Left ventricular mass normalization in child and adolescent athletes must account for sex differences

Hubert Krysztofiak, Marcel Młyńczak, Łukasz A. Małeł, Andrzej Folga, Wojciech Braksator

1 Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland, 2 National Centre for Sports Medicine, Warsaw, Poland, 3 Faculty of Mechatronics, Institute of Metrology and Biomedical Engineering, Warsaw University of Technology, Warsaw, Poland, 4 Department of Epidemiology, Cardiovascular Disease Prevention and Health Promotion, National Institute of Cardiology, Warsaw, Poland, 5 Department of Sports Cardiology and Noninvasive Cardiovascular Imaging, 2nd Medical Faculty, Medical University of Warsaw, Warsaw, Poland

* hkrystofik@imdik.pan.pl

Abstract

Background
To assess left ventricular hypertrophy, actual left ventricular mass (LVM) normalized for body size has to be compared to the LVM normative data. However, only some published normative echocardiographic data have been produced separately for girls and boys; numerous normative data for the pediatric population are not sex-specific. Thus, this study aimed to assess whether the LVM normative data should be developed separately for girls and boys practicing sports.

Methods
Left ventricular mass was computed for 331 girls and 490 boys, 5–19 years old, based on echocardiography. The effect of sex on the relationship between LVM and body size was evaluated using a linear regression model. Seven sets of the LVM normative data were developed, using different methodologies, to test concordance between sex-specific and non-specific normative data. Every set consisted of normative data that was sex-specific and non-specific. Upon these normative data, for every study participant, seven pairs of LVM z-scores were calculated based on her/his actual LVM. Each pair consisted of z-scores computed based on sex-specific and non-specific normative data from the same set.

Results
The regression lines fitted to the data points corresponding to LVM of boys had a higher slope than of girls, indicating that sex affects the relationship between LVM and body size. The mean differences between the paired LVM z-scores differed significantly from 0. The percentage of discordant indications, depending on the normalization method, ranged from 66.7% to 100% in girls and from 35.4% to 50% in boys. Application of the LVM normative
data that were not sex-specific made relative LVM underestimated in girls and overestimated in boys.

**Conclusion**

The LVM normative data should be developed separately for girls and boys practicing sports. Application of normative data that are not sex-specific results in an underestimation of relative LVM in girls and overestimation in boys.

**Introduction**

Echocardiography is recommended as a first-line diagnostic tool for cardiac size evaluation in both children and adults [1–3]. Direct measurements of left ventricular muscle and chamber dimensions and further computation of left ventricular mass (LVM), provide the basis to diagnose hypertrophy [2,4].

In general, the presence of left ventricular hypertrophy (LVH) is associated with increased risk for adverse cardiovascular (CV) outcomes [5,6]. In turn, in athletes, LVH is recognized as an adaptive and physiological feature related to exercise [7–9]. Although exercise is considered as a strong counter-measure against cardiovascular disease (CVD) [10–13], athletes and physically active people are not CV disease-immune population. Sometimes in athletes, LVH has to be differentiated when there is suspicion or presence of such clinical problems as hypertrophic cardiomyopathy (HCM), hypertension, or valvular insufficiency or stenosis [3,14,15].

Since cardiac size depends on body size, the normalization for body size is necessary for better left ventricular (LV) assessment; the absolute values of LVM or other LV measures have to be normalized upon body size variable [2,16]. Such normalization is especially needed for children and adolescents because of continuous body size changes during development and the significant differences in body size, even between children of the same age [1].

To diagnose or manage LVH, actual LVM normalized for body size has to be compared to properly developed normative data. In our recent studies, we analyzed a problem of the correct body size variable for cardiac LVM normalization [17] and the issue of an accurate and convenient method for cardiac size scaling [18]. In previous studies, we developed normative data for children and adolescents practicing sport and compared them to the normative data generated for the general pediatric population [19,20]. When we were working on the topic of LVM normalization for body size, a question arose: should LVM normative data, or generally normative data of the LV dimensions, be sex-specific or not?

A review of articles published on this issue shows that this question is still open. In most of the works related to the pediatric population, the developed echocardiographic normative data are not sex-specific. Sometimes, there is no information on why they are developed in this way [21,22]. Sometimes, the authors evaluated the influence of sex on the result of the measurement and found no significant effect [23–25]. Some other times, the authors found a significant statistical effect but recognized it as not meaningful from a clinical perspective [26]. On the other side, there are important works where sex-specific LVM normative data were presented because researchers noted significant differences in relative LVM between boys and girls [27–30].

An interesting issue is a search for a body size variable for which the effect of sex on the relationship with LVM is not significant. Such a variable, used as an explanatory one, would enable generating normative data for the pooled population, without division on sex.
considered that lean body mass has such properties and that allometrically adjusted height might give the same result [31,32].

Thus, should LVM normative data be sex-specific or not? To provide a substantive basis for answering this question, we designed a study to explore the effect of sex on the relationship between LVM and body size variables used in cardiac size scaling and evaluate the concordance between sex-specific and non-specific LVM normative data developed according to different methods. The study aimed to assess whether, for reliable evaluation of LVM in children and adolescents, left ventricular mass normative data should be developed separately for girls and boys.

**Materials and methods**

**The study participants**

It was a retrospective study conducted as a continuation of our previous works on normative echocardiographic data of LVM for youth athletes and the methodology of LVM normalization upon body size. The medical data used in this study were collected between 2013 and 2018. The study participants were children and adolescents practicing sport, engaged in regular athletic training at the local or national level. Starting with the most popular sports, they had practiced: soccer, swimming, basketball, handball, fencing, rowing, tennis, dancing, distance running, speed skating, cycling, sailing, and martial sports like karate, taekwondo, judo, and wrestling. Since these were child and adolescent athletes, predominantly amateur, their training was focused mainly on general physical performance, building the aerobic capacity, and motor skills. They were examined during periodic preparticipation physical evaluation. The study group consisted of 331 girls and 490 boys (821 children and adolescents in total). Both girls and boys were aged from 5 to 19 years. All the participants were white. Echocardiography was ordered because of innocent heart murmurs or suspicion of abnormal electrocardiographic findings. However, the athletes in whom echocardiography revealed significant acquired or congenital heart diseases, affecting heart size and hemodynamics, were not included in the study. Height and body mass were measured during the main examination.

**Echocardiography**

Echocardiographic examinations were performed by experienced sonographers using a commercially available ultrasound scanner (Toshiba Aplio 400, Toshiba Medical Systems Europe, Zoetermeer, the Netherlands), according to recent guidelines. All measurements were taken in the 2-dimensional parasternal long-axis view (PLAX) at end-diastole and included the basic linear cardiac dimensions necessary for LVM computing: left ventricular internal dimension (LVIDd), interventricular septal thickness (IVSd), and posterior wall thickness (PWTd). All measurements were taken from the inner edge to inner edge and reported to within 1 mm. Left ventricular mass was computed according to the formula of Devereux et al. [4]:

\[
LVM = 0.8 \{1.04[(\text{LVIDd} + \text{PWTd} + \text{IVSd})^3 - (\text{LVIDd})^3]} + 0.6
\]

**Ethical considerations**

The Ethics Committee of the Medical University of Warsaw approved the study procedure (approval AKBE/75/17). As the study was retrospective, and the data used were collected during routine medical monitoring, neither written nor verbal consent was required for this particular study. However, each subject, or the subject’s parent or legal guardian, had signed the informed consent form for the routine medical monitoring, including a statement of agreement to the use of the results for scientific purposes.
Evaluation of the relationship between LVM and body size in girls and boys

We started with an evaluation of the effect of sex on the relationship between LVM and body size. For each selected body size parameter, we compared two regression lines representing this relationship for girls and boys, respectively. To perform distinct analyzes, we selected four body size variables: body mass, height, body surface area (BSA), and computed lean body mass (cLBM). Body surface area was calculated according to the Haycock formula [33], and cLBM was calculated based on equations introduced by Foster et al. [34].

