OUES, provided an allometric approach is used. However, previous research is equivocal on which body size variable to use, with both BM (4, 11, 25, 29) and BSA (9-11, 35) being frequently used. BSA has been suggested for use, due to its ability to normalise

for pulmonary volume (24). However due to progressive declining of lung function observed in individuals with CF (19), it is unclear whether BSA appropriately normalises for pulmonary volume, a point further supported by the significant differences in lung function between groups in the current study. In addition, whilst BM remains a suitable anthropometric scaling variable, ideally, FFM should be used as it better reflects the metabolic cost of exercise (1). However this measure is not routinely collected by CF clinics, and body composition data, as estimated from skinfold and bioelectrical impedance methods, have poor accuracy at the individual level (2). As such, there is no evidence to suggest superiority of either BM or BSA for use in scaling OUES. Therefore, the suitability of each anthropometric variable needs to be investigated further to ensure future standardisation of research.

Clinicians involved in the management of CF perceive CPET as a useful tool (32), with regular exercise testing recommended for individuals with CF (21). Given the clinical importance of exercise testing, it is therefore essential that appropriate measures and methodologies are being utilised to analyse outcomes. In order to streamline analyses for clinical teams, the *b* exponent values for BM and BSA provided here may be utilised, provided patient characteristics are in line with current study. However, the purpose of this study was not to create a universal scaling exponent for OUES, as it is likely that scaling exponents may change between patient cohorts, and therefore future studies should utilise these described methodologies to derive their own exponents to ensure a size-free expression of OUES.

CONCLUSION

This study has identified that ratio-standard scaling of the OUES is an invalid scaling method when using stature, BSA or BM as a significant relationship still exists with body size. In

contrast, allometric scaling of BM and BSA was better able to control for body size in young people with CF and age and sex matched controls, and should be used in future research investigating the clinical utility of OUES in this patient group. Therefore, this study recommends that allometrically scaled BM or BSA should be promoted for use in future research and/or clinics where OUES is sought as an outcome measure from a CPET.

ACKNOWLEDGEMENTS

We declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The authors would like to thank the participants who volunteered to be involved, the CF team at the Royal Devon and Exeter NHS Foundation Trust Hospital for their assistance throughout this study. The authors extend appreciation to Mr James Shelley, Miss Lucy Chubbock, Dr Emma Cockcroft, Dr Zoe Saynor and Dr Dan Stevens for assistance in data collection and analysis.

FUNDING

Funding was provided by the Royal Devon and Exeter NHS Foundation Trust, Exeter. Results of the present study do not constitute endorsement of the American College of Sports Medicine, and there are no conflicts of interest to declare.

REFERENCES

1. Akkerman M, Van Brussel M, Bongers BC, Hulzebos EH, Helders PJ, Takken T. Oxygen Uptake Efficiency Slope in Healthy Children. *Pediatric Exercise Science*. 2010;22(3):431-41.
2. Alicandro G, Battezzati A, Bianchi ML et al. Estimating body composition from skinfold thicknesses and bioelectrical impedance analysis in cystic fibrosis patients. *Journal of Cystic Fibrosis*. 2015;14(6):784-91.
3. Armstrong N, Welsman JR. Assessment and interpretation of aerobic fitness in children and adolescents. *Exercise and Sport Sciences Reviews*. 1994;22(1):435-76.
4. 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. *Journal of the American College of Cardiology*. 1996;28(6):1567-72.
5. Barker AR, Williams CA, Jones AM, Armstrong N. Establishing maximal oxygen uptake in young people during a ramp cycle test to exhaustion. *British Journal of Sports Medicine*. 2011;45(6):498-503.
6. Barron A, Francis DP, Mayet J et al. Oxygen Uptake Efficiency Slope and Breathing Reserve, Not Anaerobic Threshold, Discriminate Between Patients With Cardiovascular Disease Over Chronic Obstructive Pulmonary Disease. *JACC: Heart Failure*. 2016;4(4):252-61.
7. Batterham AM, Vanderburgh PM, Mahar MT, Jackson AS. Modeling the influence of body size on VO2 peak: effects of model choice and body composition. *Journal of Applied Physiology*. 1999;87(4):1317-25.

8. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas-exchange. *Journal of Applied Physiology*. 1986;60(6):2020-7.

9. Bongers BC, Hulzebos EHJ, Arets BGM, Takken T. Validity of the Oxygen Uptake Efficiency Slope in Children With Cystic Fibrosis and Mild-to-Moderate Airflow Obstruction. *Pediatric Exercise Science*. 2012;24(1):129-41.

