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Novel Z Scores to Correct Biases Due to Ventricular Volume Indexation to Body Surface Area in Adolescents and Young Adults

Short title

Z Scores for Ventricular Volumes by cMRI

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ABSTRACT

BACKGROUND: Reference values for cardiac magnetic resonance imaging (cMRI) in children and young adults are scarce. This leads to risk stratification of patients with congenital heart diseases to be based on volumes indexed to body surface area (BSA). We aimed to produce cMRI Z score equations for ventricular volumes in children and young adults and test whether indexing to BSA resulted in an incorrect assessment of ventricular dilatation according to sex, body composition and growth.

METHODS: We retrospectively included 372 subjects aged <26 years with either normal hearts or conditions with no impact on ventricular volumes (reference group), and 205 subjects with repaired tetralogy of Fallot (TOF) aged <26 years. We generated Z score equations using multivariable regression modelling. Right ventricular dilatation was assessed using Z scores and was compared to indexation to BSA in TOF subjects.

RESULTS: Ventricular volume Z scores were independent from age, sex and anthropometric measurements, while volumes indexed to BSA showed significant residual association with sex and body size. In TOF subjects, indexation overestimated dilatation in growing children and underestimated dilatation in females compared to males, and in overweight compared to lean subjects.

CONCLUSIONS: Indexed ventricular volumes measured with cMRI did not completely adjust for body size and resulted in a differential error in the assessment of ventricular dilatation according to sex and body size. Our proposed Z score equations solved this problem. Future studies should evaluate if ventricular volumes expressed as Z scores have a better prognostic value compared to volumes indexed to BSA.

KEYWORDS

Cardiac magnetic resonance imaging | Reference values | Z scores | Ventricular volumes | Indexation

BRIEF SUMMARY

Reference values for ventricular volumes by cardiac magnetic resonance imaging in children and young adults are scarce. The authors found that in tetralogy of Fallot patients, ventricular volume indexation to body surface area led to an underestimation of ventricular dilatation in females and in overweight subjects, and to an overestimation of dilatation in rapidly growing children, compared to their respective counterparts. This differential error was solved by Z score equations based on multivariable models.

ABBREVIATION LIST

cMRI: Cardiac magnetic resonance imaging | RV: Right ventricle | TOF: Tetralogy of Fallot | RVEDV: Right ventricle end-diastolic volume | BSA: Body surface area | LBM: Lean body mass | IQR: Interquartile range | BMI: Body mass index

INTRODUCTION

Cardiac magnetic resonance imaging (cMRI) is increasingly used to measure cardiac ventricular volumes in children and adults with congenital heart disease.[1] As ventricular volumes naturally increase with body size, pathological ventricular dilatation must be evaluated against validated reference values that are adequately normalized for age, body size and sex.[2]

Despite their importance, cMRI reference values for children and adolescents are scarce[3] and most are derived from small single centre studies using indexed volumes.[4-7] Only two pediatric studies have proposed Z scores based on body surface area (BSA).[8, 9] Current recommendations for risk stratification of patients with congenital right-sided disease remained based on ventricular volumes indexed to body surface area (BSA).[10, 11] Previous studies have shown that simple indexing to BSA does not completely adjust for body size.[8, 12-14] This raises the possibility of inaccurate risk stratification especially in growing children and patients with abnormal body mass.

In this study, we assessed whether indexing ventricular volumes to BSA creates a differential error according to sex, body composition and growth, and we tested whether using Z score based on multivariable models could provide a valid alternative. To do this, we first derived novel cMRI Z score equations for ventricular volumes, ejection fraction and stroke volumes in adolescents and young adults. We then tested the following hypotheses: 1) indexing RV end-diastolic volume (RVEDV) to BSA does not completely remove the influence of sex and body size; 2) the use of an indexed RVEDV cut-off of 160 mL/m^2 yields different degrees of RV dilatation according to sex and body composition in children with tetralogy of Fallot (TOF); and 3) BSA indexation overestimates dilatation in growing children with TOF.

METHODS

Study design

This is a retrospective multicentre international study involving nine academic centers. We used a cross-sectional design to determine Z score equations in a reference group, and a cohort design to evaluate the difference in the estimation of ventricular dilatation between indexing and Z scores in a sample of subjects with repaired TOF. We collected data from cMRI scans conducted on individuals <26 years of age between 2008 and 2017. The list of participating institutions is available in the supplementary material (Table S1). Each institution's research ethics board reviewed and approved the study. Individual consent was waived because the analysis was done on retrospective de-identified data.

Reference group

We included cMRI scans from subjects with a clinical indication for cMRI, where the latter was either normal or led to the diagnosis of conditions that do not affect ventricular volumes and function. These include vascular rings, bicuspid aortic valve with isolated aortopathies, patients assessed for non-frequent arrhythmias (<5% of non-sinus beats on Holter monitoring), and patients with small extra-cardiac or epicardial masses. We also included cMRI scans from healthy research subjects previously recruited for another study.[15] We excluded subjects with neuromuscular, mitochondrial or metabolic diseases, cardiomyopathy, ribcage abnormalities, history of cardiac transplant, aneuploidy or with suboptimal imaging. Patients screened for arrhythmogenic right ventricular dysplasia were excluded regardless of the test result.

Tetralogy of Fallot group

We collected data on cMRI studies performed on patients with repaired TOF <26 years of age between 2008 and 2017 in any of the participating institutions. Patients with other concomitant conditions that could affect ventricular volumes and function were excluded as described above.

Clinical data collection

Data were collected and managed using the electronic data-capture tool REDCap.[16] We collected data on sex, age, weight, height, and indication for the cMRI from medical charts for clinical scans, or from the original research database for research studies.

Cardiac MRI data collection

We collected end-diastolic and end-systolic volumes for both ventricles from the cMRI reports. When volumes were not available, we attempted to extract de-identified DICOM images to remeasure them. We calculated stroke volumes and ejection fraction using end-systolic and end-diastolic volumes. Technical information such as slice orientation, slice thickness, inter-slice gap, sedation and breathing protocol, tracing method, and type of scanner was either extracted from the cMRI reports or directly collected from local investigators responsible for the cMRI studies at their institution.

All cMRI volumes were obtained using steady-state free precession. All participating centres adhered to the following guidelines when measuring ventricular volumes.[17] For LV volumes, the papillary muscles were excluded, and matching long-axis planes were used to differentiate the ventricle from the atrium, the aorta or the pulmonary artery. For RV volumes, the trabeculations, the moderator band, and the RV outflow tract below the level of the pulmonary valve were included in the blood pool.