At first, we inspected graphical presentations of these relationships. Separate scatter plots of LVM against each body size variable were drawn. On every scatter plot, both girls’ and boys’ data points were presented, and specific regression lines were fitted, respectively. To compare y-intercepts and slopes of the two regression lines, we constructed a linear regression model introducing a dummy variable representing sex. We coded girls as 0, and boys as 1. In our model, LVM was a dependent variable, and a body size parameter, the dummy variable, and the product of the body size parameter and the dummy variable were independent variables.

For combined groups of girls and boys, the model was expressed using the following equation:

\[ y = \beta_0 + \beta_1 x + \beta_2 z + \beta_3 x z \]

where \( y \) is LVM, \( x \) is body size variable, and \( z \) is the dummy variable. So, when \( z = 0 \), the regression is:

\[ y = \beta_0 + \beta_1 x \]

and for \( z = 1 \), it will be:

\[ y = (\beta_0 + \beta_2) + (\beta_3 + \beta_1) x \]

If the coefficient \( \beta_2 \) in the presented model is different from 0, it means that the y-intercepts of the sex-specific regression lines are different; there is a fixed difference in LVM between girls and boys, across the whole range of body size parameter’s magnitude. If the coefficient \( \beta_3 \) (interaction term) is significantly different from 0, it means that the slopes of the sex-specific regression lines are divergent; the difference in LVM between girls and boys is significant and varies for different values of the body size parameter.

Development of sex-specific and non-specific LVM normative data

In this part of the study, based on our study group, we developed seven sets of normative data of LVM. The sets were generated using different methodologies and body size parameters. For each set, normative data were generated first for a combined group of girls and boys, and next, separately for girls and boys. Thus, every set consisted of LVM normative data that were non-sex-specific and sex-specific. Then, using all these LVM normative data, for every study participant, seven pairs of LVM z-score values were calculated based on her/his actual LVM. Each pair consisted of LVM z-scores computed based on sex-specific normative data and LVM z-score calculated based on non-sex-specific normative data from the same set.

At first, three sets of LVM normative data, according to the LMS method [35], were developed with height, BSA, and cLBM, respectively, as explanatory variables. This procedure was applied previously by Foster et al. [29,36]. In the LMS method, based on the relationship between LVM and body size variable in the tested group, the expected mean LVM (M), coefficient of variation (S), and skewness (L) for each level of body size variable are generated. In our study, the corresponding L, M, and S values were developed first for the combined group, and then separately for girls and boys. For an individual child, the LVM z-scores were
calculated from the L, M, and S values corresponding to the child’s body size parameter’s magnitude, according to the equation:

\[ z\text{-score} = \frac{\left( \frac{\text{actual LVM}}{M} \right)^L - 1}{L \times S} \]

Then, two sets of LVM normative data were computed based on the commonly used LVM indices—the ratio of LVM to BSA and the ratio of LVM to height raised to the power of 2.7, respectively. In this method, normative data are developed as a mean and standard deviation of the LVM indices for the tested group. In our study, after calculating individual LVM index for every participating child and adolescent, the mean and standard deviation was computed first for the combined group, and next separately for girls and boys. The LVM z-scores are calculated, according to the equation:

\[ z\text{-score} = \frac{\text{actual LVM index} - \text{mean LVM index (normative data)}}{\text{standard deviation (normative data)}} \]

Next, one set was constructed based on the ratio of LVM to the allometrically adjusted BSA. The procedure proposed by Lopez et al. [26] was applied. Single allometric exponent specific for our combined study group—without division on sex was determined. The allometric equation was fitted for the bivariate relationship between LVM and BSA. This equation has the general form: \( LVM = a(BSA)^b \), where \( b \) is an allometric exponent. Logarithmic transformation gives the linearized form of this equation: \( \ln(LVM) = \ln(a) + b \ln(BSA) \), allowing estimation of the allometric coefficients using linear least squares regression modeling [37]. The procedure of LVM normative data preparation and calculation of individual z-scores was the same as for the commonly used LVM indices.

Finally, one set was developed based on the ratio of LVM to the allometrically adjusted height according to the method proposed in our previous study [18]. Based on the bivariate relationship between LVM and height, an allometric exponent for the combined group and then two distinct allometric exponents for girls and boys were determined respectively. Then, corresponding LVM indices were calculated, and normative data for the combined and sex-specific groups were obtained, respectively. The LVM normative data preparation and calculation of individual z-scores were made in the same way as for the ratio of LVM to the allometrically adjusted BSA and the commonly used LVM indices. Examples of LVM z-score calculations from the L, M, and S values corresponding to the body size parameter’s magnitude, and based on the mean and standard deviation of LVM indices, were presented in a supporting file in our previous article [18].

**Method for comparison of sex-specific and non-specific LVM normative data**

All the comparisons were made between LVM z-scores computed based on sex-specific normative data and LVM z-scores calculated based on non-sex-specific normative data from the same set. We started with graphical presentations of the computed LVM z-scores on scatter plots. For each set of data, the sex-specific z-scores were displayed against the non-specific ones. Besides, a line of equality was drawn on the graph as well as one horizontal line and one vertical line at LVM z-score equal to +1.65, indicating the limit for diagnosis of LV hypertrophy [18,38].

Then, we examined whether the mean differences between the paired z-scores differ from 0. To check whether the mean differences differ between girls and boys, we used the
independent two-sample t-test. We have deepened this analysis and constructed scatter plots of the differences between non-specific and sex-specific z-score against the averages of non-specific and sex-specific z-scores. The scatter plots were similar to Bland-Altman plots [39]. However, the data for girls and boys were separated on each scatter plot. On these plots, we drew two horizontal lines corresponding to the mean difference for girls and boys, respectively. We fitted regression lines to the sex-specific data and tested for significance of slopes to verify whether the differences are uniform. The statistically significant slope indicates that the differences are not uniform.

To test the concordance between the LVM z-scores, we used contingency tables. Assuming that the LVM z-score above +1.65 indicates LV hypertrophy, we examined the percentage of discordant LV hypertrophy indications.

Analyses were made using IBM SPSS Statistics 25 (PS IMAGO PRO, Predictive Solutions, Poland) and LMS Chartmaker Pro (Medical Research Council, United Kingdom). For all statistical tests, a significance level of \( \alpha = 0.05 \) was used.

