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Abstract

Despite the clinical utility of echocardiography to measure cardiac target organ injury (TOI) there are scarcities of data about the reference intervals (RIs) and percentiles of left ventricular (LV) mass (LVM) and derived indexes (LVMI and $LVMI^{2.7}$), relative wall thickness (LVRWT) and ejection fraction (LVEF) from population-based studies in children and adolescents. The aim of this study was to generate reference intervals RIs of LVM and derived indexes (LVMI and $LVMI^{2.7}$), LVRWT, and LVEF obtained in healthy children, adolescents, and young adults from a South-American population. Echocardiographic studies were obtained in 1096 healthy subjects (5–24 years). Age and sex-specific RIs of LVM, LVMI, $LVMI^{2.7}$, LVRWT, and LVEF were generated using parametric regression based on fractional polynomials. After covariate analysis (i.e., adjusting by age, body surface area) specific sex-specific RIs were evidenced as necessaries. Age and sex-specific 1st, 2.5th, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97.5th, and 99th percentile and curves were reported and compared with previously reported RIs. RIs showed high concordance and complementarity with what was previously reported for the population of North-American children (0–18 years old). In conclusion, in children and adolescents the interpretation of the LVM, LVMIs, LVRWT, and LVEF RIs requires sex-related RIs. This study provides the largest Argentinean database concerning RIs and percentile curves of LVM, LVMIs, LVRWT, and LVEF as markers of cardiac TOI obtained in healthy children and adolescents. These data are valuable in that they provide RIs values with which data of populations of children, adolescents can be compared.

Keywords (separated by '-'): Left ventricular mass - Left ventricular hypertrophy - Echocardiography - Adolescents - Children - Epidemiology - Pediatrics - Reference values - Percentiles

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ORIGINAL ARTICLE

Reference Intervals and Percentile Curves of Echocardiographic Left Ventricular Mass, Relative Wall Thickness and Ejection Fraction in Healthy Children and Adolescents

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Abstract

Despite the clinical utility of echocardiography to measure cardiac target organ injury (TOI) there are scarcities of data about the reference intervals (RIs) and percentiles of left ventricular (LV) mass (LVM) and derived indexes (LVMI and $LVMI^{2.7}$), relative wall thickness (LVRWT) and ejection fraction (LVEF) from population-based studies in children and adolescents. The aim of this study was to generate reference intervals RIs of LVM and derived indexes (LVMI and $LVMI^{2.7}$), LVRWT, and LVEF obtained in healthy children, adolescents, and young adults from a South-American population. Echocardiographic studies were obtained in 1096 healthy subjects (5–24 years). Age and sex-specific RIs of LVM, LVMI, $LVMI^{2.7}$, LVRWT, and LVEF were generated using parametric regression based on fractional polynomials. After covariate analysis (i.e., adjusting by age, body surface area) specific sex-specific RIs were evidenced as necessaries. Age and sex-specific 1st, 2.5th, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97.5th, and 99th percentile and curves were reported and compared with previously reported RIs. RIs showed high concordance and complementarity with what was previously reported for the population of North-American children (0–18 years old). In conclusion, in children and adolescents the interpretation of the LVM, LVMIs, LVRWT, and LVEF RIs requires sex-related RIs. This study provides the largest Argentinean database concerning RIs and percentile curves of LVM, LVMIs, LVRWT, and LVEF as markers of cardiac TOI obtained in healthy children and adolescents. These data are valuable in that they provide RIs values with which data of populations of children, adolescents can be compared.

