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ORIGINAL ARTICLE

# Echocardiographic nomograms in children living at high altitude according to sex

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## Abstract

**Aims**

This study aimed to establish 2D and M-mode echocardiographic reference values for cardiac chambers, outflow tracts, and great vessels for school children living at high altitudes, differentiated between males and females.

**Methods and results**

This *post hoc* analysis included children with normal echocardiography from a cluster randomized cross-sectional survey of rheumatic heart disease among school children in Peru. The echocardiograms were acquired with a portable machine and the images were analysed centrally with a standardized methodology. Body surface area (BSA) was used as an independent variable to predict the mean values of echocardiographic measurements for both male and female groups. Reference values are presented on z-scores and nomograms based on sex. Propensity score matching was used to compare sexes. A total of 985 students aged 5–16 years were included. The Haycock formula provided the best fit and was used when presenting data as predicted values for a given BSA. The z-score and nomograms for all essential parameters of cardiac chambers, great vessels, and functional surrogates are presented based on sex. The majority of the parameters were significantly different per sex after propensity score matching.

**Conclusion**

Normal reference values and nomograms of cardiac chambers, outflow tracts, and great arteries in healthy school children living at high altitudes based on sex were reported. These data partly addressed the existing gaps in paediatric echocardiographic nomograms.

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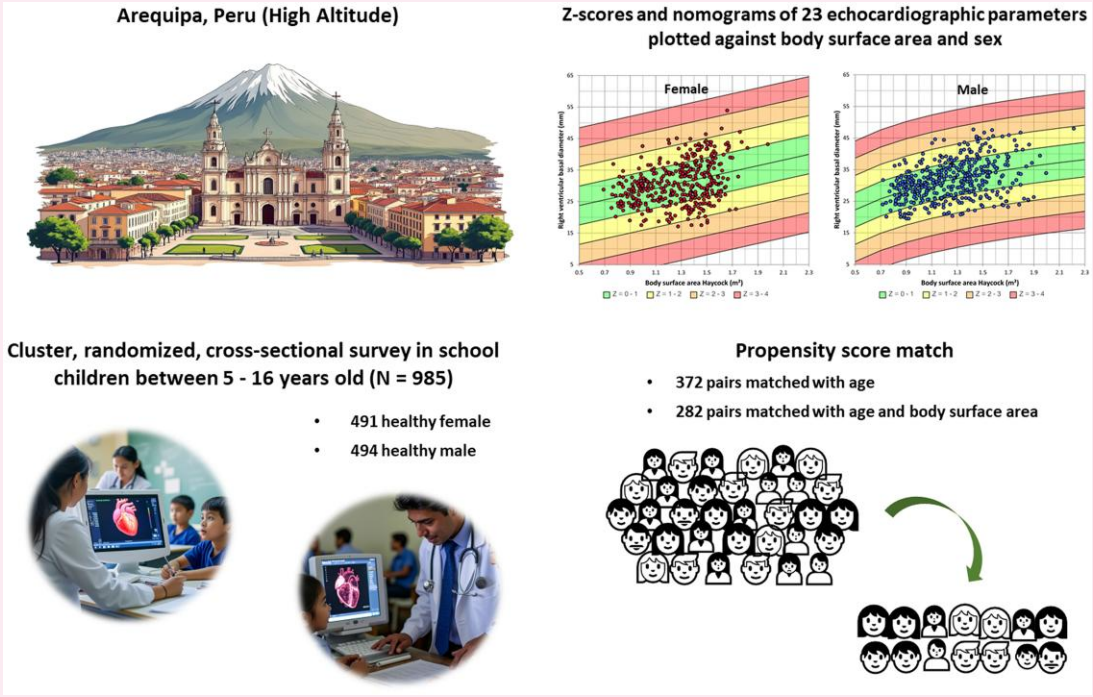
## Graphical Abstract




Echocardiographic nomograms and quantitative comparisons among female and male children from Arequipa, Peru. The three drawings on the left were made by Grok, x.AI Corp.

**Keywords** echocardiography • nomogram • high altitude • reference value • propensity score matching

# Introduction

Quantitative measurements of cardiac structures using echocardiography play a significant role in the diagnosis of heart disease and assessments of growth in children. Echocardiography is widely available and can provide real-time measurements, but its use requires the availability of adequate reference values, especially in the paediatric population.[1] Geographical background may determine physiological adaptations, not only based on the local genetic pool but also by extrinsic factors.[2–4] Among the later, altitude is known to play a role in cardiac physiology but there is limited data on children living at high altitude (between 1500 and 3500 ms above the sea level).[2,5] A previous study in Peru reported symptomatic altitude-related pulmonary hypertension and structural cardiac abnormalities in participants living above 4000 m above the sea level (very high altitude). The authors emphasized the need for a detailed analysis of congenital heart disease presentations across altitude ranges.[2] Approximately 500 million people (6.58% of the world population) live above 1500 m and only 14.4 million (0.19% of the world population) above 3500 m. Ethiopia has the largest population living ≥ 1500 m, and China has the greatest living >3500 m.[6] Most cities above 1500 m are situated in South America, Asia, and Africa.

Development of reference values is attainable when sufficient representative data are included in the reference population, which requires adequate sampling strategies. For this reason, limiting the target sample to very restricted areas or to hospital-based populations may not be adequate for reference values generation.[3,4,7] More specifically, authors must ensure that the reference population is composed by healthy volunteers, which is possible through population-based studies.[4]

This article summarizes echocardiographic data acquired from school children in Arequipa, Peru at an average altitude of 2328 m above sea level, which links the coastal and highland regions of Peru. The primary study consisting of a two-stage sampling observational study for screening of rheumatic heart disease (RHD) has been previously reported.[8] Interestingly, the study concluded that RHD prevalence was considerably lower in this region than that of endemic geographies, such as sub-Saharan Africa, but the number of undetected congenital heart disease was comparable. This report obtained data from healthy participants and aimed to establish two-dimensional (2D) and M-mode echocardiographic nomograms on heart chambers, outflow tracts and great arteries. Furthermore, nomograms are also separately presented in male and female population, aiming to cover the gap in current literature reporting sex specific normal reference values in children, which typically focused on only specific parameters such as valve dimensions, coronary arteries, and aortic root (in normal and Marfan syndrome).[7–9]

# Methods

## Study design and patient population

We performed a-*post hoc* analysis of a cluster randomized cross-sectional survey of RHD among school-going children in Arequipa, Peru with an altitude of 2328 m above sea level.[8] Among 1023 children of 5–16 years old enrolled for screening, children with confirmed pathological findings, including congenital heart disease and RHD ($n = 37$) were excluded. One child with severe malnutrition was also excluded from this analysis. The data collection strategy has been previously described.[8]