### Results

#### The study participants’ characteristics

The characteristics of the study participants are presented in Table 1. It shows the group of girls, boys, and the combined group, respectively, that were used for the evaluation of the effect of sex on the relationship between LVM and body size as well as the normative data development.

|                         | Girls | Boys | Combined groups |
|-------------------------|-------|------|-----------------|
| \( n \)                 | 331   | 490  | 821             |
| Age [years]             | 12.0 (5.0) | 13.0 (5.0) | 12.0 (5.0) |
| Height [cm]             | 153.0 (23.0) | 163 (34.0)  | 158.0 (85.0) |
| Body mass [kg]          | 41.8 (20.4) | 50.25 (30.8) | 46.3 27.2 |
| BSA [m\(^2\)]           | 1.33 (0.41) | 1.51 (0.61)  | 1.41 (0.56) |
| cLBM [kg]               | 29.78 (13.25) | 38.41 (23.87) | 33.10 (20.38) |
| LVM [g]                 | 103.98 (44.01) | 126.42 (80.36) | 113.27 (62.57) |
| LVIDd [mm]              | 42.0 (6.0) | 46.0 (9.0) | 44.0 (8.0) |
| IVSd [mm]               | 8.0 (1.0) | 8.0 (2.0) | 8.0 (2.0) |
| PWTd [mm]               | 7.0 (1.0) | 8.0 (2.0) | 8.0 (2.0) |
| RWT                     | 0.35 (0.05) | 0.36 (0.06) | 0.36 (0.06) |
| RHR [beats/min]         | 75 (15) | 68 (15) | 71 (16) |
| SBP [mm/Hg]             | 111 (19) | 116 (17) | 114 (18) |
| DBP [mm/Hg]             | 64 (12) | 65 (10) | 64 (11) |
| Training [min]          | 240 (180) | 270 (180) | 270 (180) |

Data are expressed as “median (interquartile range)”; BSA, body surface area according to the Haycock formula [33]; cLBM, lean body mass computed according to Foster et al. equations [34]; LVM, left ventricular mass; LVIDd, left ventricular internal dimension; IVSd, interventricular septal thickness; PWTd, posterior wall thickness; RWT, relative wall thickness calculated as \( RWT = 2 \times PWTd / LVIDd \) [2]; Training stands for the weekly volume of training. It is a measure of participation in sports activity and was estimated as the product of the average number of training sessions per week and the average duration of a single session; RHR, resting heart rate; SBP and DBP, systolic, and diastolic blood pressure, respectively.

https://doi.org/10.1371/journal.pone.0236632.t001
Effect of sex on the relationship between LVM and body size

The scatter plots of LVM against height, BSA, cLBM, and body mass, respectively, with sex-specific regression lines fitted to data points representing LVM of girls and boys, are shown in Fig 1. The slopes of the regression lines fitted to the data points corresponding to LVM of girls are different from the slopes of the regression lines for boys. For all the body size variables, the lines for boys have a higher slope than for girls, suggesting that sex affects the relationship between LVM and body size.

Table 2 presents the coefficients estimated upon the regression model that had been constructed to compare the y-intercepts and slopes of the regression lines. For all the analyzed relationships of LVM against body mass variable, the coefficient \( \beta_3 \) is significantly different from 0. Then, the slopes of the sex-specific regression lines are divergent, and this indicates that the difference in LVM between girls and boys is significant and varies with the body size parameter’s magnitude.

The coefficient \( \beta_2 \) in the presented model is significantly different from 0 for all body size parameters except cLBM. Thus, only for cLBM, the y-intercepts of the sex-specific regression lines are not different. However, this effect is redundant in the presence of significant \( \beta_3 \).

The sex-specific and non-specific LVM normative data

Three sets of LVM normative data, generated using the LMS method, are presented as the L, M, and S values corresponding to each level of height, BSA, and cLBM, respectively, in (S1, S2, and S3 Datasets, respectively). The means and standard deviations, presented in Table 3, are LVM normative data that were produced based on the LVM indices. The individual LVM z-scores for subsequent comparison were computed upon the L, M, and S values, as well as the means and standard deviations. Table 3 also shows the exponents that were used in the allometrically adjusted indices. These include exponents, which were estimated upon our data to adjust BSA and height.

Comparison of sex-specific and non-specific LVM normative data

The scatter plots with the sex-specific LVM z-scores against the non-specific are presented in Figs 2 and 3. Fig 2 contains the z-scores calculated from the normative data generated using the LMS method. In Fig 3 the z-scores calculated on normative data based on LVM indices are shown.

In all the scatter plots, presenting LVM z-scores computed on seven different methods of LVM normalization, the data points of girls are separated from the points of boys. Both the points of girls and boys deviate from the equality line. The setting of the regression lines fitted to the respective data points helps to see this clearly. It suggests that the sex-specific LVM z-scores differ from the non-specific. The dependent t-test for paired samples confirms it. For all the pairs, the mean differences between the paired LVM z-scores significantly differ from 0. The results of the analysis are presented in Table 4.

The mean differences between the paired LVM z-scores in girls are negative, and boys are positive. The independent two-sample t-test has verified that they differ between girls and boys (S1 Table). But what is essential, it shows that non-specific normative data underestimate relative LVM in girls and overestimate it in boys. Besides, the setting of the regression lines in scatter plots in Figs 2 and 3 suggests that the differences increase with the increase of the z-score. It has been confirmed by significant slopes of another regression lines that were fitted separately for girls and boys to the differences between non-specific and sex-specific z-scores relative to the averages of non-specific and sex-specific z-scores (S2 Table). S1 and S2 Figs contain the scatter plots displaying these regression lines, as well as two horizontal lines corresponding to the mean difference for girls and boys, respectively.
The horizontal and vertical lines on the scatter plots in Figs 2 and 3 at LVM z-score equal to +1.65, mark the limit for diagnosis of LV hypertrophy and allow seeing discordant LV hypertrophy indications. In all the scatter plots, the picture is the same—application of the LVM
normative data that are not sex-specific underestimates relative LVM in girls and overestimates in boys.

We used contingency tables to analyze the concordance, and assuming that the LVM z-score above +1.65 indicates LV hypertrophy, we examined the percentage of discordant LV hypertrophy indications. The results of this analysis are presented in Table 5, and they confirm the picture from the scatter plots in Figs 2 and 3. The percentage of discordant indications, depending on the normalization method, ranges from 66.7% to 100% in girls and from 35.4% to 50% in boys.

**Discussion**

The most important result of our study is a demonstration that normative data of left ventricular mass should be developed separately for girls and boys. Application of normative data that

For the combined groups of girls and boys, the regression model has a form of the following equation: \( y = \beta_0 + \beta_1 x + \beta_2 z + \beta_3 xz \), where \( y \) is LVM, \( x \) is body size variable, and \( z \) is the dummy variable representing sex.