Body surface area was calculated using the Haycock *et al*. formula.[18] Lean body mass (LBM) was estimated from the height, weight, age and sex using the equations proposed by Foster *et al*.[13] Body mass index (BMI) was expressed as kg/m^2. For children, BMI was normalized for age and sex and expressed as Z scores using the World Health Organization reference values for children.[19, 20] We calculated BMI Z scores for adults using the pediatric normal values of an 18.9-year-old to obtain comparable categories and avoid breaks in normal curves. BMI-for-age categories were defined as lean (BMI-for-age Z score ≤ -1), normal weight ($-1 <$ BMI-for-age Z score <1), and overweight (BMI-for-age Z score ≥ 1).[20]

Z score equations

The reference group was used to generate Z score equations. The entire reference group was used to model the predicted mean, but only subjects ≥120 cm in height were used to model the standard deviation since we were not able to adequately model the latter in individuals <120 cm (see results for details). Prediction models and Z scores were computed using a systematic and standardized approach that has been successfully used in the past (see the supplemental material for the detailed methodology).[21, 22] Briefly, we first modelled the relationship between cMRI parameters and anthropometric measurements using parametric regression. We used an iterative strategy to choose final models; simpler univariate models were first tested and evaluated according to residual association with body size and age. More complex multivariate models were used if univariate models did not completely remove the effect of body size and age. Z score equations were derived from the regression results. Z scores were validated by assessing linearity, homoscedasticity, departure from the normal distribution and residual association with body size, sex and age (see the supplemental material for details on Z score validation strategies).

Calculation of an adjusted weight for overweight individuals

To minimize the bias induced by weight in overweight and obese subjects,[12, 23] we used an "adjusted weight" approach that we have used successfully in the past.[21] The subject's weight was included in the regression models, but a cut-off was imposed when the subject's BMI-for-age was >85th percentile. For example, if a subject had a BMI-for-age at the 50th percentile, their actual weight was used in the model. If a subject had a BMI-for-age >85th percentile, an estimation of their weight at the limit of the 85th percentile BMI-for-age was calculated. This value was then used as the adjusted weight in the model instead of the subject's actual weight.

Comparison of Z scores and volume indexation to BSA in reference subjects

We assessed whether indexation to BSA completely adjusted ventricular volumes for body size and age. We plotted indexed volumes from the reference group against age, height, weight, BSA, BMI-for-age and LBM, and compared them to their Z score counterparts. We considered any significant residual association with body size as an indication of an incomplete adjustment.

Estimation of RV dilatation by Z scores and indexation to BSA in TOF subjects

In TOF subjects, we first tested the hypothesis that the median degree of RV dilatation at the 160 mL/m^2 cut-off would differ between males and females, and between BMI-for-age categories. We used the 160 mL/m^2 cut-off as it is the proposed threshold to consider pulmonary valve replacement.[24] We defined RV dilatation as the number of mL above the predicted mean (Z=0). We assessed RV dilatation according to sex and BMI-for-age categories. We also compared RVEDV Z scores corresponding to the 160 mL/m^2 cut-off according to sex and BMI-for-age.

We also hypothesized that indexing RVEDV to BSA overestimates RV dilatation in growing children. To test this, we used TOF subjects with ≥2 cMRI and assessed the change in RV dilatation

(i.e., the change in volume above the predicted mean) between the first and the last cMRI scan. An increase in RV dilatation with time equates to a "worsening" dilatation. This progression of RV dilatation was assessed when the predicted mean was estimated from the Z scores compared to that predicted from indexation to BSA. A positive difference between the two methods indicates that RV indexation estimated a faster progression of RV dilatation in time compared to Z scores. We evaluated whether the difference between the two methods was associated with growth (i.e., with height and weight gains between the first and last cMRI).

Influence of cMRI modalities and indications

To assess data quality, we tested whether cMRI technical modalities influenced Z scores in the reference group. These included slice orientation, type of scanner, tracing method, sedation and breathing protocol, cMRI indication, institution and type of scan (clinical vs. research). Results of this assessment is presented in the supplementary results.

Statistics

All analyses were done using SAS for Windows version 9.4 (SAS Institute Inc., Cary, NC, USA). Continuous variables were presented as median and interquartile range (IQR), while categorical variables were expressed as frequencies. The Wilcoxon rank-sum test was used to assess median differences between groups. Linear regression was used to estimate p-values for residual associations between Z scores and independent variables, and to test association between RV dilatation overestimation and weight and height gain over time. Departure from a normal distribution was evaluated by using the Shapiro-Wilk diagnostic test and by visual assessment (distribution histograms, box plots, and normal probability plots). A p-value <0.05 was considered

statistically significant, except for the Shapiro-Wilk statistic where a p-value <0.01 was considered statistically significant.

RESULTS

Subject characteristics

For the reference group, 949 subjects with clinical cMRI studies were screened for eligibility. We identified 112 subject who met the inclusion criteria. Of them, we retrieved ventricular volumes from the clinical report for 64 studies and we were able to remeasure volumes from DICOM images for an additional 48 studies. Lastly, we added 260 cMRI studies previously done for research purposes.[15] These 372 studies formed our reference group. Additionally, we collected 290 cMRI studies from 205 TOF subjects, which constituted our TOF group. There were 85 TOF subjects with longitudinal data. The study population characteristics are presented in Table 1.

Preliminary analysis for Z score equations

Preliminary analyses to determine the final models are detailed in the supplementary results. Briefly, no single variable could fully adjust for body size. Multivariable models using a combination of height, weight and age were used. As observed in previous studies,[12, 21, 23] the subject's weight had an independent effect on all ventricular volumes, especially in males. Including weight in our models decreased residual associations, but it introduced a distortion by over-adjusting volumes in overweight subjects. We therefore used an "adjusted weight" to account for the differential effect of muscle mass and fat mass, a strategy that we used successfully in the past to remove residual associations with weight and BMI-for-age (see supplementary results for details).[21]

It was not possible to adequately model the standard deviation across the entire reference group. We lacked sufficient sample size to accurately model the standard deviation for individuals <120 cm and all attempts yielded obviously overfitted models (data not shown). Consequently, standard deviation was assessed for subjects ≥120 cm. For those subjects ≥120 cm, we found no statistically significant heteroscedasticity for all parameters (Table S2 in the supplemental material). The absence of a reliable predicted standard deviation for subjects <120 cm of height implies that departure from the mean can be evaluated, but Z score cannot be reliably computed in this subset of subjects.

Final Z score equations

Equations 1 and 2 are used to calculate predicted means and Z scores, respectively. The coefficients for these equations are presented in Tables S3 (males) and S4 (females) in supplementary results. For all calculations, the height is in cm, the weight is in kg, the age is in years, all ventricular volumes are in mL and ejection fractions are expressed as a percentage.

Equation 1

$$\text{Predicted mean} = (\text{a} \times \textit{height}^2) + (\text{b} \times \textit{height}) + (\text{c} \times \textit{weight}) + (\text{d} \times \text{age}) + \text{e}$$

Equation 2

$$\text{Z} = \frac{\text{observed value} - [(\text{a} \times \textit{height}^2) + (\text{b} \times \textit{height}) + (\text{c} \times \textit{weight}) + (\text{d} \times \text{age}) + \text{e}]}{\mathbf{f}}$$

An Excel Z score calculator is provided in the supplemental material. The Excel Z score calculator automatically adjusts Z scores for overweight and obese individuals.