Keywords Left ventricular mass · Left ventricular hypertrophy · Echocardiography · Adolescents · Children · Epidemiology · Pediatrics · Reference values · Percentiles

Introduction

Hypertension (HTN) impacts on heart producing early functional or structural changes that can be detected, even in children and adolescents [1]. Left ventricular hypertrophy (LVH) is defined as an increase in left ventricular mass (LVM) in response to a disease state, due to an increase in left ventricular (LV) wall thickness and/or in cavity size [2]. The first epidemiological studies that document the relationship between the risk of cardiovascular disease and LVH were based on its electrocardiographic detection [3]. In pediatric HTN, the electrocardiography (ECG) adds little information to early diagnosis of target organ injury or damage (TOI) [1, 4–7]. LVM can be estimated non-invasively using a several techniques. They include M-mode, two (2DE) and three dimensional echocardiography and magnetic resonance imaging; all of them are associated with its own strengths and weaknesses [2, 9]. The Recommendations for Quantification Methods During the Performance of a Pediatric Echocardiogram standardize measurements of the LV but offer little guidance on how to interpret measurements and there is no mention of LVH in the report [10]. However, recently the New Clinical Practice Guideline for AQ1

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the Management of High Blood Pressure in Children and Adolescents consider *the best-studied and recommended echocardiographic measures of LV TOI are: LVM, LV relative wall thickness (LVRWT) and LV ejection fraction (LVEF)* [7].

Ethnic-based differences in LV size and function are widely studied in adults [11, 12] but little is known in children and adolescents. Despite the clinical utility of echocardiographic derived TOI markers there are scarcities of data in the Southern Cone of Latin America about the reference intervals (RIs) and percentiles of LVM, LVRWT and LVEF from prospective population-based studies in healthy children and adolescents. Considering that in pediatric clinical practice, is absolutely essential normalize the LVM considering the body surface area (BSA) and/or the body height, RIs and percentiles curves were obtained by non-normalized and normalized LVM indexes [13–15].

In this context, our research main purpose was to generate RIs and percentile curves of LVM, LVRWT, and LVEF obtained from 2DE and M-mode echocardiography in a cohort of children, adolescents and young adults non-exposed to cardiovascular risk factors (CRFs) from a healthy South-American population.

Methods

This study is part of population-based study in Tandil, Argentina. Preliminary data and particularly RIs for cardiovascular variables have recently been published [16–18]. This study was approval by the Institutional Ethics Committee and written informed consent was obtained.

Asymptomatic and healthy subjects (5–24 years old) from the community were considered for enrolment. The upper limit of the analyzed population of subjects was set up to 24 years old to ensure that body growth and development were completed and that adulthood was undoubtedly reached [19, 20]. In each subject a clinical interview, cardiovascular examination, anthropometric assessment and blood sampling evaluation were performed. Normotensive [1, 21] subjects were included and none had history of hyperlipidaemia, diabetes [1, 21, 22], cardiovascular, renal or pulmonary disease. Inclusion and exclusion criteria are detailed in *supplementary material*. After applying the inclusion and exclusion criteria, 1095 subjects were included (Table 1).

Echocardiographic Measurements

Echocardiographic measurements were performed according to the Recommendations for Cardiac Chamber Quantification [10, 23] and performed by a single researcher using an Esaote MyLab 40 ultrasound system (Esaote, Genoa, Italy). Echocardiographic methods are detailed in the *supplementary material*.

Using the leading edge-to-leading edge technique, the LV end-diastolic and end-systolic dimension (LVEDD and LVESD, respectively), inter-ventricular septum thickness (IVSD and IVSS, respectively), and posterior wall thickness (PWD and PWS, respectively) were measured from 2DE images [10, 23]. LVEDD, IVSD, and PWD obtained from the 2D-guided M-mode images were used to calculate LVM by an anatomically validated formula [10, 23, 24].

As can be seen in Figure S1 and Table S1 (*supplementary material*), all the measured parameters showed high intra-observer repeatability.