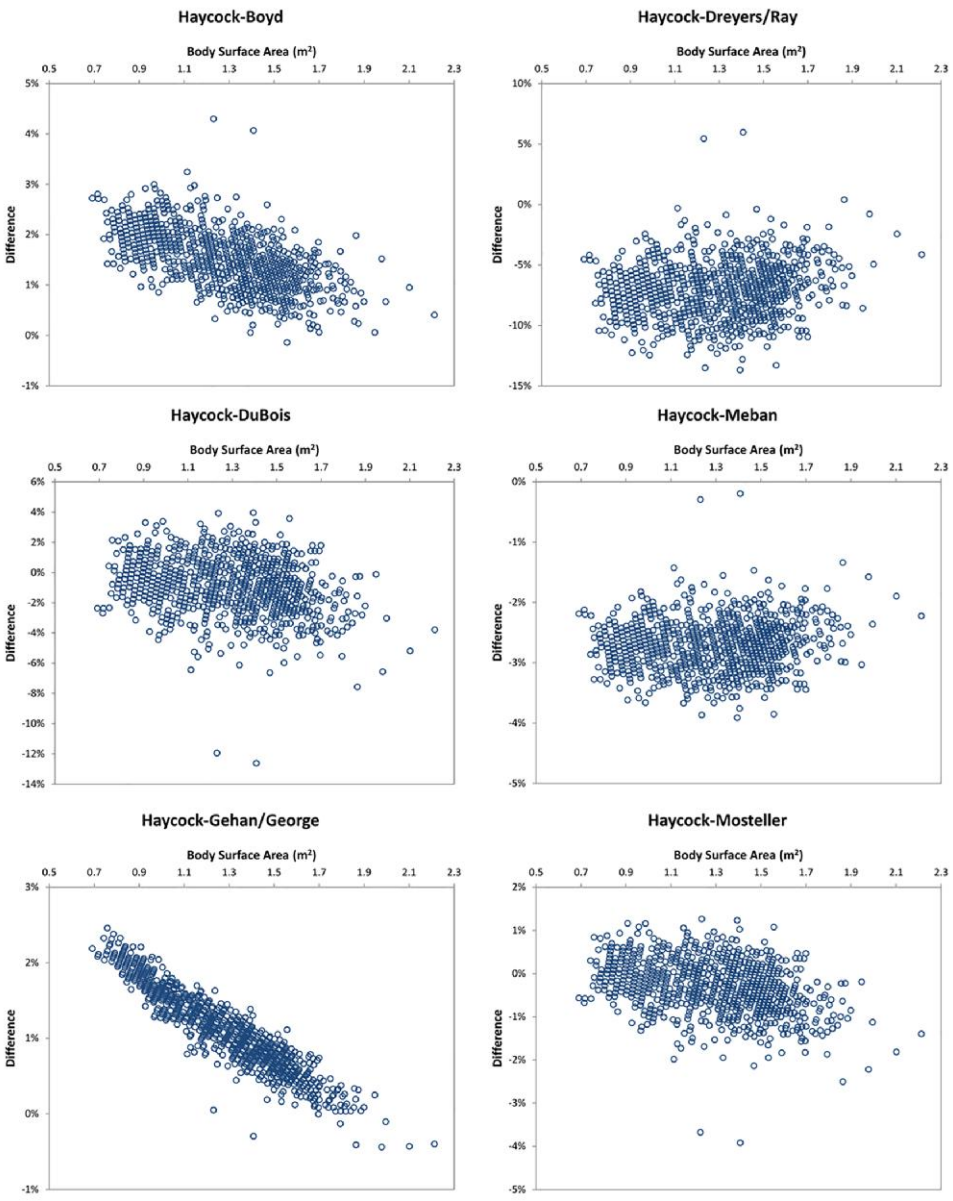



**Figure 1** Relationship between the six calculating formulas on BSA with reference to the Haycock formula. The circled dots demonstrate BSA distributions.

Ethical approval was obtained from the Human Research Ethics Committee of the University San Martín de Porres, Lima, Peru (Officio No. 48-2014-CIEI-USMP-CCM). Local authorizations were granted by the Regional Administrations of the Health and Education Ministries, as well as from each school's principal. Written consent was obtained from parents/guardians, and written assent from all children.

## Echocardiographic data acquisition and analysis

The echocardiographic examinations were performed by a single, dedicated cardiologist following a standard acquisition protocol.[8] A portable ultrasound system MyLabAlpha (Esaote, Italy) was used with the PA122E transthoracic phased array probe, with a frequency range of 3–8 MHz. Echocardiographic data were digitally stored and analysed by research fellows in the echocardiographic core lab at Bern University Hospital (Switzerland) using MyLabDesk (Esaote, Italy) and at Cardialysis (Rotterdam, The Netherlands) using TomTec Arena (TomTec Imaging Systems GMBH, Germany).

Echocardiographic images were analysed according to a standardized core lab analysis plan based on the applicable echocardiographic guidelines,[10] covering essential parameters of the heart chambers, ventricular function, valves, and great vessels (see Supplementary data online, *Table S1*). Measurements were made only when image quality was sufficient. Thus, not all measurements were expected to be feasible in all subjects (see Supplementary data online, *Table S2A–E*).

## Statistical analysis

All echocardiographic variables indexed on body surface area (BSA)[1] were first tested with a trend test. The variables with significant trend *P* values

were taken into further analysis. Models using linear ($y = a + bx$), logarithmic ($y = a + b \times \ln[x]$, $\ln[y] = a + bx$), exponential ($\ln[y] = a + b \times \ln[x]$), and square root ($y = a + b \times \sqrt{x}$, $\sqrt{y} = a + bx$, and $\sqrt{y} = a + b \times \sqrt{x}$) equations were tested to examine the relationships between the echocardiographic variables and the BSA. Among the models that satisfied the assumption of homoscedasticity and normality of residuals, the model with the highest $R^2$ value was considered to provide the best fit. The Koenker Basset and Breusch–Pagan tests were used to test heteroscedasticity, and the Shapiro–Wilk and Kolmogorov–Smirnov tests for the normality. $P < 0.05$ was considered statistically significant.

To evaluate the potential differences, BSA was calculated according to seven previously published methods (*Figure 1*).[10–12] We tested different methods but specifically investigated the Haycock method ($BSA = weight^{0.5378} \times height^{0.3964} \times 0.024265$) as this was reported most accurately in a previous study.[13] The z-score, a standardized value indicating by how many standard deviations (SDs) a value is above or below the mean in a normally distributed population, was calculated by dividing the residual values by the modelled standard error of the residual value. Finally, we established z-score values with mean ± 1.96 SD using BSA for all measured dimensions of cardiac chambers and great arteries in males and females separately. SPSS 20 (SPSS, Inc, Chicago, IL) was used for statistical analysis.

To further ascertain the difference in values in each parameter between the male and female, we performed the propensity score matching using the Greedy matching method with a calliper value of 0.1 with the age and BSA as covariates. SAS V9.4 (SAS Institute Inc., North Carolina, USA) was used.

# Results

## Characteristics of the study population

In total, 985 school children (491 female, 494 male) with ages ranging from 5 to 16 years were included in this sub-study (graphical abstract). The body mass index ranged from 17.8 ± 2.3 to 22.9 ± 2.6 kg/m$^2$ in females and 17.5 ± 1.7 to 20.8 ± 2.1 kg/m$^2$ in males (see Supplementary data online, *Table S3*). The distribution of BSA based on the Haycock formula is shown in *Figure 2*. Almost all (97.6% male and 98.4% female) of the students had a BSA ranging from 0.8 to 2.0 m$^2$.

We present 23 echocardiographic parameters for female and male children according to BSA (see Supplementary data online, *Table S1*) and age. The feasibility of analysis in each echocardiographic variable is shown in Supplementary data online, *Table S2A–E*. The majority of the echocardiographic parameters had more than 90% feasibility for analysis.

## Regression models

The BSA was calculated using seven formulas as mentioned in the methods. The relationship between BSA based on the Haycock formula and the other six formulas is shown in *Figure 1*. We found that Meban and Dreyers–Ray underestimated BSA whereas Boyd and Gehan–George overestimated BSA compared with the Haycock formula. The Mosteller formula provides comparable BSA values to the Haycock formula but shows underestimated BSA after the cut-off of 1.5 m$^2$ (*Figure 1*). BSA calculated based on the Haycock formula was chosen for testing the regression models in this study based on our findings.