10. Bongers BC, Hulzebos HJ, Blank AC, van Brussel M, Takken T. The oxygen uptake efficiency slope in children with congenital heart disease: construct and group validity. *European Journal of Cardiovascular Prevention and Rehabilitation*. 2011;18(3):384-92.

11. Breithaupt PG, Colley RC, Adamo KB. Using the Oxygen Uptake Efficiency Slope as an Indicator of Cardiorespiratory Fitness in the Obese Pediatric Population. *Pediatric Exercise Science*. 2012;24(3):357-68.

12. 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. *European journal of preventive cardiology*. 2015;22(3):356-63.

13. Culhane S, George C, Pearo B, Spoede E. Malnutrition in cystic fibrosis: a review. *Nutrition in Clinical Practice*. 2013;28(6):676-83.

14. Cystic Fibrosis Trust. *Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis*. London2011.

15. Cystic Fibrosis Trust. UK Cystic Fibrosis Registry 2015 Annual Data Report. 2016.

16. Drinkard B, Roberts MD, Ranzenhofer LM et al. Oxygen-uptake efficiency slope as a determinant of fitness in overweight adolescents. *Medicine and Science in Sports and Exercise*. 2007;39(10):1811-6.

17. Graves LE, Batterham AM, Foweather L et al. Scaling of peak oxygen uptake in children: a comparison of three body size index models. *Medicine and Science in Sports and Exercise*. 2013;45(12):2341-5.

18. Gruet M, Brisswalter J, Mely L, Vallier JM. Clinical utility of the oxygen uptake efficiency slope in cystic fibrosis patients. *Journal of Cystic Fibrosis*. 2010;9(5):307-13.

19. Harun SN, Wainwright C, Klein K, Hennig S. A systematic review of studies examining the rate of lung function decline in patients with cystic fibrosis. *Paediatric respiratory reviews*. 2016;20:55-66.

20. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: A height-weight formula validated in infants, children, and adults. *The Journal of Pediatrics*. 1978;93(1):62-6.

21. Hebestreit H, Arets HG, Aurora P et al. Statement on Exercise Testing in Cystic Fibrosis. *Respiration*. 2015;90(4):332-51.

22. Hebestreit H, Schmid K, Kieser S et al. Quality of life is associated with physical activity and fitness in cystic fibrosis. *BMC Pulmonary Medicine*. 2014;14:26.

23. Heine M, Verschuren O, Kwakkel G. Validity of Oxygen Uptake Efficiency Slope in patients with multiple sclerosis. *Journal of Rehabilitation Medicine*. 2014;46(7):656-61.

24. Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. *Journal of the American College of Cardiology*. 2000;36(1):194-201.

25. Marinov B, Mandadzhieva S, Kostianev S. Oxygen-uptake efficiency slope in healthy 7- to 18-year-old children. *Pediatric Exercise Science*. 2007;19(2):159-70.

26. Nevill AM, Ramsbottom R, Williams C. Scaling physiological measurements for individuals of different body size. *European Journal of Applied Physiology and Occupational Physiology*. 1992;65(2):110-7.

27. Pérez M, Groeneveld IF, Santana-Sosa E et al. Aerobic fitness is associated with lower risk of hospitalization in children with cystic fibrosis. *Pediatric Pulmonology*. 2014;49(7):641-9.

28. Pianosi P, LeBlanc J, Almudevar A. Peak oxygen uptake and mortality in children with cystic fibrosis. *Thorax*. 2005;60(1):50-4.

29. Rogowski MP, Guilkey JP, Stephens BR, Cole AS, Mahon AD. The Influence of Maturation on the Oxygen Uptake Efficiency Slope. *Pediatric Exercise Science*. 2012;24(3):347-56.

30. Saynor ZL, Barker AR, Oades PJ, Williams CA. A protocol to determine valid VO2max in young cystic fibrosis patients. *Journal of Science and Medicine in Sport*. 2013;16(6):539-44.

31. Saynor ZL, Barker AR, Oades PJ, Williams CA. Reproducibility of maximal cardiopulmonary exercise testing for young cystic fibrosis patients. *Journal of Cystic Fibrosis*. 2013;12(6):644-50.

32. Stevens D, Oades PJ, Armstrong N, Williams CA. A survey of exercise testing and training in UK cystic fibrosis clinics. *Journal of Cystic Fibrosis*. 2010;9(5):302-6.

33. Tanner JM. Fallacy of Per-Weight and Per-Surface Area Standards, and Their Relation to Spurious Correlation. *Journal of Applied Physiology*. 1949;2(1):1-15.