No significant residual association with height, weight, age, BSA, LBM or BMI-for-age was found for any ventricular volume Z scores. Scatter plots of RVEDV Z scores against height, weight, and BSA are presented as examples in Figure 1. Details on residual associations for all variables are shown in Table S2 in the supplementary material. As stated in the supplementary material, ejection fraction could not be modelled (no clear pattern with body size or age). There was a small but statistically significant residual association between RV ejection fraction and body size (see Table S2 in the supplementary results). Assessment of the distribution of Z scores is detailed in the supplementary material.

Residual association for ventricular volumes indexed to BSA

Significant residual associations with all anthropometric measurements and age were found when ventricular volumes were indexed to BSA. Figure 1 shows scatter plots of indexed RVEDV against height, weight and BSA (see Supplementary Figure S1 for residual associations with age, LBM and BMI-for-age). Furthermore, residual associations were different according to sex. This indicated that indexing to BSA does not fully adjust for body size and that it creates a potential differential error according to sex. Similar results were found for right and left ventricular end-diastolic volumes, end-systolic volumes, and stroke volumes (data not shown).

Estimation of RV dilatation by Z scores and indexation to BSA in TOF subjects

Figure 2 shows that the use of the 160 mL/m^2 cut-off for RV volume resulted in important variations in the degree of RV dilatation amongst TOF subjects. We found that the same 160 mL/m^2 cut-off meant greater dilatation as the BMI-for-age increased, and greater dilatation in females compared to males. This suggests that males and lean individuals would reach the 160 mL/m^2 cut-off sooner (with less dilatation) compared to females and overweight individuals, respectively. In

females, the number of mL above the predicted mean (degree of dilatation) at the 160 mL/m^2 cut-off increased as BMI-for-age increased: for lean, normal weight and overweight subjects, the median number of mL (IQR) above the predicted mean was 96.5 (89.1 - 104.0) mL, 109.2 (102.5 - 117.1) mL and 131.8 (128.2 - 159.3) mL, respectively. This trend was also observed in males, but the differences were less marked. All differences between medians were statistically significant between sex and BMI-for-age categories, except between lean females and males.

We also calculated Z scores corresponding to the 160 mL/m^2 cut-off for TOF subjects and found that the magnitude of the departure from the predicted mean was higher in females compared to males, and in subjects with higher BMI-for-age. This analysis is detailed in the supplements.

Differential error in RV dilatation for growing children

We tested whether the assessment of the progression of RV dilatation in growing children with TOF would be different according to the method used to measure RV dilatation. To do this, we compared the progression of RV dilatation (the change in the number of mL above the predicted mean between the first and last cMRI scans) according to BSA indexation and Z score. Figure 3 presents the difference in the assessment of the progression of RV dilatation between Z scores and indexation according to growth (height and weight gain). A positive difference means that RV indexation estimated a faster progression of ventricular dilatation compared to Z scores. The figure shows that the more children have grown between cMRI (height gain between the first and last cMRI), the larger the difference in the estimated progression of RV dilatation ($p=0.001$ in females and $p=0.002$ in males). Weight gain was also strongly associated with a difference in the progression of RV dilatation in males ($p <.001$), but not in females.

DISCUSSION

We proposed novel cMRI Z score equations for ventricular volumes for adolescents and young adults. Our Z score equations yielded predicted means that were independent to body size, age and sex, which will help differentiate pathological ventricular dilatation from physiological variation according to body size, age and sex. We also confirmed that indexing ventricular volumes to BSA did not fully adjust for body size and sex. Finally, we found that this incomplete adjustment led to erroneous assessment of ventricular dilatation, as the same indexed volume meant different degrees of dilatation in males compared to females, and in lean compared to overweight individuals.

It has been advocated that dividing cardiac volumes by BSA removes the influence of body size, owing to early studies from Graham and collaborators showing a somewhat linear correlation between heart size and BSA.[25] This approach remains widely used, likely due to its simplicity, despite numerous reports of its shortcomings.[12, 14, 26-28] Two major problems arise when ventricular volumes are indexed to BSA. First, the incomplete adjustment for body size by simple indexation leads to inaccurate prediction of the population mean.[26, 29] Second, the sole use of BSA to predict heart size underestimates the strong contribution of height.[12] It also blurs the distinct effects of muscle mass and fat mass on heart size.[12, 30] The results from this study confirm that indexing ventricular volumes to BSA does not accurately estimate the degree of ventricular dilatation, and that Z scores can mitigate this issue.

The various approaches to model heart size to body size have been reviewed[2, 26, 31] and there is no clear consensus on how to determine reference values. We[12] and others[32, 33] have shown in the past the limitations of using BSA to normalize cardiac size, especially in overweight and obese subjects. We found that multivariable models were superior to models with BSA to predict vessel diameters in children,[12] and that using an adjusted weight for overweight subjects helped to correct the bias

caused by increased fat mass.[21] In the current study, we used a similar approach and showed that Z scores were fully independent from BMI-for-age, indicating minimal or no bias caused by fat mass.

Multiple studies have proposed reference values for cMRI ventricular volumes. However, many are small single centre studies and only two proposed Z score equations. In children, all but two studies[7, 9] included <60 subjects.[4-6, 8] One study by Sarikouch et al. was done on 114 prospectively recruited children and young adults.[7] The authors provided percentile limits but did not propose Z score equations. In a recent study, Olivieri et al. prospectively included 149 children aged 22 days to 12 years and proposed Z scores based on BSA.[9] In adults, most studies proposing reference values for ventricular volumes reported means and standard deviations stratified by age and/or sex and used volumes indexed to height and/or BSA.[15, 34-37] Three of them stratified their results for age and showed that ventricular volumes decreased with advancing age despite indexing.[15, 35, 38]

We believe that accurate adjustment of ventricular volume on body size will increase our ability to assess the extent of ventricular dilatation or hypoplasia. However, the optimal way of measuring the departure from the reference mean has yet to be clarified. It is logical that a ventricular volume that is 100 mL above the mean does not represent the same degree of dilatation in an infant, a school-age prepubertal girl, and a tall young adult male. There are clear benefits in expressing the departure from the mean as Z scores.[27, 39] However, it has yet to be shown whether expressing ventricular dilatation as the number of standard deviations above the mean (Z score) is a better predictor of morbidity than absolute volumes. In our cohort, the 160 ml/m^2 cut-off corresponded to median Z scores of 3.5 and 5.7 for normal weight males and females, respectively. This matter requires further research, especially considering the smaller observed predicted standard deviation in females compared to males.

Our study has limitations. Part of our reference group comprises subjects with indications for cMRI and thus cannot be strictly considered as normal. We elected to use such a population to efficiently increase our sample size without the burden of prospectively performing cMRI on healthy children volunteers. Furthermore, ventricular volumes that were extracted from clinical reports could be influenced by the type of scanner, tracing method and variability between observers. We were reassured by the lack of differences between volumes measured in a standardized research setting and those extracted from clinical studies, indicating that no clear differential error was present in our data set. Also, ventricular mass was rarely reported in the included clinical reports, and we lacked a sufficient number of pediatric subjects to include ventricular mass in the analysis. Finally, as we could not reliably estimate the SD for subjects <120 cm, our Z score equations should be used only for subjects with height >120 cm and further studies are needed for smaller children.