Left Ventricular Function

LV end-diastolic and end-systolic volumes (LVEDV and LVESV, respectively) were measured from 2DE images, using the biplane method of disks' summation (modified Simpson's Rule). LVEF was then calculated from the respective 2DE-derived volumes with the following formula:

$$\mathrm{LVEF} = ((\mathrm{SV})/\mathrm{LVEDV}) \times 100, \quad (1)$$

where SV (stroke volume) is LVEDV-LVESV. LV endocardial and midwall shortening fraction (LVeSF and LVmSF, respectively) were calculated using 2D-guided M-mode images as:

- $$\mathrm{LVeSF\%} = (\mathrm{LVEDD} - \mathrm{LVESD}) \times 100/(\mathrm{LVEDD}); \quad (2)$$
- $$\mathrm{LVmSF\%} = \left[(\mathrm{LVEDD} + \mathrm{PWD}/2 + \mathrm{IVSD}/2) - (\mathrm{LVESD} + \mathrm{IVSS}/2 + \mathrm{IVSS}/2)\right] / (\mathrm{LVEDD} + \mathrm{PWD}/2 + \mathrm{IVSD}/2) \times 100; \quad (3)$$

Left Ventricular Mass

LVM was calculated using a linear method from 2D-guided M-mode images:

- $$\mathrm{LVM} = 0.8 \times \left\{1.04 \times \left[(\mathrm{IVSD} + \mathrm{LVEDD} + \mathrm{PWD})^3 - \mathrm{LVEDD}^3\right]\right\} + 0.6; \quad (4)$$

Additionally, LVM indexes were derived by dividing LVM with BSA (LVMI; g/m^2) and body height to the allometric power of 2.7 (LVMI$^{2.7}$; g/m$^{2.7}$) [13–15].

Relative LV Wall Thickness

End-diastolic LVRWT was calculated from 2DE images as [23]:

$$\mathrm{LVRWT} = 2 \times \mathrm{PWD}/\mathrm{LVEDD} \quad (5)$$

Table 1 Children and adolescents characteristics

	All ($n = 1095$)				Male ($n = 683$)				Female ($n = 412$)				p value
	MV	SD	Min	Max	MV	SD	Min	Max	MV	SD	Min	Max	(Male vs. Female)
A. Demographic, anthropometric and hemodynamic characteristics													
Age (years)	15.53	3.24	5.00	24.42	15.67	3.02	5.00	24.42	15.30	3.56	5.17	24.33	**0.068**
Body weight (Kg.)	59.32	15.23	15.00	110.00	63.20	15.60	15.00	110.00	52.94	12.18	15.00	88.00	**< 0.001**
Body Height (cm)	164.15	15.02	102.00	197.00	167.97	14.89	104.00	197.00	157.81	12.95	102.00	180.00	**< 0.001**
BSA (m^2)	1.64	0.28	0.66	2.44	1.71	0.28	0.66	2.44	1.52	0.23	0.66	2.01	**< 0.001**
BMI (Kg./m^2)	21.60	3.31	7.91	29.94	22.00	3.26	13.61	29.94	21.02	3.31	7.91	29.82	**< 0.001**
Brachial SBP (mmHg)	111.97	9.76	74.00	135.00	114.20	9.53	74.00	135.00	108.27	8.98	81.00	134.00	**< 0.001**
Brachial DBP (mmHg)	62.59	7.04	39.00	84.00	62.06	7.07	39.00	83.33	63.46	6.92	45.00	84.00	**0.001**
Brachial PP (mmHg)	49.38	8.70	21.67	83.00	52.15	8.60	21.67	83.00	44.80	6.70	24.00	65.00	**< 0.001**
Brachial MBP (mmHg)	79.05	6.93	53.56	99.33	79.44	6.86	53.56	99.22	78.40	6.99	61.67	99.33	**0.016**
Heart rate (beats/min)	70.20	12.55	38.00	116.00	68.31	12.01	38.00	116.00	73.34	12.82	45.00	113.00	**< 0.001**
Hematocrit (%)	40.75	2.52	36.00	47.00	40.63	2.47	36.00	47.00	40.95	2.59	36.00	47.00	**0.047**
Glicaemia (mg/dl)	82.20	8.77	63.00	97.00	82.27	8.76	63.00	97.00	82.07	8.80	63.00	97.00	**0.720**
Creatinine (mg/dl)	0.84	0.12	0.57	1.10	0.84	0.12	0.57	1.10	0.84	0.12	0.59	1.10	**0.954**
Total cholesterol (mg/dl)	157.76	22.00	100.00	198.00	158.81	22.41	100.00	198.00	156.00	21.21	100.00	198.00	**0.045**
Triglycerides (mg/dl)	72.41	20.75	40.00	127.00	72.06	20.59	40.00	127.00	72.99	21.03	40.00	126.00	**0.480**
B. Cardiovascular structural properties													
LVEDD (mm)	49.06	5.11	32.00	58.00	50.92	4.71	34.40	58.00	45.96	4.15	32.00	55.90	**< 0.001**
LVEDD/BSA (mm/m^2)	30.46	4.39	21.73	57.31	30.26	4.27	21.73	57.31	30.80	4.57	21.92	53.22	**0.049**
LVESD (mm)	31.55	3.44	19.60	39.70	32.65	3.28	20.70	39.70	29.72	2.87	19.60	37.50	**< 0.001**
IVSD (mm)	7.35	1.11	4.10	10.00	7.67	1.08	4.10	10.00	6.83	0.95	4.20	10.00	**< 0.001**
IVSS (mm)	11.64	2.06	6.10	18.80	12.26	2.05	6.10	18.80	10.61	1.64	6.20	14.80	**< 0.001**
PWD(mm)	7.39	1.06	4.10	10.00	7.69	1.02	4.10	10.00	6.90	0.94	4.30	10.00	**< 0.001**
PWS (mm)	12.70	2.00	8.00	18.90	13.25	2.04	8.00	18.90	11.80	1.58	8.00	16.70	**< 0.001**
EDIVST and EDPWT average (mm)	7.37	1.04	4.10	10.00	7.68	1.01	4.10	10.00	6.86	0.89	4.40	9.60	**< 0.001**
LVRWT	0.30	0.03	0.19	0.47	0.30	0.03	0.21	0.42	0.30	0.04	0.19	0.47	**0.264**
LVM (gr)	121.13	37.71	30.81	216.34	135.31	36.64	30.81	216.34	97.62	25.85	31.76	198.12	**< 0.001**
LVMI (gr/m^2)	72.44	14.57	39.83	120.50	77.78	13.70	40.00	120.50	63.58	11.30	39.83	104.34	**< 0.001**
LVMI (gr/$m^{2.7}$)	31.09	6.34	13.03	94.98	32.81	6.17	18.59	94.98	28.24	5.54	13.03	48.04	**< 0.001**
Aortic root diameter (mm)	26.46	3.40	14.60	36.20	27.52	3.30	15.30	36.20	24.70	2.79	14.60	35.60	**< 0.001**
LA dimension (mm)	32.36	4.23	18.00	42.90	33.66	4.05	18.70	42.90	30.21	3.60	18.00	39.90	**< 0.001**
LA volume (ml)	38.70	10.18	11.50	78.80	41.19	10.70	11.50	78.80	34.56	7.65	13.00	71.00	**< 0.001**
LA volume/BSA ratio (ml/m^2)	23.31	3.28	11.12	43.27	23.73	3.34	13.88	40.28	22.62	3.05	11.12	43.27	**< 0.001**
LVEDV (ml)	114.87	26.59	40.96	166.56	124.87	24.86	48.79	166.56	98.31	20.36	40.96	153.03	**< 0.001**
LVEDV/BSA ratio (ml/m^2)	69.77	10.23	36.78	103.92	72.73	9.04	43.49	97.75	64.87	10.22	36.78	103.92	**< 0.001**

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Table 1 (continued)