The regression model with the highest $R^2$ was chosen as the best-fit model. The coefficients for the regression models and results of heteroscedasticity and normality tests are shown in Supplementary data online, *Table S4* for the female and male population. The predicted values for all measures are shown in *Table 1* (female and male). For both female and male population, the predicted mean values of all cardiac measures (except the heart rate) increased with the BSA with a slightly increased SDs. The most prominent increase was seen in the LV mass.

Differentiated between male (blue dots) and female (red dots), the Z-score boundaries with actual measured plots are presented, including the left ventricular dimensions and mass (*Figure 3*) and right ventricular dimensions (*Figure 4*). The other cardiac dimensions and functional surrogates are shown in the supplements: heart rate (see Supplementary data online, *Figure S1*), left ventricular outflow tract and aorta dimensions (see Supplementary data online, *Figures S2*), left and right ventricles' functional measures (mitral and tricuspid annular plane systolic excursion with M-mode, Supplementary data online, *Figure S3*), atrial chambers and inferior vena cava diameter (see Supplementary data online, *Figure S4*), right ventricular outflow tract (proximal and distal) and pulmonary artery measurements (see Supplementary data online, *Figure S5*). Majority of the plots were seen within Z-score of 0–3 (indicating up to 3SD) with very limited outliers in the range Z-score > 3. As the BSA values increased, the dispersion of plots was stable (within the range of Z-score 0–3). The only exception was seen in the LV mass that the more plots were seen in the range of Z-score 1–2 and 2–3 (the yellow and orange colour zones in *Figure 3, 4*) and the colour zones in the nomograms were seen more diverging following the increase of the BSA.

Only one dependent variable (right ventricular outflow tract proximal diameter during systole) was fit for both sexes as a linear

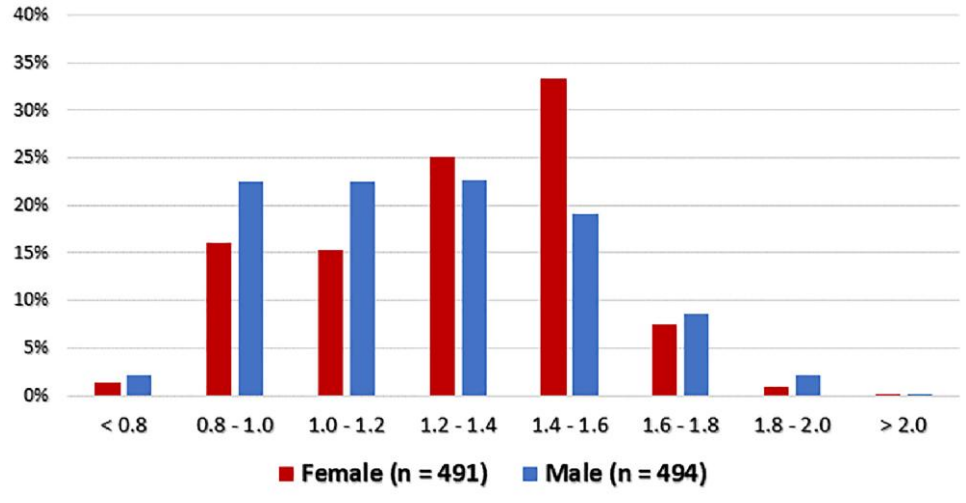



**Figure 2** BSA distribution (x-axis) among the study population. The red bars indicate the female proportion and blue the male.

**Table 1 Predicted values of echocardiographic parameters by BSA based on Haycock formula in the female and male population**

| Echocardiographic parameter | BSA ($m^2$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **0.6** | **0.8** | **1** | **1.2** | **1.4** | **1.6** | **1.8** | **2** | **2.2** |
| (a) Female | | | | | | | | | |
| Heart rate (beats per minute) | | | | | | | | | |
| (–)2 SD | 68.61 | 67.26 | 66.2 | 65.35 | 64.62 | 63.99 | 63.43 | 62.94 | 62.49 |
| Mean | **83.25** | **81.9** | **80.84** | **79.98** | **79.26** | **78.63** | **78.07** | **77.58** | **77.13** |
| (+)2SD | 97.89 | 96.53 | 95.48 | 94.62 | 93.9 | 93.27 | 92.71 | 92.21 | 91.76 |
| Interventricular septum (mm) | | | | | | | | | |
| (–)2SD | 3.45 | 3.77 | 4.05 | 4.28 | 4.5 | 4.69 | 4.86 | 5.03 | 5.18 |
| Mean | **5.4** | **5.91** | **6.34** | **6.71** | **7.04** | **7.34** | **7.62** | **7.87** | **8.11** |
| (+)2SD | 8.45 | 9.25 | 9.92 | 10.5 | 11.02 | 11.49 | 11.92 | 12.32 | 12.7 |
| Left ventricular posterior wall (mm) | | | | | | | | | |
| (–)2SD | 2.61 | 3.11 | 3.49 | 3.81 | 4.08 | 4.31 | 4.51 | 4.69 | 4.86 |
| Mean | **4.95** | **5.45** | **5.83** | **6.15** | **6.41** | **6.65** | **6.85** | **7.03** | **7.2** |
| (+)2SD | 7.29 | 7.78 | 8.17 | 8.49 | 8.75 | 8.98 | 9.19 | 9.37 | 9.53 |
| Left ventricular end-diastolic diameter (mm) | | | | | | | | | |
| (–)2SD | 24.6 | 26.7 | 28.88 | 31.15 | 33.51 | 35.96 | 38.49 | 41.1 | 43.8 |
| Mean | **30.38** | **32.7** | **35.12** | **37.62** | **40.21** | **42.88** | **45.64** | **48.48** | **51.42** |
| (+)2SD | 36.76 | 39.32 | 41.97 | 44.7 | 47.51 | 50.41 | 53.4 | 56.48 | 59.64 |
| Left ventricular end-systolic diameter (mm) | | | | | | | | | |
| (–)2SD | 13.87 | 15.27 | 16.67 | 18.07 | 19.47 | 20.87 | 22.26 | 23.66 | 25.06 |
| Mean | **18.96** | **20.36** | **21.76** | **23.15** | **24.55** | **25.95** | **27.35** | **28.75** | **30.15** |
| (+)2SD | 24.04 | 25.44 | 26.84 | 28.24 | 29.64 | 31.04 | 32.44 | 33.84 | 35.24 |
| Left ventricular mass (g) | | | | | | | | | |
| (–)2SD | 19.75 | 26.84 | 34.05 | 41.35 | 48.74 | 56.2 | 63.72 | 71.29 | 78.92 |
| Mean | **30.6** | **41.58** | **52.75** | **64.07** | **75.52** | **87.07** | **98.72** | **110.46** | **122.27** |
| (+)2SD | 47.41 | 64.43 | 81.73 | 99.27 | 117 | 134.9 | 152.95 | 171.14 | 189.44 |
| Mitral annular plane systolic excursion (mm) | | | | | | | | | |
| (–)2SD | 10.04 | 10.9 | 11.62 | 12.24 | 12.79 | 13.29 | 13.75 | 14.17 | 14.56 |
| Mean | **12.87** | **13.98** | **14.9** | **15.7** | **16.41** | **17.05** | **17.64** | **18.18** | **18.68** |
| (+)2SD | 16.51 | 17.93 | 19.12 | 20.14 | 21.05 | 21.87 | 22.62 | 23.32 | 23.96 |
| Left atrial area ($cm^2$) | | | | | | | | | |
| (–)2SD | 4.66 | 5.64 | 6.54 | 7.39 | 8.19 | 8.95 | 9.68 | 10.38 | 11.06 |
| Mean | **6.62** | **8.02** | **9.3** | **10.5** | **11.64** | **12.72** | **13.76** | **14.75** | **15.72** |
| (+)2SD | 9.41 | 11.4 | 13.22 | 14.93 | 16.54 | 18.08 | 19.55 | 20.97 | 22.35 |
| Left atrial volume (mL) | | | | | | | | | |
| (–)2SD | 4.32 | 6.65 | 9.11 | 11.68 | 14.31 | 17 | 19.74 | 22.52 | 25.34 |
| Mean | **12.23** | **15.97** | **19.69** | **23.38** | **27.05** | **30.71** | **34.36** | **38** | **41.63** |
| (+)2SD | 24.16 | 29.32 | 34.28 | 39.1 | 43.81 | 48.44 | 52.99 | 57.49 | 61.94 |
| Inferior vena cava diameter (mm) | | | | | | | | | |
| (–)2SD | 0.36 | 2.17 | 3.58 | 4.73 | 5.7 | 6.54 | 7.29 | 7.95 | 8.55 |
| Mean | **6.38** | **8.19** | **9.6** | **10.75** | **11.72** | **12.56** | **13.31** | **13.97** | **14.57** |
| (+)2SD | 12.4 | 14.21 | 15.62 | 16.77 | 17.74 | 18.58 | 19.33 | 19.99 | 20.59 |
| Right atrial area ($cm^2$) | | | | | | | | | |
| (–)2SD | 4.35 | 5.19 | 5.95 | 6.65 | 7.31 | 7.93 | 8.53 | 9.1 | 9.64 |
| Mean | **6.23** | **7.43** | **8.52** | **9.52** | **10.47** | **11.36** | **12.21** | **13.02** | **13.8** |
| (+)2SD | 8.92 | 10.64 | 12.19 | 13.63 | 14.98 | 16.26 | 17.47 | 18.64 | 19.75 |
| Right ventricular basal diameter (mm) | | | | | | | | | |
| (–)2SD | 12.33 | 14.13 | 15.93 | 17.74 | 19.54 | 21.34 | 23.14 | 24.95 | 26.75 |
| Mean | **24.66** | **26.47** | **28.27** | **30.07** | **31.88** | **33.68** | **35.48** | **37.28** | **39.09** |
| (+)2SD | 37 | 38.81 | 40.61 | 42.41 | 44.21 | 46.02 | 47.82 | 49.62 | 51.43 |