CONCLUSION

We propose novel cMRI Z score equations for ventricular volumes that are independent of age, body size and sex. These Z scores can improve patient care by allowing true comparison between children and young adults of different sizes and age, as well as serially follow ventricular dilatation. Given the shortcomings of indexing cardiac volumes to BSA, we believe that Z scores should be the preferred method for normalizing ventricular volumes for body size. Further research is required to validate these Z score equations on other healthy populations, and to determine which expression of ventricular dilatation carries increased prognostic value and enables better risk stratification for congenital cardiac diseases.

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Disclosures

The authors have nothing to disclose.

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FIGURES

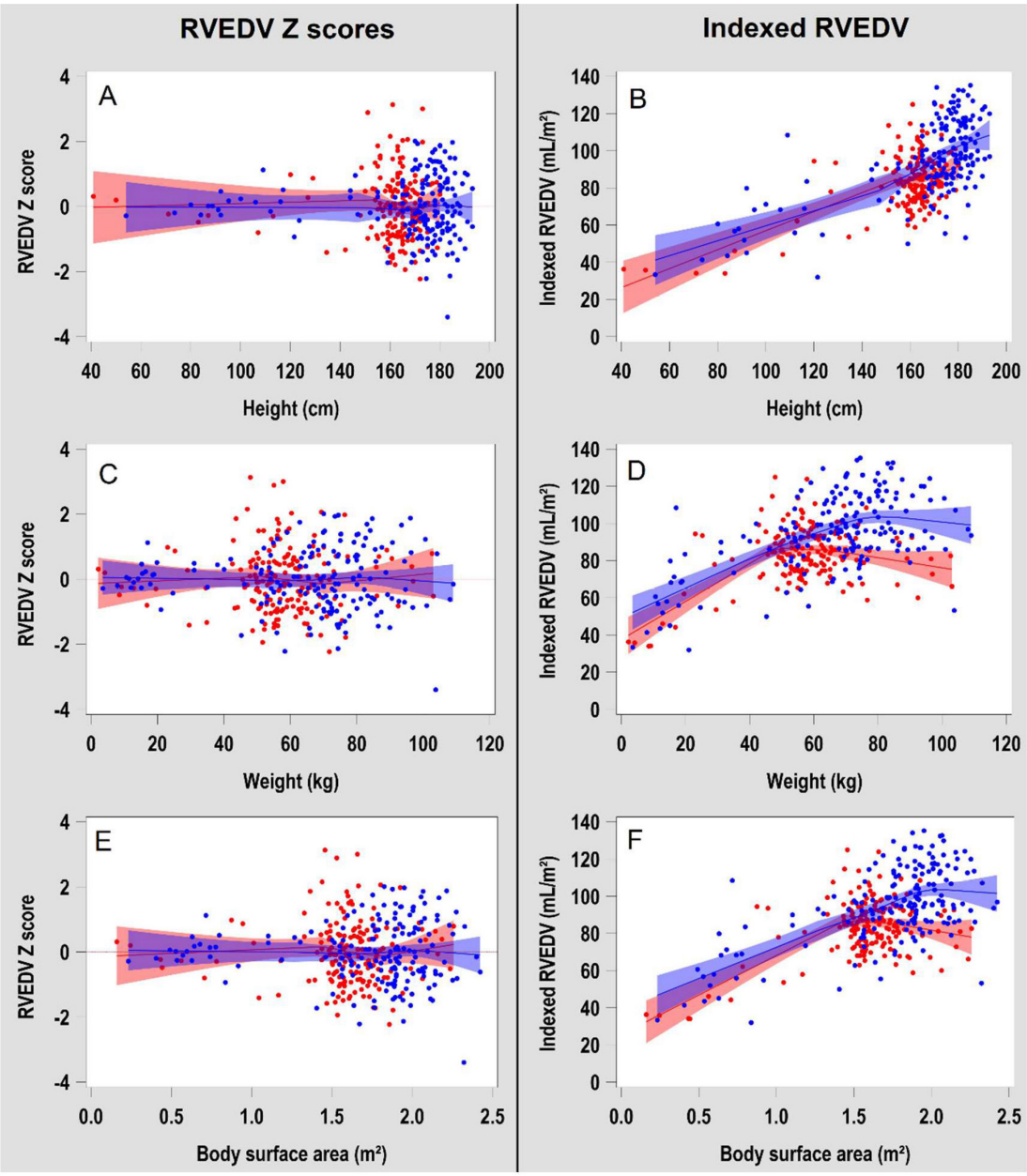


Figure 1. Residual association of height (panels A and B), weight (panels C and D), and body surface area (panels E and F) with right ventricular end-diastolic volume (RVEDV) Z scores and RVEDV indexed to body surface area. Male and female subjects are represented in blue and red respectively. The solid line represents the smoothed regression curve (locally estimated scatterplot smoothing) and the shaded area is the 95% confidence margins of the predicted mean.

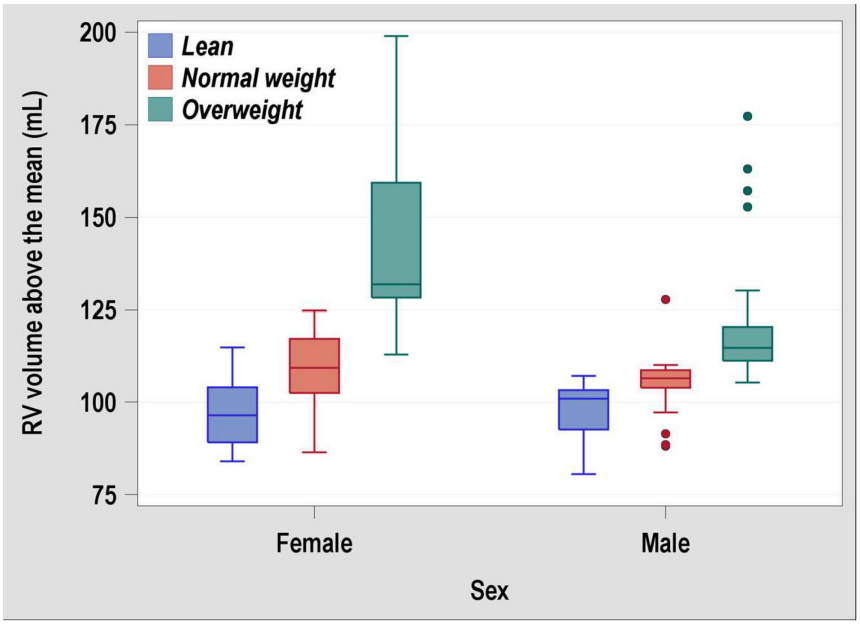


Figure 2. Box-plots of estimated right ventricular dilatation (RV) (number of ml above the predicted mean) at the 160 mL/m^2 cut-off according to sex and body mass index (BMI) categories. Lean: BMI-for-age Z score < −1.0. Normal weight: −1.0 ≤ BMI-for-age Z score ≤ 1.0. Overweight: BMI-for-age > 1.0.