**Table 2. Coefficients estimated in the applied regression model.**

| LVM vs. | \( \beta_0 \) | \( \beta_1 \) | \( \beta_2 \) | \( \beta_3 \) |
|---------|--------------|--------------|--------------|--------------|
| Height  | -145.8641    | 1.6473       | -62.9753     | 0.5205       |
| p value | <0.0001      | <0.0001      | <0.0001      | <0.0001      |
| BSA     | -17.7802     | 91.1975      | -27.8703     | 31.5822      |
| p value | 0.0025       | <0.0001      | = 0.0001     | <0.0001      |
| cLBM    | 17.2105      | 2.8826       | -4.9287      | 0.3549       |
| p value | <0.0001      | <0.0001      | 0.3186       | = 0.0152     |
| Body mass | 26.1783   | 1.8052       | -11.4169     | 0.5877       |
| p value | <0.0001      | <0.0001      | = 0.0190     | <0.0001      |

Table 3. The LVM normative data computed based on LVM indices.

| Groups   | Allometric exponent | LVM index         |
|----------|---------------------|-------------------|
| Girls    |                     |                   |
| LMV indexed to BSA | N/A               | 77.4121 (11.1118) |
| LMV indexed to height \( b^2 \) | 2.7               | 33.2248 (5.0743)  |
| LMV indexed to BSA \( b \) | 1.3100          | 71.0274 (10.0675) |
| LMV indexed to height \( b^2 \) | 2.4340         | 37.1008 (5.5716)  |
| Boys     |                     |                   |
| LMV indexed to BSA | N/A               | 90.0531 (17.3508) |
| LMV indexed to height \( b^2 \) | 2.7               | 37.6220 (7.2802)  |
| LMV indexed to BSA \( b \) | 1.3100          | 80.2761 (13.8976) |
| LMV indexed to height \( b^2 \) | 2.5776         | 39.7813 (7.6853)  |
| Combined groups |                     |                   |
| LMV indexed to BSA | N/A               | 84.9567 (16.3620) |
| LMV indexed to height \( b^2 \) | 2.7               | 35.8492 (6.8284)  |
| LMV indexed to BSA \( b \) | 1.3100          | 76.5473 (13.2882) |
| LMV indexed to height \( b^2 \) | 2.6217         | 37.1058 (7.6667)  |

The LVM normative data are expressed as “mean (standard deviation).” For BSA \( b \), the BSA is raised to the power of \( b \), where \( b \) is equal to the allometric exponent estimated for the combined group; for height \( b^2 \), the height is raised to the power of \( b^2 \), where \( b^2 \) is equal to the allometric exponent that is group-specific—estimated separately for the combined group, for girls, and boys, respectively.

https://doi.org/10.1371/journal.pone.0236632.t003
Fig 2. Scatter plots of the LVM z-scores calculated from the normative data generated using the LMS method. The sex-specific z-scores are displayed against the non-specific. The data points corresponding to girls are red, and to boys are blue. Regression lines are fitted to the sex-specific data—the solid red line to girls and the solid blue line to boys, respectively. The line of equality (solid black line) is drawn on each graph, as well as one horizontal line (dotted line) and one vertical line (dashed line) at LVM z-score equal to +1.65, indicating the limit for diagnosis of LV hypertrophy. BSA, body surface area according to the Haycock formula [33]; cLBM, lean body mass computed according to Foster’s at al. equations [34].

https://doi.org/10.1371/journal.pone.0236632.g002
are generated on the combined group of girls and boys results in an underestimation of relative LVM in girls and overestimation in boys. From the clinical perspective, this increases the frequency of LV hypertrophy diagnosis in boys, but in girls, it may cause that LV hypertrophy is
unrecognized. This finding is consistent with the result of the evaluation of the relationship between LVM and body size we have made. The course of changes of LVM relative to body size during development is different in girls and boys. The regression line for the relationship

Table 4. The differences between non-specific and sex-specific LVM z-scores.

|          | Mean difference | p-value |
|----------|-----------------|---------|
| Girls   |                 |         |
| LVM for Height (LMS) | -0.3218 (0.2184) | p<0.0001|
| LVM for BSA (LMS) | -0.3725 (0.2653) | p<0.0001|
| LVM for cLBMI (LMS) | -0.1670 (0.1608) | p<0.0001|
| LMV indexed to BSA | -0.4611 (0.3209) | p<0.0001|
| LMV indexed to height^{2.7} | -0.3843 (0.2569) | p<0.0001|
| LMV indexed to BSA^{b} | -0.4154 (0.2438) | p<0.0001|
| LMV indexed to height^{bs} | -0.3943 (0.2858) | p<0.0001|
| Boys    |                 |         |
| LVM for Height (LMS) | 0.2171 (0.0956) | p<0.0001|
| LVM for BSA (LMS) | 0.2507 (0.0622) | p<0.0001|
| LVM for cLBMI (LMS) | 0.1118 (0.0845) | p<0.0001|
| LMV indexed to BSA | 0.3115 (0.0604) | p<0.0001|
| LMV indexed to height^{2.7} | 0.2596 (0.0662) | p<0.0001|
| LMV indexed to BSA^{b} | 0.2806 (0.0459) | p<0.0001|
| LMV indexed to height^{bs} | 0.2664 (0.0730) | p<0.0001|

The data are expressed as “mean difference (standard deviation).” LMS in brackets means that these LVM normative data were produced using the LMS method. For BSA^{b}, the BSA is raised to the power of b, where b is equal to the allometric exponent estimated for the combined group; for height^{bs}, the height is raised to the power of bs, where bs is equal to the allometric exponent that is group-specific—estimated separately for the combined group, for girls, and boys, respectively.

https://doi.org/10.1371/journal.pone.0236632.t004

The subjects were classified as having LVH when their LVM z-score > +1.65. Confidence intervals (CI) for the proportions are Clopper-Pearson exact confidence intervals. The designations of LVM normalization methods are the same as in Table 4.

Table 5. The number of indications of LV hypertrophy based on sex-specific and non-specific LVM normative data.

|          | Sex-specific normative data | Non-specific normative data | Percent of discordant indications (95% CI) |
|----------|-----------------------------|-----------------------------|-------------------------------------------|
| Girls    |                             |                             |                                           |
| LVM for Height (LMS) | 15                          | 5                           | 66.7% (38.3–88.2%)                        |
| LVM for BSA (LMS) | 19                          | 1                           | 94.7% (73.9–99.9%)                        |
| LVM for cLBMI (LMS) | 21                          | 5                           | 76.2% (52.8–91.8%)                        |
| LMV indexed to BSA | 20                          | 0                           | 100% (83.2–100%)                         |
| LMV indexed to height^{2.7} | 16                          | 2                           | 87.5% (61.6–98.5%)                        |
| LMV indexed to BSA^{b} | 19                          | 2                           | 89.5% (66.9–98.7%)                        |
| LMV indexed to height^{bs} | 15                          | 2                           | 86.7% (59.5–98.3%)                        |
| Boys     |                             |                             |                                           |
| LVM for Height (LMS) | 20                          | 31                          | 35.4% (19.2–54.6%)                        |
| LVM for BSA (LMS) | 19                          | 33                          | 42.4% (25.3–60.8%)                        |
| LVM for cLBMI (LMS) | 18                          | 28                          | 35.7% (18.5–55.9%)                        |
| LMV indexed to BSA | 29                          | 50                          | 42.0% (28.2–56.8%)                        |
| LMV indexed to height^{2.7} | 22                          | 42                          | 47.6% (32.0–63.6%)                        |
| LMV indexed to BSA^{b} | 26                          | 50                          | 48.0% (33.7–62.6%)                        |
| LMV indexed to height^{bs} | 22                          | 44                          | 50.0% (34.6–65.4%)                        |

https://doi.org/10.1371/journal.pone.0236632.t005
between LVM and body size is steeper in boys comparing to girls. It means that for a given body size LVM in boys is higher than in girls.