*Continued*

**Table 1** *Continued*

| Echocardiographic parameter | BSA ($m^2$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **0.6** | **0.8** | **1** | **1.2** | **1.4** | **1.6** | **1.8** | **2** | **2.2** |
| Right ventricular mid-cavity diameter (mm) | | | | | | | | | |
| (−)2SD | 10.78 | 12.97 | 14.9 | 16.65 | 18.26 | 19.75 | 21.16 | 22.48 | 23.75 |
| Mean | **20.95** | **23.14** | **25.07** | **26.82** | **28.43** | **29.92** | **31.33** | **32.66** | **33.92** |
| (+)2SD | 31.12 | 33.31 | 35.25 | 36.99 | 38.6 | 40.09 | 41.5 | 42.83 | 44.09 |
| Right ventricular outflow tract distal diameter systole (mm) | | | | | | | | | |
| (−)2SD | 8.69 | 9.57 | 10.32 | 10.97 | 11.55 | 12.08 | 12.57 | 13.02 | 13.44 |
| Mean | **12.61** | **13.89** | **14.98** | **15.92** | **16.77** | **17.54** | **18.25** | **18.9** | **19.52** |
| (+)2SD | 18.31 | 20.17 | 21.74 | 23.12 | 24.34 | 25.46 | 26.49 | 27.44 | 28.34 |
| Right ventricular outflow tract distal diameter diastole (mm) | | | | | | | | | |
| (−)2SD | 10 | 11.3 | 12.42 | 13.42 | 14.33 | 15.17 | 15.95 | 16.68 | 17.37 |
| Mean | **13.82** | **15.61** | **17.17** | **18.55** | **19.81** | **20.96** | **22.04** | **23.05** | **24** |
| (+)2SD | 19.1 | 21.58 | 23.73 | 25.64 | 27.37 | 28.97 | 30.46 | 31.86 | 33.17 |
| Right ventricular outflow tract proximal diameter systole (mm) | | | | | | | | | |
| (−)2SD | 14.49 | 16.14 | 17.8 | 19.45 | 21.1 | 22.76 | 24.41 | 26.06 | 27.71 |
| Mean | **23.18** | **24.83** | **26.49** | **28.14** | **29.79** | **31.45** | **33.1** | **34.75** | **36.41** |
| (+)2SD | 31.87 | 33.53 | 35.18 | 36.83 | 38.49 | 40.14 | 41.79 | 43.45 | 45.1 |
| Right ventricular outflow tract proximal diameter diastole (mm) | | | | | | | | | |
| (−)2SD | 17.09 | 18.19 | 19.33 | 20.5 | 21.7 | 22.94 | 24.21 | 25.52 | 26.86 |
| Mean | **23** | **24.27** | **25.58** | **26.92** | **28.3** | **29.71** | **31.16** | **32.64** | **34.15** |
| (+)2SD | 29.78 | 31.22 | 32.71 | 34.22 | 35.77 | 37.36 | 38.98 | 40.63 | 42.32 |
| Tricuspid annular plane systolic excursion (mm) | | | | | | | | | |
| (−)2SD | 12.92 | 14.07 | 15.08 | 16 | 16.84 | 17.62 | 18.35 | 19.05 | 19.71 |
| Mean | **18.28** | **19.43** | **20.44** | **21.36** | **22.2** | **22.98** | **23.71** | **24.41** | **25.07** |
| (+)2SD | 23.64 | 24.79 | 25.8 | 26.71 | 27.55 | 28.34 | 29.07 | 29.77 | 30.43 |
| Left ventricular outflow tract diameter (mm) | | | | | | | | | |
| (−)2SD | 11.12 | 11.69 | 12.29 | 12.91 | 13.57 | 14.26 | 14.99 | 15.75 | 16.55 |
| Mean | **13.46** | **14.14** | **14.86** | **15.62** | **16.41** | **17.25** | **18.13** | **19.05** | **20.02** |
| (+)2SD | 16.28 | 17.11 | 17.98 | 18.9 | 19.86 | 20.87 | 21.93 | 23.05 | 24.22 |
| Aortic annulus diameter (mm) | | | | | | | | | |
| (−)2SD | 9.21 | 10.5 | 11.63 | 12.64 | 13.56 | 14.42 | 15.21 | 15.96 | 16.67 |
| Mean | **11.38** | **12.98** | **14.37** | **15.62** | **16.76** | **17.81** | **18.79** | **19.72** | **20.6** |
| (+)2SD | 14.06 | 16.03 | 17.75 | 19.29 | 20.7 | 22 | 23.22 | 24.36 | 25.45 |
| Sinus of Valsalva diameter (mm) | | | | | | | | | |
| (−)2SD | 14.22 | 15.71 | 16.98 | 18.1 | 19.09 | 20 | 20.84 | 21.62 | 22.35 |
| Mean | **16.74** | **18.51** | **20** | **21.31** | **22.49** | **23.56** | **24.54** | **25.46** | **26.32** |
| (+)2SD | 19.72 | 21.79 | 23.55 | 25.1 | 26.48 | 27.74 | 28.9 | 29.98 | 30.99 |
| Sinotubular junction diameter (mm) | | | | | | | | | |
| (−)2SD | 10.2 | 11.51 | 12.63 | 13.63 | 14.54 | 15.37 | 16.15 | 16.87 | 17.56 |
| Mean | **12.61** | **14.22** | **15.6** | **16.84** | **17.96** | **18.99** | **19.95** | **20.85** | **21.69** |
| (+)2SD | 15.57 | 17.56 | 19.28 | 20.8 | 22.19 | 23.46 | 24.64 | 25.75 | 26.8 |
| Proximal ascending aorta diameter (mm) | | | | | | | | | |
| (−)2SD | 11.53 | 12.59 | 13.71 | 14.87 | 16.07 | 17.33 | 18.63 | 19.98 | 21.37 |
| Mean | **14.62** | **15.81** | **17.06** | **18.35** | **19.69** | **21.07** | **22.5** | **23.98** | **25.51** |
| (+)2SD | 18.07 | 19.4 | 20.77 | 22.2 | 23.67 | 25.18 | 26.75 | 28.36 | 30.01 |
| Main pulmonary artery diameter (mm) | | | | | | | | | |
| (−)2SD | 7.51 | 8.5 | 9.36 | 10.13 | 10.82 | 11.46 | 12.06 | 12.62 | 13.15 |
| Mean | **11.15** | **12.63** | **13.9** | **15.04** | **16.08** | **17.03** | **17.92** | **18.75** | **19.54** |
| (+)2SD | 16.57 | 18.76 | 20.65 | 22.35 | 23.88 | 25.3 | 26.62 | 27.86 | 29.03 |