	All ($n = 1095$)				Male ($n = 683$)				Female ($n = 412$)				p value
	MV	SD	Min	Max	MV	SD	Min	Max	MV	SD	Min	Max	(Male vs. Female)
LVESV (ml)	40.32	10.17	12.09	68.76	43.69	9.88	13.89	68.76	34.74	7.95	12.09	60.02	**< 0.001**
C. Cardiovascular functional properties													
SV (ml)	74.55	17.51	27.41	112.70	81.17	16.27	31.07	112.70	63.57	13.54	27.41	105.11	**< 0.001**
LVEF (%)	64.94	3.25	57.04	76.28	65.09	3.20	57.04	75.85	64.70	3.34	58.11	76.28	**0.057**
LVeSF (%)	35.68	2.51	30.19	45.21	35.89	2.44	30.19	44.77	35.33	2.58	30.36	45.21	**< 0.001**
LVmSF (%)	22.54	2.69	13.39	35.53	22.55	2.67	15.18	35.53	22.53	2.72	13.39	32.02	**0.893**
CO (l)	5.14	1.22	2.19	10.21	5.47	1.20	2.19	10.21	4.60	1.04	2.30	8.33	**< 0.001**
CI (l/m^2)	3.16	0.67	1.37	6.00	3.22	0.63	1.86	5.84	3.07	0.71	1.37	6.00	**< 0.001**
SVR (mmHg/l)	1.21	0.28	0.61	2.48	1.14	0.25	0.61	2.48	1.33	0.29	0.71	2.37	**< 0.001**
Doppler E wave (cm/s)	0.92	0.15	0.50	1.45	0.93	0.14	0.50	1.37	0.92	0.15	0.57	1.45	**0.143**
Doppler A wave (cm/s)	0.44	0.11	0.17	0.95	0.44	0.11	0.17	0.95	0.45	0.12	0.20	0.93	**0.375**
Doppler E/A ratio	2.21	0.60	1.01	6.12	2.23	0.62	1.01	6.12	2.16	0.57	1.05	4.36	**0.065**

MV mean value, *SD* standard deviation, *Min. and Max*. minimal and maximal value, respectively, *BSA* body surface area, *BMI* body mass index, *SBP, DBP, PP and MBP* systolic, diastolic, pulse and mean blood pressure, respectively, *LVEDD and LVESD* left ventricle end-diastolic and end-systolic dimension (diameter), respectively, *SIVD and SIVS* end-diastolic and end-systolic inter-ventricular septum thickness, respectively, *PWD and PWS* end-diastolic and end-systolic left ventricle posterior wall thickness, respectively, *LVRWT* left ventricle radius-wall thickness ratio, *LVM and LVMI* left ventricle mass and mass index, respectively, *LV* left ventricle, *ES* end-systolic, *LA* left atrium, *LVEDV and LVESV* left ventricle end-diastolic and end-systolic volume, respectively, *SV and SW* stroke volume and work, respectively, *SVR* systemic vascular resistance, *CO* cardiac output, *CI* cardiac index, *LVEF* left ventricle ejection fraction, *LVeSF and LVmSF* left ventricle endocardial and midwall shortening fraction, respectively

A p˂0.05 (two tailed) was considered statistical significant

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Mathematical and Statistical Analysis

A step-wise data analysis was done as is described following:

First, we evaluate if LVM, LVM-derived indexes, LVRWT, and LVEF RIs for males and females were necessary. Then, sex influence was examined before and after adjustment for co-factors, previously identified through simple bivariate and point-biserial correlations (Table 2), applying covariance analysis (ANCOVA) (Table 3). ANCOVA allows to compare each variable (i.e., LVM) in two or more groups (i.e., males vs. females) considering the variability of other covariates. Always, prior to the ANCOVA, Levene's test for equality of variances and Homogeneity of regression slopes' test were performed. If the Levene test is statistical significant ($P<0.05$) then the variances in the groups are different (i.e., male and female groups are not homogeneous), and therefore the assumptions for ANCOVA are not met. Additionally, the interpretation of ANCOVA and the associated adjusted (marginal) means relies on the assumption of homogeneous regression slopes for the compared groups; if this assumption is not met ($P<0.05$) the ANCOVA results are unreliable. After statistical analysis, as a result, generation of sex-specific RIs of LVM, LVM-derived indexes, LVRWT, and LVEF for males and females were considered as necessaries.