Such an analysis of the relationship between LVM and body size has been made previously by others [27,28,30,40–43], and it seems, that there is an agreement that when considering the relationship between LVM and the elementary body size parameters, like body mass and height, the courses of changes of LVM in relation to these parameters are different in girls and boys. The difference becomes evident at puberty, and after puberty, boys definitively have higher LVM comparing to girls [42]. Adult men have higher unindexed LVM than women [44]. In athletes, both adolescents and adults, the pattern is the same—male athletes have higher LVM comparing to female athletes [14,15,45].

According to some researchers, there is no difference between boys and girls in the course of changes of LVM against LBM. They argue that since lean body mass (or fat-free mass, FFM) is the strongest determinant of LVM, the sex-related differences in LVM can be explained by the differences in LBM between boys and girls [41,46]. Similar suggestions were made for adult males and females, including athletes [44,47].

Recognizing LBM as a pivotal physiological determinant of LVM made this body size parameter potentially optimal for cardiac size scaling [29,32,46]. Since LBM cannot be measured directly, advanced indirect methods such as double X-ray absorptiometry, computed tomography, magnetic resonance imaging, or bioelectrical impedance analysis are required for reliable measurements. These measurements are not routinely available in the cardiac imaging laboratory, so researchers seek a surrogate parameter for LBM by allometrically transforming height, for example [32,42,48]. The most often used is the height raised to the power of 2.7 [48]. For LVM normalization, the LBM or FFA predictive equations, based on the elementary body size variables and their derivatives, are also proposed [34,46].

In our study, we evaluated not only the relationship between LVM and body mass, height, and BSA but also between LVM and LBM computed based on the predictive equations introduced by Foster et al. [34]. For all the four body size parameters, including the computed LBM, there was a significant difference between the slopes of the lines fitted to the LVM data points of girls and boys, respectively.

Daniels et al. [32] and de Simone et al. [42] claimed that after proper normalization, the relationship between the normalized LVM and body size is not statistically significant, and normative data can be produced without division on sex. Yet the results of our study show that if we want to avoid errors when diagnosing LV hypertrophy, we should use sex-specific normative data. It is consistent with the indication of Pela et al. [43], who recommend sex-specific normative data in the cardiovascular screening of adolescent athletes.

There are studies where the sex-specific LVM normative data for the pediatric population were developed because the authors noted a significant difference in relative LVM between boys and girls [27–30]. However, in many others, the LVM normative data were constructed without division on sex. Pettersen et al. [21] produced echocardiographic normative data for the combined group of girls and boys and made no statements on why they did not take into account the potential sex differences. Similarly did Kampmann et al. [22]. In other studies, the authors evaluated the influence of sex on the result of the measurement and found no significant effect [23–25]. Lopez et al. [26] found a significant statistical impact but recognized it as not significant from a clinical perspective. They argued that the differences between R² in the regression models with sex and R² in the models without sex were small, and comparisons of echocardiographic dimensions that were predicted based on these models, exercised on two hypothetical boys, had shown small differences between the models.

Therefore, in the crucial part of our study, we developed normative data using different methods and different body size parameters as explanatory variables. We developed sets
containing pairs of sex-specific and non-specific LVM normative data and compared them mutually within the sets. The results of that comparison confirmed this intuitive indication that emerged after the analysis of the relationship between LVM and the body size parameters: If we want to avoid errors when diagnosing LV hypertrophy, we should use sex-specific normative data, regardless of the body size parameter used as the explanatory variable. Examples of LVM z-scores calculations are presented in the (S1 Text). They picture the overestimation of relative LVM in boys and underestimation in girls when the LVM normative data that are not sex-specific are used.

The clinical perspective seems to be particularly important here because, as we have shown, choosing LVM normative data that are not sex-specific can result in LVH not being identified in an adolescent girl who practices sport. Consequently, the etiology of hypertrophy will not be differentiated and proper medical management, required in case of diagnosed cardiac pathology, not introduced. This approach increases cardiac risk in girls participating in sport. In turn, relying on non-specific normative data in medical evaluation of boy practicing sports can lead to a false-positive diagnosis of LVH. Unnecessary measures are then introduced, such as exclusion from sport and unjustified additional clinical tests that can cause anxiety in the boy and his family.

In everyday clinical practice, only LV wall thickness measurements are often used to identify and monitor LV hypertrophy. Still, it should be noted that the sensitivity, specificity, and prognostic accuracy of LV mass in detecting LV hypertrophy are higher than when measuring only LV wall thickness [4,49]. However, left ventricular mass should be appropriately normalized for body size. It is particularly important in children and adolescents, because of high variability in height and body mass, even among similar aged children.

The study participants were child and adolescent athletes. The athletic population may be considered special because regular exercise contributes to an increase in cardiac size [15], and specific LVM normative data are recommended for child and adolescent athletes [20]. A question may thus arise as to whether the results of the study should be applied to all children and adolescents.

The increase in cardiac size in response to exercise is an adaptive phenomenon linked to the improvement of exercise capacity. Not only athletes but generally all healthy children, both boys, and girls, have higher LVM when their exercise capacity is higher [50]. However, boys have higher exercise capacity than girls of the same age, and this is true for both athletic and non-athletic populations [51]. Perhaps in the youngest, the difference is not seen, but after the age of about twelve, it becomes significant [52]. The same pattern is observed in the case of LVM. Before puberty, LVM in healthy boys and girls is similar, and at puberty, the difference between boys and girls becomes evident, with higher LVM in boys [53].

Thus, higher exercise capacity is associated with higher LVM, and within comparable groups of healthy children, especially adolescents, boys have higher exercise capacity and LVM than girls. That is not solely specific to athletes. Normative data for LVM should be developed separately for boys and girls for all children and adolescents, regardless of whether they practice sports or not.

**Study limitations**

Our study has limitations. Since the study was retrospective, based on historical medical records that had been collected since 2013, the intraobserver and interobserver variability for echocardiographic measurements were not analyzed. However, all these echocardiographic measurements were performed by two experienced cardiologists in one medical center.
The same groups of girls and boys were used for LVM normative data development and further comparison, and it can be considered a limitation. It might seem that comparing LVM z-scores in a group that was previously used to produce LVM normative data, upon which the z-scores were then calculated, introduces bias by reducing variability. However, if it was true, it would decrease the differences between the paired z-scores and improved concordance. The procedure is statistically valid, and the comparison made in the same group rather strengthens the significance of the results.

We used an ethnically homogenous group of child and adolescent athletes from 5 to 19 years of age for this analysis. It might be argued that such group characteristics limit the possibility of generalization. We do not question the necessity of further research to confirm the results in younger children, adults, and subjects from different ethnic groups. Yet still, we are sure that the results are reliable, good in quality, and useful.

Our analysis did not take into account other factors than body size and sex, which potentially influence LVM, like blood pressure, heart rate, or fat mass. However, the participants of the study were all healthy child and adolescent athletes, under regular medical monitoring. Thus, all pathological factors were excluded, and blood pressure and heart rate were in the physiological range. In such a situation, their influence on LVM is minimal, although statistically significant [30]. It does not interfere significantly with the effect of body size and sex on LVM.