*Continued*

**Table 1** ***Continued***

| Echocardiographic parameter | BSA ($m^2$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **0.6** | **0.8** | **1** | **1.2** | **1.4** | **1.6** | **1.8** | **2** | **2.2** |
| (b) Male | | | | | | | | | |
| Heart rate (beats per min) | | | | | | | | | |
| (−)2SD | 66.4 | 65.64 | 64.89 | 64.14 | 63.4 | 62.68 | 61.96 | 61.24 | 60.54 |
| Mean | **81.66** | **80.72** | **79.8** | **78.88** | **77.97** | **77.08** | **76.19** | **75.32** | **74.45** |
| (+)2SD | 100.43 | 99.27 | 98.13 | 97.01 | 95.89 | 94.79 | 93.7 | 92.63 | 91.56 |
| Interventricular septum (mm) | | | | | | | | | |
| (−)2SD | 2.16 | 3.05 | 3.82 | 4.53 | 5.18 | 5.78 | 6.34 | 6.88 | 7.39 |
| Mean | **4.85** | **5.74** | **6.51** | **7.22** | **7.87** | **8.47** | **9.04** | **9.57** | **10.08** |
| (+)2SD | 7.54 | 8.43 | 9.2 | 9.91 | 10.56 | 11.16 | 11.73 | 12.26 | 12.77 |
| Left ventricular posterior wall (mm) | | | | | | | | | |
| (−)2SD | 3.28 | 3.59 | 3.93 | 4.27 | 4.63 | 5.01 | 5.4 | 5.8 | 6.22 |
| Mean | **5.12** | **5.51** | **5.92** | **6.34** | **6.78** | **7.23** | **7.7** | **8.18** | **8.68** |
| (+)2SD | 7.37 | 7.84 | 8.32 | 8.82 | 9.34 | 9.87 | 10.41 | 10.97 | 11.55 |
| Left ventricular end-diastolic diameter (mm) | | | | | | | | | |
| (−)2SD | 21.89 | 26.17 | 29.49 | 32.2 | 34.5 | 36.48 | 38.24 | 39.8 | 41.22 |
| Mean | **28.79** | **33.07** | **36.39** | **39.1** | **41.39** | **43.38** | **45.13** | **46.7** | **48.12** |
| (+)2SD | 35.69 | 39.97 | 43.29 | 46 | 48.29 | 50.28 | 52.03 | 53.6 | 55.01 |
| Left ventricular end-systolic diameter (mm) | | | | | | | | | |
| (−)2SD | 14.1 | 15.62 | 16.96 | 18.17 | 19.29 | 20.33 | 21.3 | 22.22 | 23.1 |
| Mean | **19.77** | **21.29** | **22.64** | **23.85** | **24.96** | **26** | **26.98** | **27.9** | **28.77** |
| (+)2SD | 25.45 | 26.97 | 28.31 | 29.52 | 30.64 | 31.68 | 32.65 | 33.57 | 34.45 |
| Left ventricular mass (g) | | | | | | | | | |
| (−)2SD | 19.34 | 27.93 | 37.15 | 46.89 | 57.09 | 67.71 | 78.71 | 90.05 | 101.71 |
| Mean | **29.47** | **42.56** | **56.6** | **71.44** | **86.99** | **103.17** | **119.93** | **137.2** | **154.97** |
| (+)2SD | 44.91 | 64.85 | 86.24 | 108.86 | 132.55 | 157.2 | 182.73 | 209.06 | 236.12 |
| Mitral annular plane systolic excursion (mm) | | | | | | | | | |
| (−)2SD | 9.19 | 10.08 | 10.77 | 11.33 | 11.81 | 12.22 | 12.59 | 12.91 | 13.21 |
| Mean | **13.78** | **14.67** | **15.36** | **15.92** | **16.4** | **16.81** | **17.18** | **17.5** | **17.8** |
| (+)2SD | 18.37 | 19.26 | 19.95 | 20.52 | 20.99 | 21.41 | 21.77 | 22.1 | 22.39 |
| Left atrial area ($cm^2$) | | | | | | | | | |
| (−)2SD | 2.33 | 4.25 | 5.74 | 6.96 | 7.99 | 8.89 | 9.68 | 10.38 | 11.02 |
| Mean | **6.28** | **8.21** | **9.7** | **10.92** | **11.95** | **12.84** | **13.63** | **14.33** | **14.97** |
| (+)2SD | 10.24 | 12.16 | 13.65 | 14.87 | 15.9 | 16.8 | 17.58 | 18.29 | 18.93 |
| Left atrial volume (mL) | | | | | | | | | |
| (−)2SD | −0.23 | 4.02 | 7.76 | 11.14 | 14.25 | 17.15 | 19.87 | 22.44 | 24.88 |
| Mean | **13.19** | **17.43** | **21.17** | **24.56** | **27.67** | **30.56** | **33.28** | **35.85** | **38.3** |
| (+)2SD | 26.6 | 30.85 | 34.59 | 37.97 | 41.08 | 43.98 | 46.7 | 49.27 | 51.72 |
| Right ventricular basal diameter (mm) | | | | | | | | | |
| (−)2SD | 13.27 | 16.27 | 18.59 | 20.49 | 22.09 | 23.48 | 24.71 | 25.81 | 26.8 |
| Mean | **24.18** | **27.17** | **29.5** | **31.39** | **33** | **34.39** | **35.61** | **36.71** | **37.7** |
| (+)2SD | 35.08 | 38.08 | 40.4 | 42.3 | 43.9 | 45.3 | 46.52 | 47.62 | 48.61 |
| Right ventricular mid-cavity diameter (mm) | | | | | | | | | |
| (−)2SD | 10.46 | 13.31 | 15.81 | 18.08 | 20.17 | 22.11 | 23.93 | 25.66 | 27.3 |
| Mean | **20.31** | **23.15** | **25.66** | **27.93** | **30.02** | **31.96** | **33.78** | **35.51** | **37.15** |
| (+)2SD | 30.16 | 33 | 35.51 | 37.78 | 39.87 | 41.81 | 43.63 | 45.36 | 47 |
| Right ventricular outflow tract proximal diameter systole (mm) | | | | | | | | | |
| (−)2SD | 17.91 | 19.2 | 20.49 | 21.79 | 23.08 | 24.37 | 25.67 | 26.96 | 28.26 |
| Mean | **25.92** | **27.22** | **28.51** | **29.8** | **31.1** | **32.39** | **33.69** | **34.98** | **36.27** |
| (+)2SD | 33.94 | 35.23 | 36.53 | 37.82 | 39.12 | 40.41 | 41.7 | 43 | 44.29 |