Second the mean value and standard deviation (SD) age-related equations (for males and females) were obtained for LVM, LVM-derived indexes, LVRWT and LVEF. With this purpose, parametric regression methods based on fractional polynomials (FPs) [25], previously used to generate RIs for arterial parameters in our Argentinean population [17, 18] and the European Arterial Stiffness Collaboration Group methodological strategy [26] were implemented (MedCalc Software, Ostend, Belgium). Briefly, fitting FPs for age-specific LVM, LVM-derived indexes, LVRWT, and LVEF mean value and SD regression curves were defined using iterative procedure (generalized least squares). The obtained results enabled to estimate age-specific mean and SD for the selected parameters. For instance, LVM mean equation could be: = $a + b * \text{age}^p + c * \text{age}^q + \ldots$, where *a, b, c,…* are the coefficients, and *p, q, …* are the powers, with numbers selected from the set [–1–3, –1, −0.5, 0, 0.5, 1, 2, 3] estimated from the regression for the mean LVM curve, and likewise from the regression for the SD curve. Continuing the example, FPs with powers [1, 2], that is, with $p=1$ and $q=2$, illustrate an equation with the form $a+\ b\,\text{age}+\text{c}\ *\ \text{age}^2$ [25]. Residuals were used to assess the model fit, which was deemed appropriate if the scores were normally distributed, with a mean of 0 and a SD of 1, randomly scattered above and below 0 when plotted against age. The best fitted curves, considering visual and mathematical criteria (Kurtosis and Skewness) were selected. Then, using the equations obtained, age-specific percentiles were defined using

Table 2 Bivariate association between demographic, anthropometric, hemodynamic, and blood characteristics and left ventricular parameters of children and adolescents ($n=1095$)

	LVRWT	LV mass (g)	LVMI (g/m^2)	LVMI (g/m$^{2.7}$)	LVEF (%)
Age (years)					
R	0.205	0.403	0.243	0.129	−0.064
p	0.000	0.000	0.000	0.000	0.040
Sex (1: Female, 0: Male)					
R	−0.020	−0.521	−0.479	−0.351	−0.067
p	0.519	**0.000**	**0.000**	**0.000**	**0.032**
Body weight (Kg.)					
R	0.185	0.762	0.428	0.380	-0.018
p	**0.000**	**0.000**	**0.000**	**0.000**	0.561
Body height (cm)					
R	0.161	0.726	0.442	0.123	0.021
p	**0.000**	**0.000**	**0.000**	**0.000**	0.504
BSA (m^2)					
R	0.186	0.793	0.459	0.309	−0.003
p	**0.000**	**0.000**	**0.000**	**0.000**	0.930
BMI (Kg./m^2)					
R	0.149	0.511	0.266	0.477	−0.032
p	**0.000**	**0.000**	**0.000**	**0.000**	0.314
SBP (mmHg)					
R	0.173	0.468	0.329	0.292	0.037
p	**0.000**	**0.000**	**0.000**	**0.000**	0.236
DBP (mmHg)					
R	0.104	0.041	−0.036	−0.006	−0.099
p	**0.001**	0.186	0.254	0.845	**0.002**
PP (mmHg)					
R	0.105	0.473	0.384	0.321	0.119
p	**0.001**	**0.000**	**0.000**	**0.000**	**0.000**
MBP (mmHg)					
R	0.153	0.248	0.129	0.132	−0.051
p	**0.000**	**0.000**	**0.000**	**0.000**	0.102
Heart rate (beats/min)					
R	0.172	−0.289	−0.283	−0.199	−0.025
p	**0.000**	**0.000**	**0.000**	**0.000**	0.427
Hematocrit (%)					
R	0.007	−0.018	−0.036	−0.046	−0.065
p	0.827	0.573	0.248	0.145	**0.037**
Glicaemia (mg/dl)					
R	0.033	−0.008	0.030	0.046	0.006
p	0.285	0.805	0.330	0.141	0.850
Creatinine (mg/dl)					
R	−0.048	0.006	0.019	−0.004	0.013
p	0.127	0.838	0.543	0.892	0.668
Total cholesterol (mg/dl)					
R	0.034	0.090	0.073	0.041	−0.007
p	0.279	**0.004**	**0.020**	0.187	0.813
Triglicerides (mg/dl)					
R	0.025	−0.036	−0.028	−0.008	−0.028
p	0.418	0.251	0.367	0.807	0.369