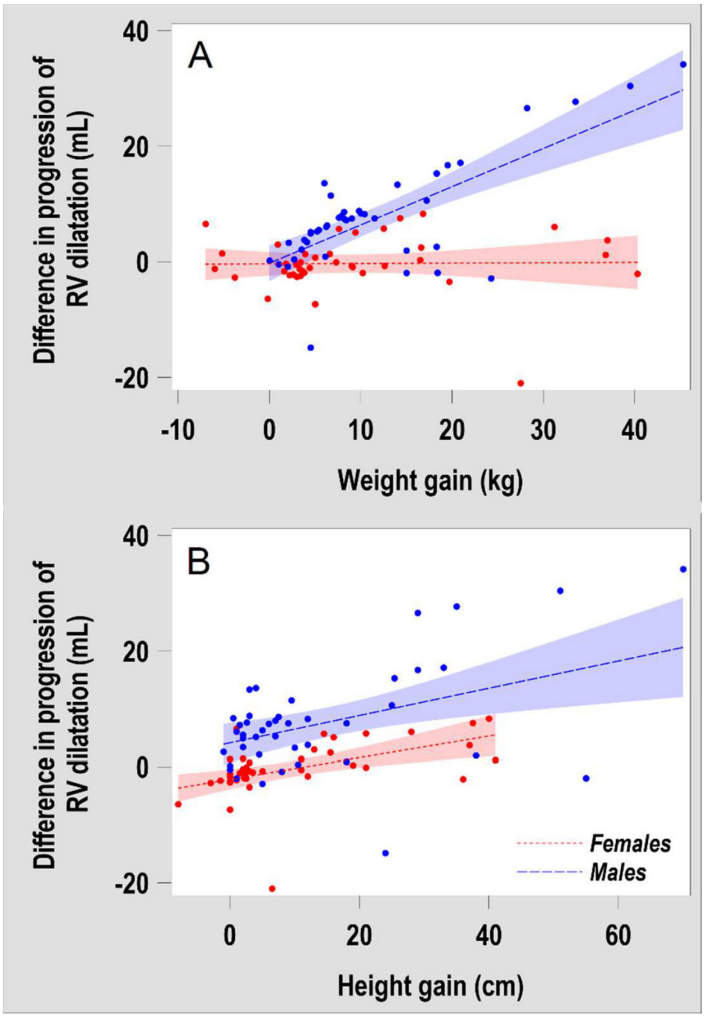


Figure 3. Difference in the estimation of the progression of right ventricular dilatation as assessed by indexation versus Z scores according to weight gain (panel A) and height gain (panel B). Male and female subjects are represented in blue and red respectively. The solid line represents the regression curve and the shaded area is the 95% confidence margins of the predicted mean.

TABLE

Table 1. Subject characteristics

Characteristics at study inclusion	Median (interquartile range) or number (%)	
	Reference group n = 372	Tetralogy of Fallot group n = 205
Sex (male)	189 (50.8%)	114 (55.6%)
Age (years)	21.4 (16.0 - 23.9)	16.0 (14.0 - 17.9)
Weight (kg)	62.3 (52.3 - 73.4)	52.3 (43.7 - 64.0)
Height (cm)	168 (160 - 176)	160 (154 - 169)
Body surface area (m^2)	1.70 (1.53 - 1.90)	1.54 (1.37 - 1.73)
Body mass index-for-age Z score	0.27 (−0.44 - 0.92)	−0.09 (−0.99 - 0.90)
Indication (reference group)		
Research purpose	260 (69.9%)	-
Cardiomyopathy screening (negative result)	16 (4.3%)	-
Screening for congenital heart disease	8 (2.2%)	-
Arrhythmias	14 (3.8%)	-
Evaluation of cardiac mass or tumor	9 (2.4%)	-
Evaluation of vascular anatomy	46 (12.4%)	-
Other/unknown	19 (5.1%)	-

SUPPLEMENTAL MATERIAL

Novel Z Scores to Correct Biases Due to Ventricular Volume Indexation to Body Surface Area in Adolescents and Young Adults

Supplemental methods

Supplementary Table S1. List of participating institutions

Institution	Location
Centre hospitalier universitaire de Sherbrooke	Sherbrooke, Quebec, Canada
Centre hospitalier universitaire de Québec	Quebec, Quebec, Canada
Centre hospitalier universitaire de Sainte-Justine	Montreal, Quebec, Canada
Institut universitaire de cardiologie et de pneumologie de Québec	Quebec, Quebec, Canada
McGill University Health Centre	Montreal, Quebec, Canada
Wilhelmina Children's Hospital	Utrecht, Utrecht, Netherlands
Winnipeg Children's Hospital	Winnipeg, Manitoba, Canada
Alberta Children's Hospital	Calgary, Alberta, Canada
IWK Health Centre	Halifax, Nova-Scotia, Canada

Rational for multivariate analysis

This method has been described and previously published.[1] Four regression models were empirically tested to optimize the goodness-of-fit between the dependent and independent variable: linear (y=ax+b), allometric (y=ax^b), second-order polynomial (y=ax^2+bx+c) and third-order polynomial (y=ax^3+bx^2+cx+d). A second-order polynomial model according to height was adequate to adjust for a substantial portion of the variation of ventricular volume according to body size, but a small residual association was present with weight and age. This meant that despite adequate modelling for height, the patient's weight was still associated with ventricular volumes (for the same height, heavier patients had larger ventricular volumes). Consequently, multivariable models with the square of height, height, weight and age were needed to adequately predict ventricular volumes. All attempts to model ventricular volumes using body surface area (BSA) or lean body mass (LBM) were not successful, either because of substantial residual associations, or because the models were more complex without improving the goodness-of-fit.

In the presence of non-constant variance (heteroscedasticity), we tested a weighted regression approach to model the standard deviation around the mean as previously described.[1]

Assessment of the validity of Z Scores

To assess if the newly computed Z scores were independent of body size and maturation, we plotted Z scores against weight, height, body mass index-for-age (BMI-for-age), LBM and age. We evaluated Z scores for the departure from a normal distribution with an expected mean of 0 and a SD of 1 by visual assessment (distribution histograms, box plots, and normal probability plots) and by using the Shapiro-Wilk statistic. Assessment of residual heteroscedasticity was done by fitting a regression curve in the absolute values of the Z scores against height. A positive slope indicates residual heteroscedasticity.