The children and adolescents whose echocardiographic data were used in this study were athletes. As the training volume and intensity have to be adapted to the athlete exercise capacity, we cannot exclude that the different intensity of training in girls and boys additionally contributed to the fact that for a given body size, LVM in boys was higher than in girls. It may raise a concern about the application of the results to all pediatric populations. Although we agree that the specificity of the population examined in this study may have influenced the results, we are convinced that athletic training might only amplify the already existing differences in LVM between boys and girls. Therefore, for all pediatric populations, one should use LVM normative data that were developed separately for girls and boys.

It should be noted that although it was not the purpose of the study to present normative data of LVM for youth athletes, we have performed controlling procedure for all the developed LVM normative data. The effectiveness of the normalization procedures was tested in terms of whether body size information was eliminated in the generated normative data. Relationships between the calculated LVM z-scores and the corresponding body size variables were analyzed. The Pearson correlation coefficient and the slope of the linear regression line were examined [37].

The LVM normative data produced based on a simple index of LVM to BSA do not meet the statistical criteria for effective normalization. The presence of the relationship between LVM z-scores and BSA has been confirmed for both sex-specific and non-specific normative data. The Pearson correlation coefficients and the slopes of the linear regression lines are statistically significant. These coefficients are also significant for LVM indexed to height raised to the power of 2.7 and LVM indexed to allometrically adjusted BSA, for sex-specific normative data of girls.

It is consistent with the results of our previous studies [17,18], and the presence of a significant relationship between LVM indexed to height raised to the power of 2.7 and height in girls additionally confirms the results of the current work.

The Pearson correlation coefficients and the slopes of the linear regression lines, which were examined to test whether body size information was eliminated in the generated normative data, are presented in S3 Table.
Conclusions

The study was designed to explore the effect of sex on the relationship between LVM and body size variables used in the normalization of cardiac size and to test concordance between sex-specific and non-specific LVM normative data developed according to different methods. The primary purpose of the study was to answer the question of whether LVM normative data should be sex-specific. The study showed that in child and adolescent athletes from 5 to 19 years of age, the course of changes of LVM relative to body size during development is different in girls and boys and that for a given body size LVM in boys is higher than in girls. Application of normative data that are not sex-specific results in an underestimation of relative LVM in girls and overestimation in boys. From the clinical perspective, this increases the frequency of LV hypertrophy diagnosis in boys, but in girls, it may cause that LV hypertrophy is unrecognized. Therefore, if we want to avoid errors when diagnosing left ventricular hypertrophy in children and adolescents, we should use normative data for left ventricular mass that were developed separately for girls and boys, regardless of the body size parameter used as the explanatory variable.

Supporting information

S1 Dataset. The sets of the L, M, and S values corresponding to each level of height. (TXT)

S2 Dataset. The sets of the L, M, and S values corresponding to each level of BSA. (TXT)

S3 Dataset. The sets of the L, M, and S values corresponding to each level of cLBM. (TXT)

S4 Dataset. The original dataset. (TXT)

S1 Table. The mean differences between the paired non-specific and sex-specific z-scores in girls and boys. (DOCX)

S2 Table. Pearson correlation coefficients and the slopes of the regression lines for relationships between the differences between non-specific and sex-specific z-score and the averages of non-specific and sex-specific z-scores. (DOCX)

S3 Table. Pearson correlation coefficients and the slopes of the regression lines for relationships between the LVM z-scores and the corresponding body size variables. (DOCX)

S1 Fig. Scatter plots of the differences between non-specific and sex-specific z-scores relative to the averages of non-specific and sex-specific z-scores for the z-scores calculated from the normative data generated using the LMS method. The data points corresponding to girls are red, and to boys are blue. Regression lines are fitted to the data points—the solid red line to girls and the solid blue line to boys. Two horizontal lines corresponding to the mean difference for girls (dashed red line) and boys (dashed blue line) are drawn as well. BSA, body surface area according to Haycock formula [33]; cLBM, lean body mass computed according to Foster’s at al. equations [34]. (TIF)
S2 Fig. Scatter plots of the differences between non-specific and sex-specific z-scores relative to the averages of non-specific and sex-specific z-scores calculated upon the normative data based on LVM indices. The design of the scatter plots is the same as for S1 Fig. 

(TIF)

S1 Text. Examples of LVM z-score calculations. They picture the overestimation of relative LVM in boys and underestimation in girls when the LVM normative data that are not sex-specific are used.

(DOCX)

Author Contributions

Conceptualization: Hubert Krysztofiak.

Data curation: Hubert Krysztofiak, Marcel Młyńczak, Andrzej Folga, Wojciech Braksator.

Formal analysis: Hubert Krysztofiak, Marcel Młyńczak.

Funding acquisition: Hubert Krysztofiak.

Investigation: Hubert Krysztofiak, Łukasz A. Małek, Andrzej Folga, Wojciech Braksator.

Methodology: Hubert Krysztofiak, Marcel Młyńczak, Łukasz A. Małek.

Project administration: Hubert Krysztofiak.

Resources: Hubert Krysztofiak.

Software: Hubert Krysztofiak.

Supervision: Hubert Krysztofiak.

Validation: Hubert Krysztofiak.

Visualization: Hubert Krysztofiak.

Writing – original draft: Hubert Krysztofiak.

Writing – review & editing: Hubert Krysztofiak, Marcel Młyńczak, Łukasz A. Małek, Andrzej Folga, Wojciech Braksator.

References

1. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, et al. Recommendations for Quantification Methods During the Performance of a Pediatric Echocardiogram: A Report From the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr 2010; 23: 465–495. https://doi.org/10.1016/j.echo.2010.03.019 PMID: 20451803

2. Lang RM, Badano LP, Mor-Avi V, Afifalo J, Armstrong A, Erande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015; 28: 1–39.e14. https://doi.org/10.1016/j.echo.2014.10.003 PMID: 25559473

3. Pelliccia A, Caselli S, Sharma S, Basso C, Bax JJ, Corrado D, et al. European Association of Preventive Cardiology (EAPC) and European Association of Cardiovascular Imaging (EACVI) joint position statement: recommendations for the indication and interpretation of cardiovascular imaging in the evaluation of the athlete’s heart. Eur Heart J 2018; 39:1949–1969. https://doi.org/10.1093/eurheartj/ehx532 PMID: 29029207

4. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings. Am J Cardiol 1986; 57: 450–458. https://doi.org/10.1016/0002-9149(86)90771-x PMID: 2936235
5. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990; 322:1561–1566. https://doi.org/10.1056/NEJM199005313222203 PMID: 2139921

6. Haider AW, Larson MG, Benjamin EJ, Levy D. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. J Am Coll Cardiol. 1998; 32(5):1454–1459. https://doi.org/10.1016/s0735-1097(98)00407-0 PMID: 980962.

7. George K, Whyte GP, Green DJ, Oxborough D, Gaze D, et al. The endurance athletes heart: acute stress and chronic adaptation. Br J Sports Med. 2012 Nov; 46 Suppl 1:i29–36. https://doi.org/10.1136/bjsports-2012-091141 PMID: 23097476.