BSA body surface area, *BMI* body mass index, *SBP, DBP, PP and MBP* systolic, diastolic, pulse and mean blood pressure, respectively, *LVRWT* left ventricle end-diastolic radius-wall thickness ratio, *LV* left

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Table 2 (continued)

ventricle, *LVMI* left ventricle mass index, *LVEF* left ventricle ejection fraction, *R* Pearson's correlation coefficient

A $p<0.05$ (two tailed) was considered statistical significant

the standard normal distribution (*Z*) (Table 4). Age-specific 1th, 2.5th, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97.5th and 99th percentile curves were calculated as (for instance) mean LVM + Z_p * SD, where *Z*p assumed the values of − 2.3263, − 1.9599, − 1.6448, − 1.2815, − 0.6755, 0, 0.6755, 1.2815, 1.6448, 1.9599, and 2.3263, respectively.

The minimum required sample size for RIs construction was 377 subjects [27]. As in previous works and according to the central limit theorem, a normal distribution was considered (considering the Kurtosis and Skewness coefficients distribution and sample size >30) [28].

Data analysis was done using MedCalc-Statistical Software (version/14.8.1., MedCalc Inc., Ostend, Belgium) and IBM-SPSS Software (SPSS Inc., Illinois, USA). A $p<0.05$ was considered statistically significant.

Results

General Characteristics of the Analyzed Population

In this research a cohort of 1095 healthy children and adolescents (683 males, 412 females) was analyzed (Table 1).

Reference intervals: discriminant analysis by sex

Table 2 shows demographic, anthropometric, blood and hemodynamic variables potentially associated with values of LVM, LVMIs, LVEF, and LVRWT. This allowed to individualize co-factors to be included in the ANCOVA. There was a significant positive association between LVM and LVMIs (LVMI, $LVMI^{2.7}$) and age, male gender, body weight, body height, BSA, and BMI (Table 2).

Table 3 show the sex-related analysis of covariance (ANCOVA) adjusting by age, BSA, total cholesterol, and/or hematocrit, destined to determine if the sex discrimination would be necessary in the RIs of LVM, LVMI, $LVMI^{2.7}$, LVRWT, and LVEF generation. Although it is important to know that associations were found between LVM or LVMI and BP and/or heart rate levels, these variables were not used as co-factors in the ANCOVA, since the differences in these variables between boys and girls of similar age are a physiological aspect that should not be "eliminated" statistically (they should not be considered as "confusing" variables).

Although the adjusted mean values of LVRWT were similar in males and females, the sex-related differences in the variance values (Levene's test $p=0.009$) and age-related slopes (Heterogeneity of slopes' test at the limit of the significance, $p=0.065$) indicate that sex-related RIs are necessary in order to carry out a robust, accurate, and meticulous statistical analysis (Table 3). The analysis of LVM, LVMI, $LVMI^{2.7}$ and LVEF shows that, after adjusting for covariates, males and females presented differences in their mean values ($p<0.05$). Consequently, for each of these variables, RIs is necessary according to sex. Furthermore, in the case of LVM and LVMI the results show sex differences not only the mean values but also show differences in the variance (Levene´s Test) and in the changes with age (slope of the relationship LVM and LVMI vs. age; Heterogeneity of slopes' test) reinforcing the need to report sex-related RIs. In summary, according to results derived from data shown in Tables 2 and 3, we opted to do sex-related RIs for all included variables: LVM, LVMI, LVEF, and LVRWT.