*Continued*

**Table 1** *Continued*

| Echocardiographic parameter | BSA ($m^2$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **0.6** | **0.8** | **1** | **1.2** | **1.4** | **1.6** | **1.8** | **2** | **2.2** |
| Right ventricular outflow tract proximal diameter diastole (mm) | | | | | | | | | |
| (−)2SD | 16.62 | 18.1 | 19.58 | 21.06 | 22.54 | 24.02 | 25.5 | 26.98 | 28.46 |
| Mean | **23.73** | **25.21** | **26.69** | **28.17** | **29.65** | **31.13** | **32.61** | **34.09** | **35.57** |
| (+)2SD | 30.85 | 32.33 | 33.81 | 35.29 | 36.77 | 38.25 | 39.73 | 41.21 | 42.69 |
| Right ventricular outflow tract distal diameter systole (mm) | | | | | | | | | |
| (−)2SD | 7.72 | 9.22 | 10.39 | 11.34 | 12.14 | 12.84 | 13.45 | 14 | 14.5 |
| Mean | **13.33** | **14.83** | **15.99** | **16.94** | **17.75** | **18.44** | **19.06** | **19.61** | **20.1** |
| (+)2SD | 18.94 | 20.44 | 21.6 | 22.55 | 23.36 | 24.05 | 24.67 | 25.21 | 25.71 |
| Right ventricular outflow tract distal diameter diastole (mm) | | | | | | | | | |
| (−)2SD | 8.95 | 10.81 | 12.26 | 13.44 | 14.44 | 15.3 | 16.06 | 16.75 | 17.36 |
| Mean | **15.13** | **17** | **18.44** | **19.62** | **20.62** | **21.49** | **22.25** | **22.93** | **23.55** |
| (+)2SD | 21.32 | 23.18 | 24.63 | 25.81 | 26.8 | 27.67 | 28.43 | 29.11 | 29.73 |
| Tricuspid annular plane systolic excursion (mm) | | | | | | | | | |
| (−)2SD | 12.2 | 13.5 | 14.51 | 15.34 | 16.04 | 16.65 | 17.18 | 17.66 | 18.09 |
| Mean | **17.72** | **19.02** | **20.03** | **20.86** | **21.56** | **22.17** | **22.7** | **23.18** | **23.61** |
| (+)2SD | 23.24 | 24.54 | 25.56 | 26.38 | 27.08 | 27.69 | 28.22 | 28.7 | 29.13 |
| Right atrial area ($cm^2$) | | | | | | | | | |
| (−)2SD | 4.23 | 5.22 | 6.14 | 7.02 | 7.85 | 8.66 | 9.44 | 10.19 | 10.93 |
| Mean | **6.12** | **7.56** | **8.9** | **10.17** | **11.38** | **12.55** | **13.67** | **14.77** | **15.84** |
| (+)2SD | 8.87 | 10.95 | 12.89 | 14.73 | 16.48 | 18.18 | 19.81 | 21.4 | 22.94 |
| Inferior vena cava diameter (mm) | | | | | | | | | |
| (−)2SD | 0.64 | 2.74 | 4.37 | 5.71 | 6.84 | 7.81 | 8.67 | 9.44 | 10.14 |
| Mean | **6.13** | **8.24** | **9.87** | **11.2** | **12.33** | **13.31** | **14.17** | **14.94** | **15.64** |
| (+)2SD | 11.63 | 13.73 | 15.37 | 16.7 | 17.83 | 18.8 | 19.67 | 20.44 | 21.13 |
| Left ventricular outflow tract diameter (mm) | | | | | | | | | |
| (−)2SD | 9.94 | 11.12 | 12.16 | 13.1 | 13.97 | 14.77 | 15.52 | 16.24 | 16.92 |
| Mean | **13.07** | **14.24** | **15.28** | **16.22** | **17.09** | **17.89** | **18.65** | **19.36** | **20.04** |
| (+)2SD | 16.19 | 17.37 | 18.41 | 19.35 | 20.21 | 21.01 | 21.77 | 22.48 | 23.16 |
| Aortic annulus diameter (mm) | | | | | | | | | |
| (−)2SD | 8.98 | 10.15 | 11.31 | 12.48 | 13.65 | 14.82 | 15.99 | 17.15 | 18.32 |
| Mean | **12.46** | **13.63** | **14.8** | **15.96** | **17.13** | **18.3** | **19.47** | **20.64** | **21.8** |
| (+)2SD | 15.94 | 17.11 | 18.28 | 19.45 | 20.61 | 21.78 | 22.95 | 24.12 | 25.29 |
| Sinus of Valsalva diameter (mm) | | | | | | | | | |
| (−)2SD | 13.82 | 15.51 | 17 | 18.34 | 19.58 | 20.73 | 21.81 | 22.83 | 23.8 |
| Mean | **17.34** | **19.03** | **20.52** | **21.86** | **23.1** | **24.25** | **25.33** | **26.35** | **27.32** |
| (+)2SD | 20.86 | 22.55 | 24.03 | 25.38 | 26.62 | 27.77 | 28.85 | 29.87 | 30.84 |
| Sinotubular junction diameter (mm) | | | | | | | | | |
| (−)2SD | 11.13 | 11.93 | 12.79 | 13.7 | 14.69 | 15.74 | 16.87 | 18.08 | 19.37 |
| Mean | **13.66** | **14.64** | **15.69** | **16.81** | **18.02** | **19.31** | **20.7** | **22.18** | **23.77** |
| (+)2SD | 16.76 | 17.96 | 19.25 | 20.63 | 22.11 | 23.7 | 25.4 | 27.22 | 29.17 |
| Proximal ascending aorta diameter (mm) | | | | | | | | | |
| (−)2SD | 12.56 | 13.18 | 13.83 | 14.52 | 15.23 | 15.98 | 16.77 | 17.6 | 18.47 |
| Mean | **15.88** | **16.66** | **17.48** | **18.35** | **19.25** | **20.2** | **21.2** | **22.24** | **23.34** |
| (+)2SD | 20.07 | 21.06 | 22.1 | 23.19 | 24.33 | 25.53 | 26.79 | 28.11 | 29.5 |
| Main pulmonary artery diameter (mm) | | | | | | | | | |
| (−)2SD | 5.42 | 7.2 | 8.58 | 9.71 | 10.66 | 11.49 | 12.22 | 12.87 | 13.46 |
| Mean | **11.52** | **13.3** | **14.68** | **15.81** | **16.76** | **17.59** | **18.32** | **18.97** | **19.56** |
| (+)2SD | 17.62 | 19.4 | 20.78 | 21.91 | 22.86 | 23.69 | 24.42 | 25.07 | 25.6 |

Data is presented according to the body surface area with an interval of 0.2 $m^2$ in mean (numbers in bold), +2SD (upper row) and −2SD (lower row).
SD, standard deviation.