8. Rowland T. Morphologic Features of the "Athlete’s Heart" in Children: A Contemporary Review. Pediatr Exerc Sci. 2016 Aug; 28(3):345–52. https://doi.org/10.1123/pe.2015-0239 Epub 2015 Dec 16. PMID: 26694944.

9. Barczuk-Falęcka M, Malek LA, Krysztiofiak H, Roik D, Brzewski M. Cardiac magnetic resonance assessment of the structural and functional cardiac adaptations to prolonged soccer training in school-aged male children. Pediatr Cardiol 2018; 39:948–954. https://doi.org/10.1007/s00246-018-1844-5 PMID: 29520462.

10. Sesso HD, Paffenbarger RS Jr, Lee IM. Physical activity and coronary heart disease in men: The Harvard Alumni Health Study. Circulation. 2000 Aug 29; 102(9):975–80. https://doi.org/10.1161/01.cir.102.9.975 PMID: 10961960.

11. Leon AS, Myers MJ, Connett J. Leisure time physical activity and the 16-year risks of mortality from coronary heart disease and all-causes in the Multiple Risk Factor Intervention Trial (MRFIT). Int J Sports Med. 1997 Jul;18 Suppl 3:S208–15. https://doi.org/10.1055/s-2007-972717 PMID: 9272851.

12. Manson JE, Hu FB, Colditz GA, Stampfer MJ, Willett WC, et al. A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women. N Engl J Med. 1999 Aug 26; 341(9):650–8. https://doi.org/10.1056/NEJM199908263410904 PMID: 1056/NEJM 19910131324 0504 PMID: 1824720

13. Sattelmair J, Pertman J, Ding EL, Kohl HW 3rd, Haskell W, Lee IM. Dose-response between physical activity and risk of coronary heart disease: a meta-analysis. Circulation. 2011 Aug 16; 124(7):789–95. https://doi.org/10.1161/CIRCULATIONAHA.110.010710 Epub 2011 Aug 1. PMID: 21810663.

14. Pelliccia A, Maron BJ, Spataro A, Proschan MA, Spriolo P. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. N Engl J Med. 1991 Jan 31; 324(5):295–301. https://doi.org/10.1056/NEJM19910131324 0504 PMID: 9809962.

15. Sharma S, Maron BJ, Whyte G, Firoozi S, Elliott PM, McKenna WJ. Physiologic limits of left ventricular hypertrophy in elite junior athletes: relevance to differential diagnosis of athlete’s heart and hypertrophic cardiomyopathy. J Am Coll Cardiol 2002; 40: 1431–6. https://doi.org/10.1016/s0735-1097(02)02270-2 PMID: 12392833.

16. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013; 34: 2159–2219. https://doi.org/10.1093/eurheartj/eht151 PMID: 23771844.

17. Krysztiofiak H, Młyniczak M, Malek LA, Folga A, Braksator W. Left ventricular mass is underestimated in overweight children because of incorrect body size variable chosen for normalization. PLoS ONE 2019; 14(5): e0217637. https://doi.org/10.1371/journal.pone.0217637 PMID: 3141818

18. Krysztiofiak H, Malek LA, Młyniczak M, Folga A, Braksator W. Left ventricular mass normalization for body size in children based on an allometrically adjusted ratio is as accurate as normalization based on the centile curves method. PLoS One. 2019 Nov 21; 14(11):e0225287. https://doi.org/10.1371/journal.pone.0225287 PMID: 31751386.

19. Krysztiofiak H, Malek LA, Młyniczak M, Folga A, Braksator W. Comparison of echocardiographic linear dimensions for male and female child and adolescent athletes with published pediatric normative data. PLoS One. 2018 Oct 11; 13(10):e0205459. https://doi.org/10.1371/journal.pone.0205459 PMID: 30308023.

20. Krysztiofiak H, Młyniczak M, Folga A, Braksator W, Malek LA. Normal Values for Left Ventricular Mass in Relation to Lean Body Mass in Child and Adolescent Athletes. Pediatr Cardiol. 2019 Jan; 40(1):204–208. https://doi.org/10.1007/s00246-018-1982-9 Epub 2018 Sep 12. PMID: 30209524.

21. Pettersen MD, Du W, Skeens ME, Humes RA. Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. J Am Soc Echocardiogr 2008; 21: 922–34. https://doi.org/10.1016/j.echo.2008.02.006 PMID: 18406572.
22. Kampmann C, Wiethoff CM, Wenzel A, Stolz G, Betancor M, Wippermann CF, et al. Normal values of M-mode echocardiographic measurements of more than 2000 healthy infants and children in central Europe. Heart 2000; 83: 667–72. https://doi.org/10.1161/heart.83.6.667 PMID: 10814626

23. Cantinotti M, Assanta N, Crocetti M, Marotta M, Murzi B, Iervasi G. Limitations of current nomograms in pediatric echocardiography: Just the tip of the iceberg—A call for standardization. https://doi.org/10.1016/j.echocardio.2013.12.002 J Am Soc Echocardiogr 2014; 27: 339. PMID: 24438752

24. Chinali M, Emma F, Esposito C, Rinelli G, Franceschini A, Doyon A, et al. Left Ventricular Mass Indexing in Infants, Children, and Adolescents: A Simplified Approach for the Identification of Left Ventricular Hypertrophy in Clinical Practice. J Pediatr 2015; 170: 193–198. https://doi.org/10.1016/j.jpeds.2015.10.085 PMID: 26670053

25. Majonga ED, Rehman AM, McHugh G, Mujuru HA, Nathoo K, Patel MS, et al. Echocardiographic reference ranges in older children and adolescents in sub-Saharan Africa. Int J Cardiol 2017; 248: 409–413. https://doi.org/10.1016/j.ijcard.2017.06.109 PMID: 28711335

26. Lopez L, Colan S, Stylianou M, Granger S, Trachtenberg F, Frommelt P, et.; Pediatric Heart Network Investigators. Relationship of Echocardiographic Z Scores Adjusted for Body Surface Area to Age, Sex, Race, and Ethnicity. The Pediatric Heart Network Normal Echocardiogram Database. Circ Cardiovasc Imaging 2017; 10. https://doi.org/10.1161/CIRCIMAGING.117.006979 PMID: 29138232

27. Daniels SR, Meyer RA, Liang YC, Bove KE. Echocardiographically determined left ventricular mass index in normal children, adolescents and young adults. J Am Coll Cardiol 1988; 12:703–708. https://doi.org/10.1016/s0735-1097(88)80060-3 PMID: 3403828

28. Khoury PR, Mitsnefes M, Daniels SR, Kimball TR. Age-specific reference intervals for indexed left ventricular mass in children. J Am Soc Echocardiogr 2009; 22:709–714. https://doi.org/10.1016/j.echo.2009.03.003 PMID: 19423289

29. Foster BJ, Khoury PR, Kimball TR, Mackie AS, Mitsnefes M. New reference centiles for left ventricular mass relative to lean body mass in children. J Am Soc Echocardiogr 2016; 29: 441–447.e2. https://doi.org/10.1016/j.echo.2015.12.011 PMID: 26850680