34. 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. *Journal of Applied Physiology*. 2006;100(6):1851-6.

35. 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. *European journal of preventive cardiology*. 2016;23(10):1045-50.

36. 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. *American Heart Journal*. 2005;149(1):175-80.

FIGURE LEGENDS

Figure 1. Relationship between oxygen uptake ($\dot{V}O_2$; $mL \cdot min^{-1}$) and minute ventilation (V_E; $L \cdot min^{-1}$) [1]; and $\dot{V}O_2$ ($mL \cdot min^{-1}$) and $\log_{10}V_E$ ($L \cdot min^{-1}$) [2] during incremental exercise in representative 13-year old boys – one with CF [A] and one without [B]. Differences in ventilation are clear between participants (i.e., linear vs. curvilinear response), however normalisation of ventilation through log transformation (thus producing OUES) allows for direct comparision between individuals.

Figure 2. Scatter plots with Pearsons correlation coefficients for CF (●, solid line) and CON (○, dashed line) groups for OUES from peak exercise when scaled utilising each variable (stature [A], body mass [B] and body surface area [C]) and procedure (absolute [1], ratio-standard [2] and allometric [3]). * Significant difference ($P < 0.05$) between the magnitude of the correlation coefficients between CF and CON.

Figure 1

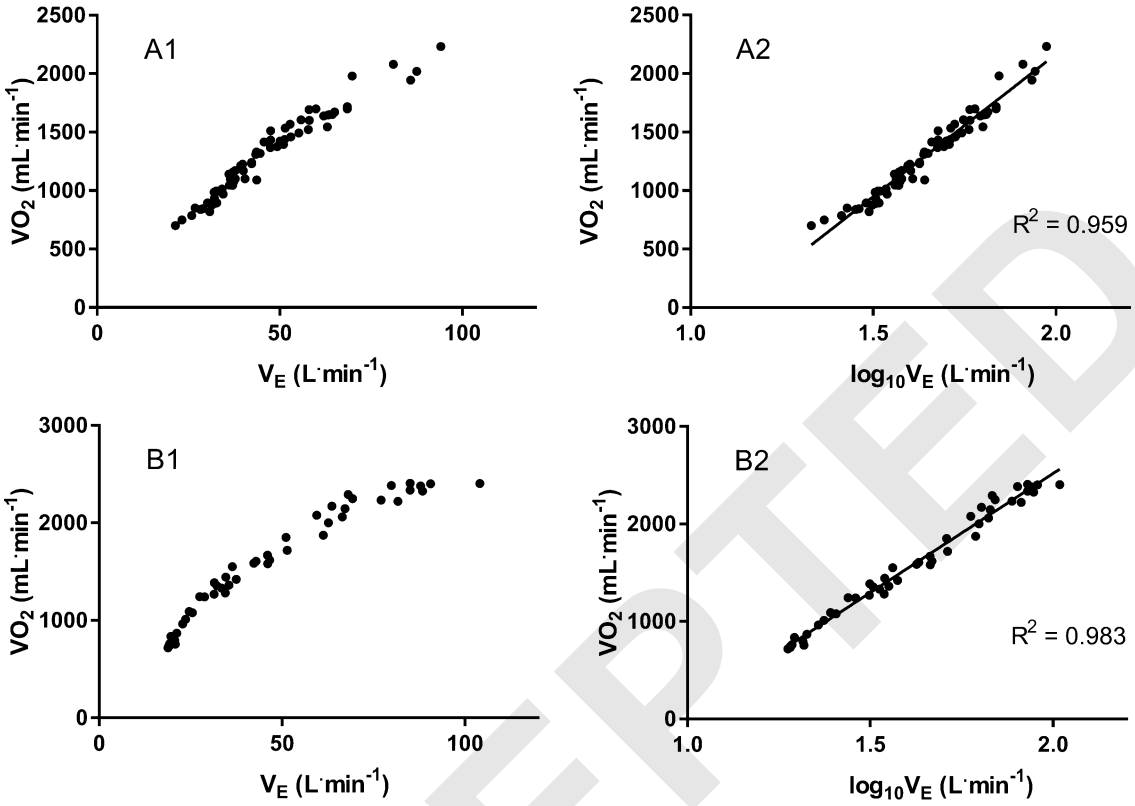
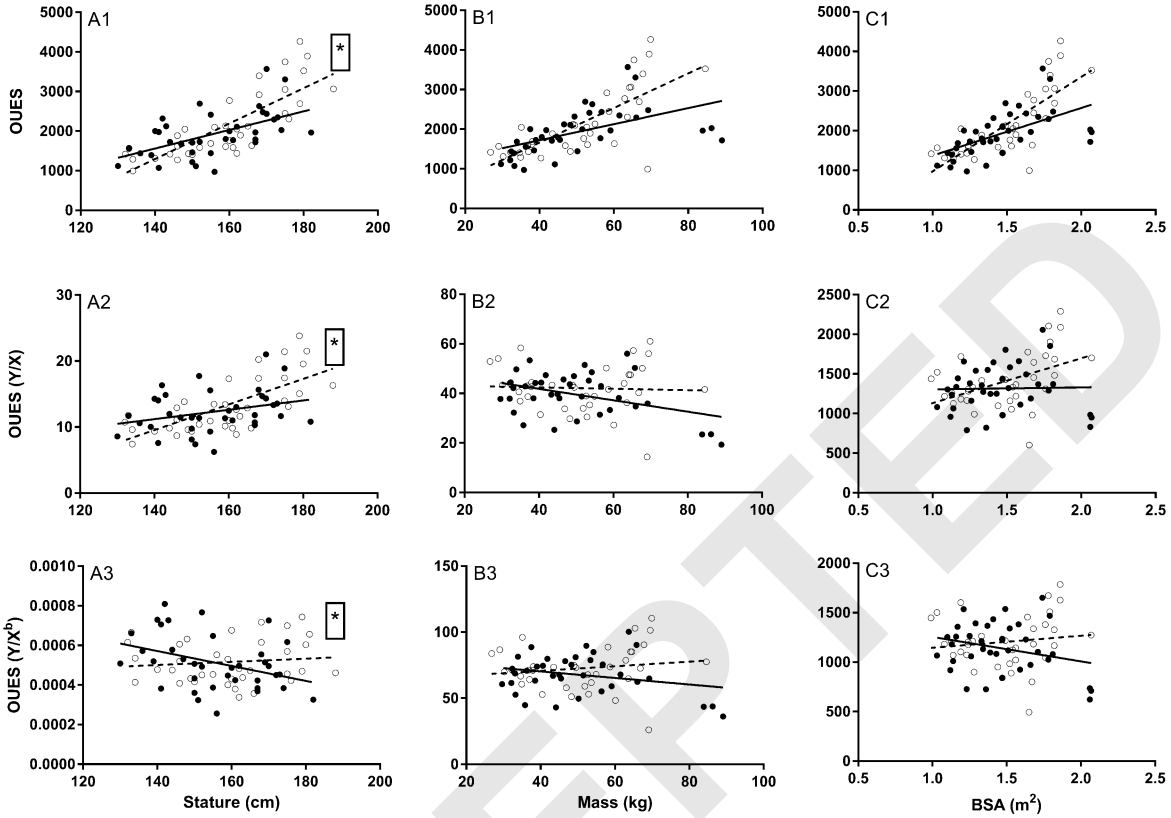