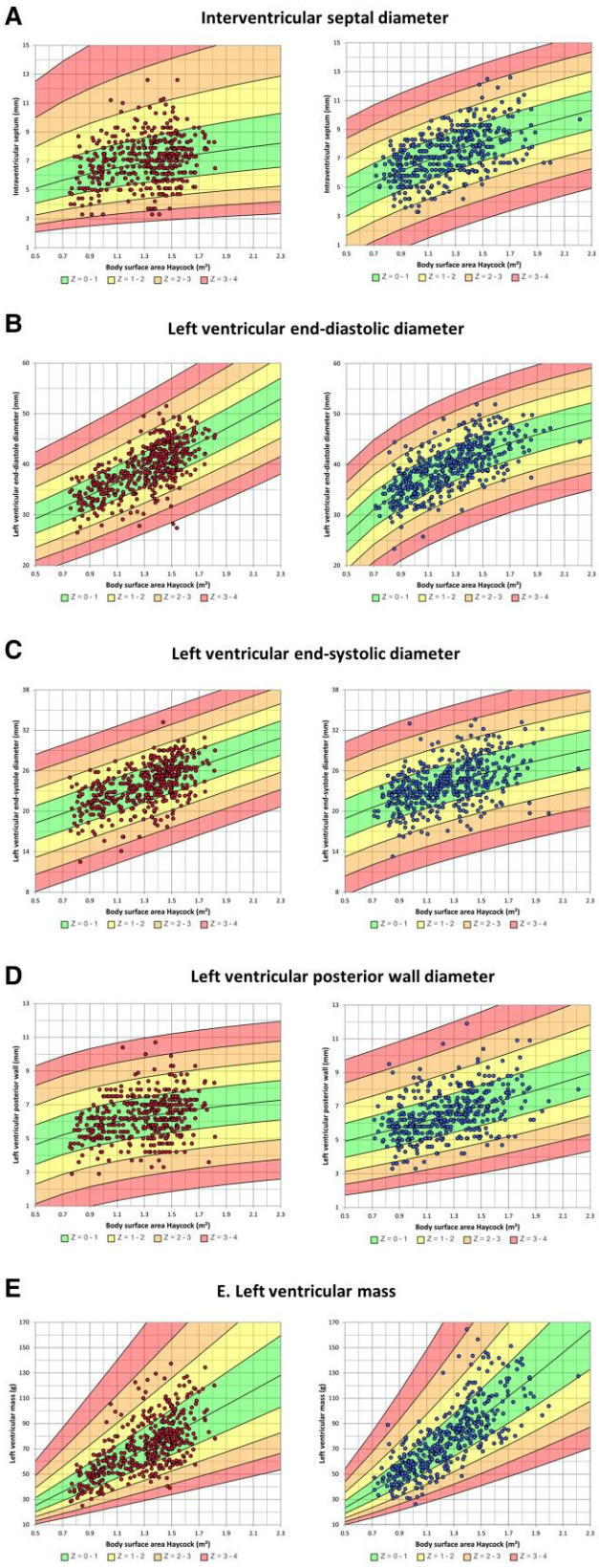



**Figure 3** Z-score nomograms for left ventricular dimensions and mass. Red dots = females; blue dots = males. The green shaded area indicates Z-score of 0–1, yellow 1–2, orange 2–3, and red 3–4. Cardiac measurements (plots) falling into higher Z-score area (the orange or red areas) might indicate abnormal values requiring further interpretation and clinical investigation.

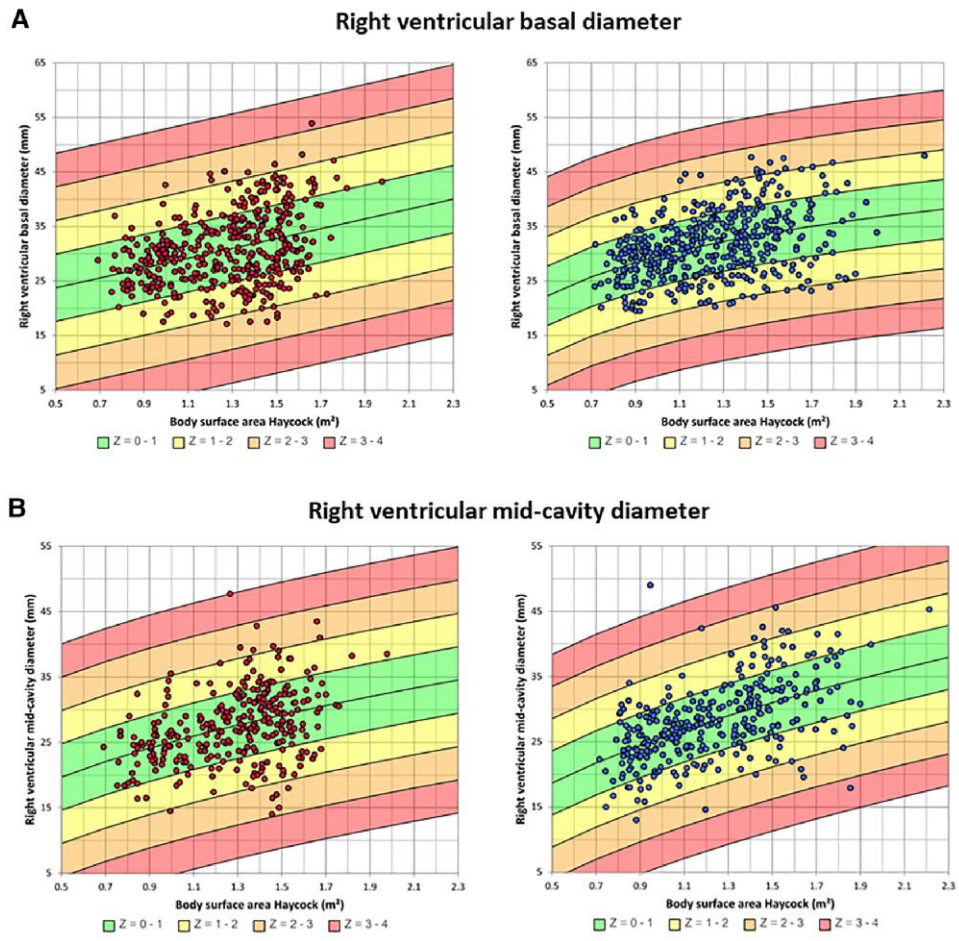



**Figure 4** Z-score nomograms for right ventricular diameters. Red dots = females; blue dots = males. The colour zones and plots as described in *Figure 3*.

regression model. The other two dependent variables from each side were in line with the linear regression model (right ventricular outflow tract proximal diameter during diastole and aortic annulus for the male population) and (left ventricular end-systolic diameter and right ventricular basal diameter for the female population). Some of the dependent variables were best-fit to complex regression models of logarithmic, exponential, and square roots.

A sample of the z-score value was taken for comparison with other study results as seen in Supplementary data online, *Table S5*. The comparison was made on specific parameters at a specific measurement of BSA (1 $m^2$). Sex-based left ventricular mass analysis among the study population revealed a higher mean value with an increase in the BSA from 0.8 $m^2$. Heart rate showed reduction with an increase in the BSA unlike other parameters (see Supplementary data online, *Figure S1*).