30. Diaz A, Zócalo Y, Bia D. Reference Intervals and Percentile Curves of Echocardiographic Left Ventricular Mass, Relative Wall Thickness and Ejection Fraction in Healthy Children and Adolescents. Pediatr Cardiol 2019; 40: 263–301. https://doi.org/10.1007/s00246-018-2000-y PMID: 30288599

31. Lauer MS, Anderson KM, Larson MG, Levy D. A new method for indexing left ventricular mass for differences in body size. Am J Cardiol. 1994 Sep 1; 74(5):487–91. https://doi.org/10.1016/0002-9149(94)90909-1 PMID: 8059731

32. Daniels SR, Kimball TR, Morrison JA, Khoury P, Witt S, Meyer RA. Effect of lean body mass, fat mass, blood pressure, and sexual maturation on left ventricular mass in children and adolescents. Statistical, biological, and clinical significance. Circulation 1995: 92: 3249–3254. https://doi.org/10.1161/01.cir.92.11.3249 PMID: 7589311

33. Haycock GB, Schwartz GJ, Wisotzky DH. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. J Pediatr 1978; 93: 62–6. https://doi.org/10.1016/s0022-3476(78)80601-5 PMID: 650346

34. Foster BJ, Platth RW, Zemel BS. Development and Validation of a Predictive Equation for Lean Body Mass in Children and Adolescents. Ann Hum Biol 2012; 39: 171–182. https://doi.org/10.3109/03014460.2012.681800 PMID: 22621754

35. Cole TJ, Green PJ. Smoothing reference centile curves: The lms method and penalized likelihood. Stat Med 1992; 11: 1305–1319. https://doi.org/10.1002/sim.4780111005 PMID: 1518992

36. Foster BJ, Gao T, Mackie AS, Zemel BS, Ali H, Platt RW, et al. Limitations of expressing left ventricular mass relative to height and to body surface area in children. J Am Soc Echocardiogr 2013; 26: 410–418. https://doi.org/10.1016/j.echo.2012.11.016 PMID: 23267782

37. Albrecht GH, Gelvin BR, Hartman SE. Ratios as a size adjustment in morphometrics. Am J Phys Anthropol 1993; 91(4): 441–468. https://doi.org/10.1002/ajpa.1330910404 PMID: 8372935

38. Foster BJ, Mackie AS, Mitsnefes M, Ali H, Mamber S, Colan SD. A novel method of expressing left ventricular mass relative to body size in children. Circulation 2006; 117(21): 2769–2775. https://doi.org/10.1161/CIRCULATIONAHA.107.741157 PMID: 16490525

39. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res. 1999 Jun; 8(2):135–60. https://doi.org/10.1177/096228029900800204 PMID: 10501650.

40. Schieken RM, Schwartz PF, Goble MM. Tracking of left ventricular mass in children: race and sex comparisons: The MCV Twin Study. Medical College of Virginia. Circulation 1998; 97:1901–1906. https://doi.org/10.1161/01.cir.97.19.1901 PMID: 9609082
41. Goble MM, Mosteller M, Moskowitz WB, Schieken RM. Sex differences in the determinants of left ventricular mass in childhood. The Medical College Virginia Twin Study. Circulation 1992; 85:1661–1665. https://doi.org/10.1161/01.cir.85.5.1661 PMID: 1572024

42. de Simone G, Devereux RB, Daniels SR, Koren MJ, Meyer RA, Laragh JH. Effect of growth on variability of left ventricular mass: assessment of allometric signals in adults and children and their capacity to predict cardiovascular risk. J Am Coll Cardiol 1995; 25: 1056–62. https://doi.org/10.1016/0735-1097(94)00540-7 PMID: 7897116

43. Pelà G, Crocamo A, Li Calzi M, Gianfreda M, Gioia M, Visioli F, et al. Sex-related differences in left ventricular structure in early adolescent non-professional athletes. Eur J Prev Cardiol 2016: 23:777–784. https://doi.org/10.1177/2047487315608826 PMID: 26405258

44. Hense HW, Gneiting B, Muscholl M, Broeckel U, Kuch B, Doering A, et al. The associations of body size and body composition with left ventricular mass: impacts for indexation in adults. J Am Coll Cardiol. 1998 Aug; 32(2):451–7. https://doi.org/10.1016/s0735-1097(98)00240-x PMID: 9708475

45. Pelliccia A, Maron BJ, Calasso F, Spataro A, Caselli G. Athlete’s heart in women. Echocardiographic characterization of highly trained elite female athletes. JAMA 1996 Jul 17; 276(3):211–5. https://doi.org/10.1001/jama.276.3.211 PMID: 8667565

46. Kuch B, Gneiting B, Dörr A, Muscholl M, Bröckel U, Schunkert H, et al. Indexation of left ventricular mass in adults with a novel approximation for fat-free mass. J Hypertens 2001; 19: 135–142. https://doi.org/10.1097/00004872-200101000-00018 PMID: 11204294

47. Whalley GA, Doughty RN, Gamble GD, Oxenham HC, Walsh HJ, Reid IR, et al. Association of fat-free mass and training status with left ventricular size and mass in endurance-trained athletes. J Am Coll Cardiol 2004; 44: 892–896. https://doi.org/10.1016/j.jacc.2004.04.051 PMID: 15312877

48. de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, et al. Left ventricular mass and body size in normotensive children and adults: Assessment of allometric relations and impact of overweight. J Am Coll Cardiol 1992; 20: 1251–1260. https://doi.org/10.1016/0735-1097(92)90385-z PMID: 1401629

49. Barbieri A, Bursi F, Mantovani F, Valenti C, Quaglia M, Berti E, et al. Left ventricular hypertrophy reclassification and death: application of the Recommendation of the American Society of Echocardiography/European Association of Echocardiography. Eur Heart J Cardiovasc Imaging. 2012; 13:109–117. https://doi.org/10.1093/eurheartj/ejr176 PMID: 21979990

50. Huang Z, Fonseca R, Sharman JE, Park C, Chatuvedi N, Howe LD, et al. The influence of fitness on exercise blood pressure and its association with cardiac structure in adolescence. Scand J Med Sci Sports. 2020 Jun; 30(6):1033–1039. https://doi.org/10.1111/sms.13645 PMID: 32100896

51. Elberg S, Hasselstrom H, Grenfeldt V, Froberg K, Svensson J, Andersen LB. Maximum oxygen uptake and objectively measured physical activity in Danish children 6–7 years of age: the Copenhagen school child intervention study. Br J Sports Med 2005; Oct; 39(10): 725–30. https://doi.org/10.1136/bjsm.2004.015230 PMID: 16183768

52. Armstrong N, Williams J, Balding J, Gentle P, Kirby B. The Peak Oxygen Uptake of British Children With Reference to Age, Sex and Sexual Maturity. Eur J Appl Physiol Occup Physiol. 1991; 62(5):369–75. https://doi.org/10.1007/BF00634975 PMID: 1874245

53. de Simone G, Devereux RB, Daniels SR, Meyer RA. Gender Differences in Left Ventricular Growth. Hypertension. 1995 Dec; 26(6 Pt 1):979–83. https://doi.org/10.1161/01.hyp.26.6.979 PMID: 7490158