Supplemental results

Preliminary Z score analysis

Preliminary analysis showed that the relation between ventricular volumes and body size was strongly influenced by sex (data not shown). Therefore, all subsequent models were stratified by sex to produce sex-specific Z score equations. The strongest predictor of end-systolic volumes, end-diastolic-volumes and stroke volumes was the square of height. However, it alone could not fully adjust for body size. Further analysis showed that no single body size variable could fully correct any ventricular volumes. Consequently, multivariable models using a combination of height, weight and age were used (see supplemental material for details). There was no clear association of ejection fraction with body size or age.

Rationale for using an adjusted weight

The subject's weight had an independent effect on all ventricular volumes, especially in males, and the inclusion of weight in our models improved prediction by decreasing residual associations. However, it introduced a distortion by over-adjusting volumes in overweight subjects. We therefore used an "adjusted weight" to account for the differential effect of muscle mass and fat mass, a strategy that we used successfully in the past to remove residual associations with weight and BMI-for-age.[1] Supplementary Figure S2 shows that RVEDV Z scores computed without adjusting the weight had a residual association with BMI-for-age (panel A) and that this residual association was almost eliminated when Z scores were computed using the adjusted weight (panel B).

This adjusted weight is the actual subject's weight for normal weight subjects. However, a cut-off is applied when the participant's BMI-for-age is >85th percentile. Hence, for a subject with a BMI-for-age >85th percentile, an estimation of the weight at the limit of the 85th percentile BMI-for-age was calculated. This estimate (i.e., the adjusted weight), is then used in the model instead of the participant's actual weight.

Distribution of Z scores

The Shapiro-Wilk test showed a statistically significant departure from a normal distribution for right ventricle end-systolic volume, left ventricle end-systolic volumes, and RV ejection fraction (see Supplementary Table S2). However, visual assessment as well as skewness and kurtosis indexes showed that the departure from the normal distribution was small and likely inconsequential (Supplementary Figure S3).

Estimation of RV dilatation by Z scores and indexation to BSA in ToF subjects

Supplementary Figure S4 presents RVEDV Z scores at the 160 mL/m^2 cut-off for ToF subjects and shows that the degree of dilatation differs greatly for the same RVEDV indexed to BSA, i.e., the magnitude of the departure from the predicted mean was higher in females and in subjects with higher BMI-for-age. The median Z score for lean, normal weight and overweight ToF females at the 160 mL/m^2 cut-off was respectively 5.1 (4.7 - 5.5), 5.7 (5.4 - 6.2) and 6.9 (6.7 - 8.4). Furthermore, the individual Z scores corresponding to a cut-off of 160 mL/m^2 in females varied widely, ranging from 4.4 to 12.0, indicating that the same indexed RVEDV corresponded to volumes 4 to 12 standard deviations above the mean. Of note, the predicted standard deviation was larger in males, which partly explain differences between males and females.

Influence of cMRI modalities, equipment and centers

Participating institutions may have different cMRI equipment and protocols. We analyzed the influence of cMRI technical modalities on volumes adjusted for body size (Z score) to remove the potentially confounding effect of body size and age. We first tested if the mean Z score was different for clinical cMRI studies and research cMRI studies. The difference was small (0.1 Z score unit) and not statistically significant (p=0.051), suggesting that measurements in clinical settings were similar and comparable to those obtained in a standardized research environment. There were no differences for slice orientation, thickness, institution and type of scanner, except for tracing methods: manual tracing had a mean Z score 0.3 unit above automatic and semi-automatic tracing (p=0.03). However, we found that the 95% confidence interval of the absolute difference in mL between the predicted means according to tracing method was <5 mL.

Supplementary Table S2. Residual associations, heteroscedasticity and testing the departure from a normal distribution

Measurement	Residual association slopes*						Heteroscedasticity slope*	Normal distribution		p-value for mean difference between sexes
	Weight	*Height*	*Age*	*BSA*	*LBM*	*BMI-for-age*		*p-value for departure from distribution*	*% of values outside Z = 2 or Z = −2*	
RV end-diastolic volume	<0.001	<0.001	<0.001	<0.001	<0.001	0.005	0.001	0.201	3.2	>0.999
RV end-systolic volume	<0.001	<0.001	<0.001	0.001	<0.001	<0.001	0.006	<0.001	4.4	>0.999
RV stroke volume	<0.001	<0.001	0.010	0.016	<0.001	<0.001	0.002	0.776	3.5	>0.999
RV ejection fraction	0.010*	0.004	0.039*	0.430*	0.013*	0.128*	<.001	0.002	3.5	>0.999
LV end-diastolic volume	<0.001	<0.001	<0.001	0.008	<0.001	0.008	0.003	0.078	4.6	>0.999
LV end-systolic volume	<0.001	<0.001	<0.001	0.001	<0.001	<0.001	0.004	0.004	3.1	>0.999
LV stroke volume	0.002	<0.001	<0.001	0.063	0.001	0.048	0.003	0.012	7.4	>0.999
LV ejection fraction	<0.001	<0.001*	<0.001	<0.001	<0.001	0.040	0.002	0.980	5.1	>0.999

* indicates slope with a p-value <.05

BMI: Body mass index. BSA: Body surface area. LBM: Lean body mass. LV: Left ventricle. RV: Right ventricle.