Figure 2



TABLES

Table 1. Anthropometric, pulmonary and exercise-related differences between children with CF and age- and gender-matched controls.

Variable	CF	CON	*P* Value
Stature (cm)	155.6 ± 13.6	159.1 ± 15.2	0.32
Body Mass (kg)	50.15 ± 15.46	51.15 ± 14.49	0.78
Body Surface Area (m^2)	1.46 ± 0.28	1.49 ± 0.28	0.65
FEV_1 ($L \cdot min^{-1}$)*	2.46 ± 0.97	2.96 ± 0.86	0.07
FEV_1 (% Predicted)*	88.0 ± 19.6	101.9 ± 12.2	**0.002**
FVC ($L \cdot min^{-1}$)*	3.10 ± 1.14	3.44 ± 1.02	0.30
FVC (% Predicted)*	94.8 ± 15.9	100.2 ± 12.5	0.21
Peak $\dot{V}O_2$ ($L \cdot min^{-1}$)	1.74 ± 0.57	2.03 ± 0.88	0.09
Peak $\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	37.74 ± 7.74	39.93 ± 10.71	0.32
GET (% p$\dot{V}O_2$)	53.3 ± 9.3	55.0 ± 8.0	0.42
Peak Power Output (W)	146 ± 57	175 ± 72	0.06
OUES (at 100% peak $\dot{V}O_2$)	1927.58 ± 583.49	2148.77 ± 846.55	0.20
OUES (at 75% peak $\dot{V}O_2$)	1842.81 ± 541.13	2066.11 ± 892.96	0.20
OUES (at 50% peak $\dot{V}O_2$)	1604.87 ± 661.75	1815.92 ± 852.51	0.27

Values are presented as mean ± standard deviation. *P* value, independent samples *t*-test significance level. FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; peak $\dot{V}O_2$, peak oxygen uptake; GET, gas exchange threshold; OUES, oxygen efficiency uptake slope.