Between females and males, 372 pairs were identified with the model matched on age, where 282 pairs remained after further adjustment with BSA (central illustration). With age-matched model 17 parameters (73.4%) showed significant differences in values between the two sexes. The significant difference remained in 12 parameters (52.2%) after adding the BSA into the model (see Supplementary data online, *Table S6*).

# Discussion

The main contributions of this study can be summarized as follows: (i) nomograms for 2D and M-mode echocardiographic measurements are presented for healthy Peruvian children living at high altitudes; (ii) we utilize previously reported methods for the development of nomograms, including a selection of the most appropriate BSA formula, which confirmed their applicability (iii) all data are presented separately for girls and boys due to the statistically significant difference supported by the propensity score-matched analysis based on the age and BSA. To our knowledge, we believe that this is so far the most comprehensive presentation of sex-specific nomograms and Z-scores.

Previous studies revealed significant variability with age, sex, body parameters, and to some extent geographic background.[3,4,7,14–16] This was comparable to our findings where we saw significant differences per sex even in age-matched and propensity score matched by BSA for the majority of echocardiographic parameters. The process of establishing reference values requires adequate sample size, adequate representation of the target population, isolated inclusion of healthy children, and rigorous statistical analyses.[17,18] In our study, we included healthy children from the school screening after echocardiographic confirmation. Our statistical analysis was multistage and

different regression models were tested to achieve the best-fit for each dependent variable with additional propensity score matching.

BSA as an independent variable to determine normal values of cardiac parameters has been previously used.[3,13,14,19] Similarly, in our study we used BSA to prepare z-scores for cardiac chamber dimensions, outflow tracts, and great arteries. The selection of the BSA calculating formula can affect the overall findings, which was confirmed in our study. Methodologically, comparing the fitness of multiple BSA formulas appears most sensible, and we used this approach in our study, which is comparable to previous studies.[3,7]

We reported on 23 echocardiographic parameters for chamber dimensions, outflow tracts, and great arteries. Few studies have reported on a similar list of parameters obtained with M-Mode and 2D echocardiography.[7] Moreover, reference values for outflow tracts are largely unavailable in general, and specifically for high-altitude populations. Such reference values are crucial for children with right-side heart disease such as tetralogy of Fallot, to plan interventions and post-intervention follow-up.[19] Moreover, right ventricular measurements are very limited in the paediatric reference values.[3] In our study, we included right ventricular dimensions and functional parameters as a reference value for further study and use. In particular to our study population living at a high altitude of 2328 m, the parameters for right heart chambers and outflow tracts are especially important.[20,21] It is noteworthy that thoracic skeletal adaptations in response to high altitude were not a characteristic of the study population, a finding consistent with prior reports indicating that these changes may occur above 3000 m.[22,23]

Confounder analysis for sex was done by different authors that showed no significant overall effect while studying the whole age range of children.[3,7] The uniqueness of our study is that the propensity score analysis based on age and BSA was used to ascertain the differences in the cardiac and great vessel dimensions between the male and female sexes. As seen in Supplementary data online, *Table S6*, the number of parameters showing significant differences between females and males were almost doubled after matching by age and BSA than comparing in the total population. This can be explained by the population age range which included pubertal groups. This is consistent with previous reports on the variation of reference values during pubertal periods due to different growth spurts.[18]

Obese children were not excluded from our study population as they were small in number, distributed normally, and did not affect homoscedasticity. In a separate sub-study, obesity-related left ventricular changes were reported.[24] The analysis revealed that indexed left ventricular mass and diastolic dysfunction were significantly different between obese and normal weight groups. Importantly, the overall analysis in this study revealed no significant variance as depicted by the coefficient of variance and homoscedasticity. Furthermore, nomograms depict the values according to BSA based on the Haycock method, which provides additional information to clinicians.

For comparison purposes, we took a sample of cardiac dimension for comparison at BSA of 1.0 $m^2$ with two studies[18,19] that had reported on these values. The comparison for left ventricular end diastolic diameters revealed almost proportional measurement values.[25] Our study, however, is sex-specific which prevents precise comparisons. The authors of this study are committed to pooling data that would allow adequate comparisons with populations at low altitude (<1500 m) or very high altitude (>3500 m), or different geographies. It is noteworthy the existing comparisons among children living at very high altitude with children living at low altitude, primarily indicate higher pulmonary artery pressures and larger right ventricles.[26]

## Limitations

The study was conducted at the community level and on healthy children which was the key component of developing normative values. Propensity score match analysis was also made for differences with sex. Whereas, the results need to be interpreted considering the following limitations, first, this is a descriptive study from a population-based screening with echocardiography, without having information on genetic disorders that may be undiagnosed while not evident on imaging. Second, we did not restrict our analysis to non-obese patients; however, we believe that this approach provides more information to clinicians, including the z distribution for a larger range of BSA. Third, children's growth in cardiac dimensions are affected by many factors, including geography (such as high altitude), diet, and ethnicity among others. Our study was conducted in the children population in south America (Arequipa, Peru) and the results may not be generalized to other children populations (e.g. in Asia or Africa) living on the similar altitude. Finally, the availability of measurements for some parameters was low, for which *n* values are presented.

# Conclusions

We presented BSA-based sex-specific nomograms for children 5–16 years old living at a high altitude in Peru. There was a significant difference in the majority of echocardiographic parameters between the two sexes after propensity score matching using age and BSA. Findings could be used for reference tables and graphs for practitioners seeking to diagnose cardiac chamber size, outflow tract, and great artery abnormalities and partly cover a gap in existing paediatric echocardiographic nomograms.

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# Supplementary data

Supplementary data are available at *European Heart Journal - Imaging Methods and Practice* online.

**Conflict of interest:** E.S. declares institutional contracts/grants for which he receives no direct compensation from Abbott; Biosensors Europe SA, Boston Scientific; Edwards Lifesciences; Medtronic; Mixin Medtech (Suzhou) Co., Ltd.; Shanghai Microport Medical Co., Ltd.; Novo Nordisk A/S; NVT GmbH; Philips Healthcare; Pie Medical Imaging; Shanghai Shenqi Medical Technologies Co., Ltd.; and Siemens Healthcare GmbH. E.S. declares being board member of Cardialysis, European Cardiovascular Research Institute, EU-MDR Cardiovascular Collaboratory, and Academic Research Consortium. T.P. has received research grants to the institution from Biotronik, Boston Scientific, and Edwards Lifesciences, speaker fees from Biotronik and Boston Scientific, and serves as a consultant for HighLife SAS. All other authors declare no conflict of interests.

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## Data availability

The data underlying this article are not publicly available. Access to the data may be granted for comparative research purposes upon reasonable request to the corresponding author, subject to institutional approval.

# Disclosures

The authors have nothing to disclose.

## Lead author biography

Demeke Mekonnen is a consultant paediatrician and paediatric cardiologist, as well as a health science educator with more than 15 years of international experience, primarily in Ethiopia. His areas of research are rheumatic heart disease and myocardial function, including global longitudinal strain. Demeke Mekonnen has had active involvement in community service and volunteerism. He completed a subspecialty in paediatric cardiology in Israel with an award of certificate of paediatric cardiology by Save A Child's Heart (SACH). Following this, he continued his career with foetal echocardiography and clinical research. During 2024-25, he joined Cardialysis for a 1-year clinical research fellowship.

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