Table S3. Coefficients for Z score equations for males

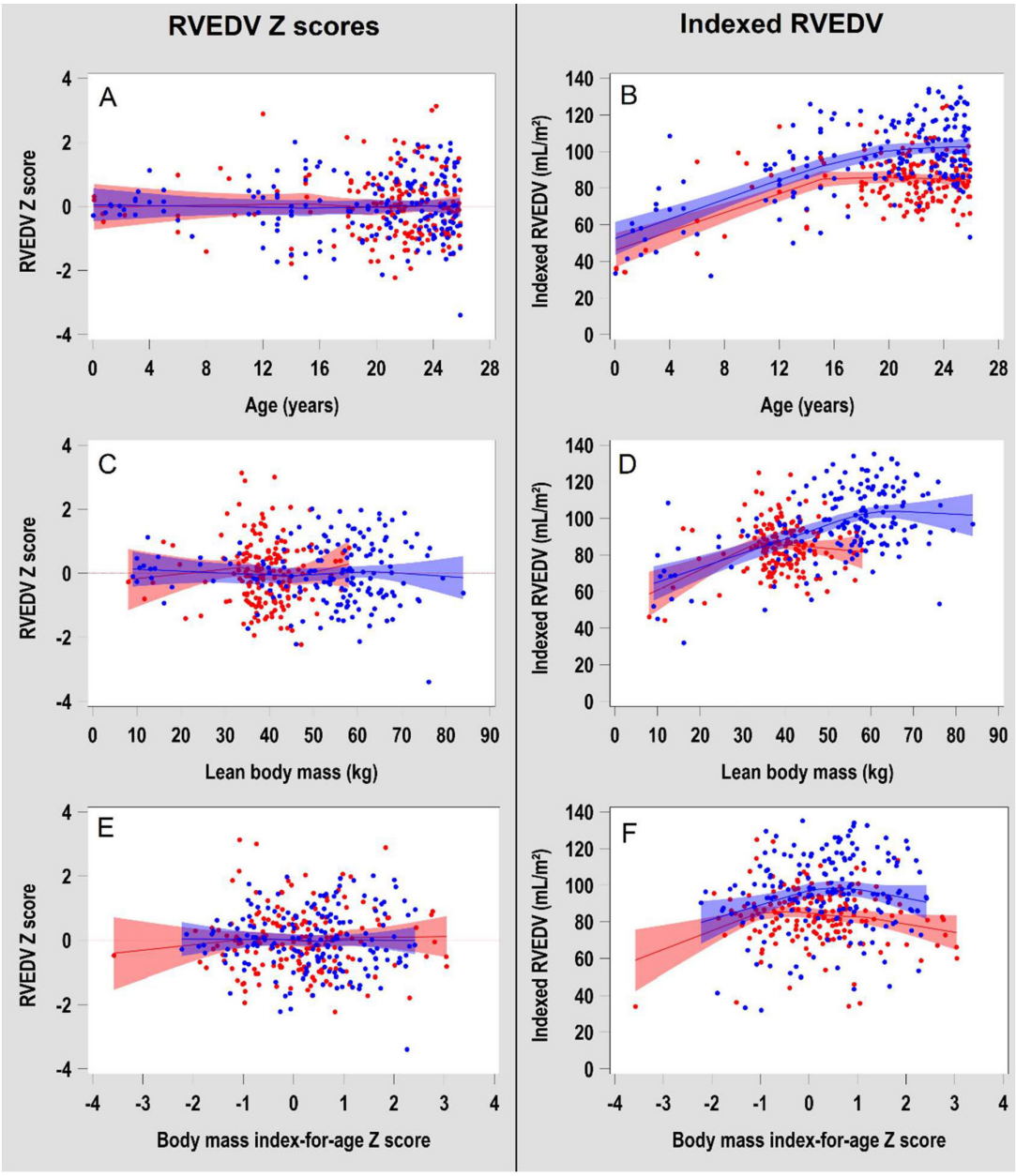
Measurement	Unit	N	Coefficients for predicted mean					Predicted standard deviation
			a	*b*	*c*	*d*	*e*	*f*
RV end-diastolic volume	mL	172	0.00337	-0.615	2.22	0.223	31.8	30.3
RV end-systolic volume	mL	172	0.00167	0.00385	0.627	-0.657	-5.66	17.8
RV stroke volume	mL	172	0.00142	-0.485	1.787	0	27.47	21.7
RV ejection fraction	%	172	0	0	0	0	58.1	7.6
LV end-diastolic volume	mL	177	0.00184	0.0558	1.79	-0.718	-6.41	23.1
LV end-systolic volume	mL	176	0.00103	0.0814	0.644	-0.874	-10.1	14.1
LV stroke volume	mL	176	0.000481	0.0190	1.250	0	1.468	14.4
LV ejection fraction	%	176	0	0	0	0	63.3	5.9

LV: Left ventricle. RV: Right ventricle. N: Number of subjects used to compute each equation.

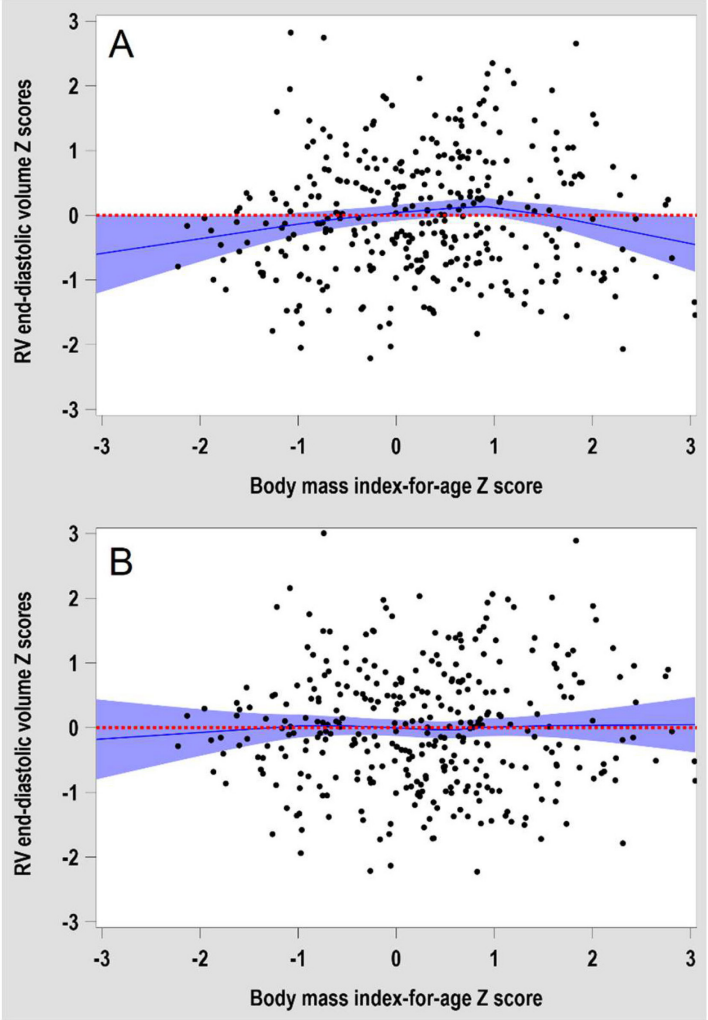
Table S4. Coefficients for Z score equations for females

Measurement	Unit	N	Coefficients for predicted mean					Predicted standard deviation
			a	*b*	*c*	*d*	*e*	*f*
RV end-diastolic	mL	170	0.00322	-0.00764	1.30	-0.578	-8.01	19.0
RV end-systolic volume	mL	168	0.00244	-0.0119	0.292	-0.867	-6.30	11.0
RV stroke volume	mL	168	0.000900	-0.00830	1.10	0	-2.00	15.2
RV ejection fraction	%	168	0	0	0	0	59.9	7.3
LV end-diastolic volume	mL	174	0.000989	0.506	1.17	-0.970	-28.5	13.2
LV end-systolic volume	mL	174	0.00164	0.0137	0.408	-0.888	-5.33	8.7
LV stroke volume	mL	174	-0.000843	0.477	0.852	0	-22.0	9.1
LV ejection fraction	%	174	0	0	0	0	64.8	5.4