* Unequal groups for pulmonary volumes (CF, n = 36; CON, n = 18).

Table 2. Pearson's correlation coefficients for OUES at peak $\dot{V}O_2$ when scaled for body size using difering scaling procedures for whole-group (CF + CON)

	CF	CON	Combined
Absolute			
Stature vs. OUES	***r* = 0.545, *P* < 0.001**	***r* = 0.800, *P* < 0.001**	***r* = 0.703, *P* < 0.001**
Mass vs. OUES	***r* = 0.536, *P* < 0.001**	***r* = 0.747, *P* < 0.001**	***r* = 0.640, *P* < 0.001**
BSA vs. OUES	***r* = 0.578, *P* < 0.001**	***r* = 0.783, *P* < 0.001**	***r* = 0.685, *P* < 0.001**
Ratio Standard			
Stature vs. OUES/Stature	$r = 0.296$, $P = 0.079$	***r* = 0.704, *P* < 0.001**	***r* = 0.543, *P* < 0.001**
Mass vs. OUES/Mass	***r* = -0.379, *P* = 0.016**	$r = -0.042$, $P = 0.806$	$r = -0.212$, $P = 0.073$
BSA vs. OUES/BSA	$r = 0.021$, $P = 0.905$	***r* = 0.447, *P* = 0.006**	***r* = 0.254, *P* = 0.031**
Allometric			
Stature vs. OUES/Stature$^{3.00}$	***r* = -0.369, *P* = 0.027**	$r = 0.111$, $P = 0.520$	$r = -0.139$, $P = 0.245$
Mass vs. OUES/Mass$^{0.86}$	$r = -0.253$, $P = 0.136$	$r = 0.150$, $P = 0.383$	$r = -0.041$, $P = 0.730$
BSA vs. OUES/BSA$^{1.40}$	$r = -0.272$, $P = 0.108$	$r = 0.129$, $P = 0.453$	$r = -0.062$, $P = 0.606$

Bold text indicates a significant ($P < 0.05$) correlation. Bivariate plots are shown in Figure 2.

Table 3. Allometric exponents for the OUES measures and body size in young patients with CF and healthy age- and gender-matched controls.

		CF		CON			COMBINED	
OUES measure	Body size variable	b	95% CI	b	95% CI	*Δb*	b	95% CI
50% peak $\dot{V}O_2$	Stature (cm)	2.77	1.19 - 4.36	4.17	3.23 - 5.10	*1.40*	3.60	2.72 - 4.47
	Body Mass (kg)	1.06	0.62 - 1.51	1.06	0.61 - 1.51	*0.00*	1.06	0.75 - 1.37
	BSA (m^2)	1.63	0.94 - 2.33	1.78	1.14 - 2.42	*0.15*	1.72	1.26 - 2.17
75% peak $\dot{V}O_2$	Stature (cm)	2.17	1.26 - 3.08	3.56	2.74 - 4.37	*1.39*	2.93	2.31 - 3.55
	Body Mass (kg)	0.68	0.42 - 0.95	0.91	0.55 - 1.27	*0.23*	0.80	0.58 - 1.02
	BSA (m^2)	1.09	0.68 - 1.49	1.52	1.00 - 2.04	*0.43*	1.31	0.98 - 1.64
Peak $\dot{V}O_2$	Stature (cm)	1.88	0.87 - 2.89	3.17	2.41 - 3.92	*1.29*	2.59	1.96 - 3.21
	Body Mass (kg)	0.66	0.39 - 0.94	0.88	0.57 - 1.18	*0.22*	0.77	0.57 - 0.98
	BSA (m^2)	1.03	0.60 - 1.47	1.44	1.00 - 1.88	*0.41*	1.24	0.94 - 1.55
AVERAGE	Stature (cm)	2.23	1.54 - 2.91	3.62	3.11 – 4.12	***1.39***	**3.00**	**2.58 - 3.43**
	Body Mass (kg)	0.78	0.58 - 0.97	0.94	0.72 - 1.15	***0.16***	**0.86**	**0.72 – 1.01**
	BSA (m^2)	1.21	0.91 - 1.51	1.57	1.26 - 1.88	***0.36***	**1.40**	**1.18 - 1.62**

b: scaling exponent; 95% CI: 95% confidence interval for b. Averaged exponents are highlighted in bold. Δb indicated difference in exponents between CF and CON groups.