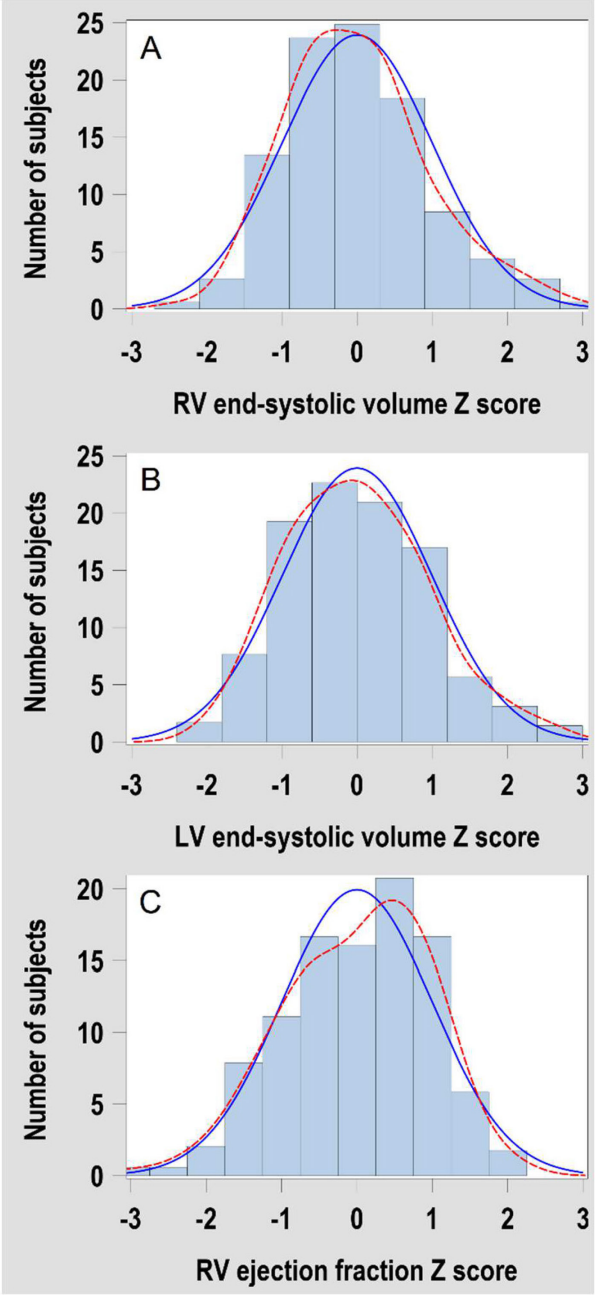
LV: Left ventricle. RV: Right ventricle. N: Number of subjects used to compute each equation.



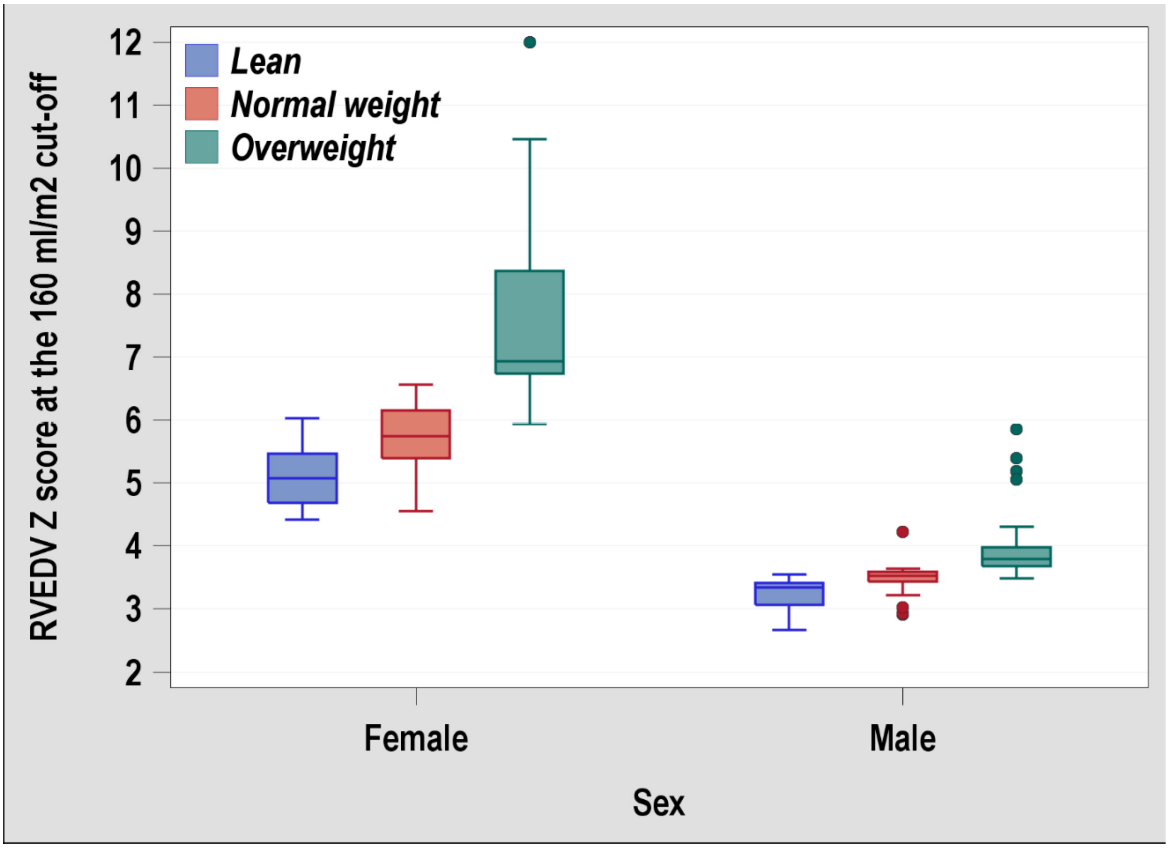
Supplementary Figure S1. Residual association of age (panels A and B), lean body mass (panels C and D), and body mass index-for-age Z score (panels E and F) with right ventricular end-diastolic volume (RVEDV) Z scores and RVEDV indexed to body surface area. Male and female subjects are represented in blue and red respectively. The solid line represents the smoothed regression curve (locally estimated scatterplot smoothing) and the shaded area is the 95% confidence margins of the predicted mean.



Supplementary Figure S2. Residual association of BMI-for-age with right ventricular end-diastolic volume (RVEDV) Z scores computed with unadjusted weight (panel A) and adjusted weight (panel B). The solid line represents the smoothed regression curve (locally estimated scatterplot smoothing) and the shaded area is the 95% confidence margins of the predicted mean.



Supplementary Figure S3. Distribution of right ventricle (RV) end-systolic volume Z scores (Panel A), left ventricle (LV) end-systolic volume Z score (Panel B), and RV ejection fraction Z scores (Panel C). The blue line represents the theoretical standard normal distribution (mean of 0 and standard division of 1) and the dotted red line represents the actual kernel density estimate.



Supplementary Figure S4. Box-plots of estimated right ventricular end-diastolic volume (RVEDV) Z scores at the 160 mL/m2 cut-off according to sex and body mass index categories. Lean: BMI-for-age Z score < −1.0. Normal weight: −1.0 ≤ BMI-for-age Z score ≤ 1.0. Overweight: BMI-for-age > 1.0.

Supplemental reference

1. Blanchard J, Blais S, Chetaille P, et al. New Reference Values for Cardiopulmonary Exercise Testing in Children. Med Sci Sports Exerc. 2018;50:1125-1133.