Equations of Mean Value and Standard Deviation According to Age for LVM, LVMIs, LVRWT, and LVEF: Basis for the Calculation of Individual *z*-Scores

After applying the described methodology (fractional polynomials), equations were obtained (see *supplementary material*). Using these equations, it is possible to quantify the mean value and SD expected for a certain age, and consequently quantify the *z*-score of a child in particular as: [*z*-score = (observed value-expected mean)/SD]. This allows AQ4 any researcher or professional to quantify the *z*-score for a particular child, as a way to evaluate how far it moves away (SD units) from the expected value for their own age and sex. For example, based on the following equations (see *supplementary material*):

(1) Log LVMI (g/m2.7) Mean = 1.6892 − 0.3650 Log(Age) + 0.01179 Age
(2) Log LVMI (g/m2.7) SD = 0.2723–0.2993 Log(Age) + 0.01049 Age

For a 12 year-old girl where the LVMI mean (expected) and standard deviation are 27.3 $g/m^{2.7}$ and 4.7 $g/m^{2.7}$, the *z*-score of a LVMI of 42.0 $g/m^{2.7}$ is: 3.8 (*z*-score or standard deviation units).

LVM, LVMI, LVEF, and LVRWT: Age and Sex-Related Reference Intervals

The mean value of LVM was 121.13 ± 37.71 g. LVM percentiles corresponding to 5 year age intervals were generated for females and males (Table 4). A similar analysis was done for each year of age (bi-monthly information from 5 to 24 years old) (Table S2 and Table S3; see *supplementary material*). Figure 1a and b show the LVM-age percentiles for females and males, respectively.

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Table 3 Sex-related analysis of covariance (ANCOVA) adjusting by age, body surface area, and others co-factors

Dependent variable	After adjustment by covariates				p	R^2-adjusted	Levene's test	Heterogeneity of slopes' test	Dependent and covariates values				Hematocrit (%)
	n	MV	SE	95% CI			(p value)	(p value)	Dependent	Age (years)	BSA (m^2)	Total cholesterol (mg/dl)	
LVRWT													
Male	683	0.300	0.00	0.298–0.303	0.4805	0.069	**0.009**	0.065	0.301	15.53	1.64	–	–
Female	412	0.302	0.00	0.299–0.306									
LVM (g)													
Male	683	130.78	0.82	129.18–132.37	< **0.0001**	0.677	< **0.001**	**0.001**	123.947	15.90	1.68	157.76	–
Female	412	112.47	1.09	110.34–114.61									
LVMI (g/m^2)													
Male	683	77.16	0.48	76.21–78.10	< **0.0001**	0.320	**0.003**	**0.020**	73.063	15.90	1.68	157.76	–
Female	412	66.18	0.64	64.92–67.44									–
LVMI ($g/m^{2.7}$)													
Male	683	32.58	0.23	32.12–33.04	< **0.0001**	0.133	0.119	0.157	31.091	15.53	1.64	–	–
Female	412	28.62	0.31	28.015–29.23									
LVEF (%)													
Male	683	64.99	0.12	64.75–65.23	**0.0121**	0.013	0.282	0.802	64.802	15.90	–	–	40.80
Female	412	64.49	0.16	64.18–64.80									

n number of subjects, *MV* mean value, *SE* standard error, *C.I.* Confidence interval, *BSA* body surface area, *LVRWT* left ventricle relative wall thickness ratio, *LVM* left ventricle mass, *LVMI* left ventricle mass index

A $p < 0.05$ was considered statistically significant

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Table 4 Age-related reference intervals for left ventricular mass (LVM, g), LVM indexes (LVMI, g/m^2; LVMI, g/m$^{2.7}$); left ventricular ejection fraction (LVEF, %) and relative wall thickness (RWT) in (a) females (*n*: 412), (b) males (*n*: 683)

Age (years)	Variable	1th	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
(a) Females (*n*: 412)												
5 (*n*: 20)	LVM	25.41	26.79	28.04	29.55	32.26	35.56	39.21	42.80	45.11	47.21	49.78
	LVMI	37.61	39.38	40.96	42.87	46.26	50.35	54.81	59.14	61.89	64.39	67.42
	LVMI$^{2.7}$	16.76	18.48	20.09	22.13	26.00	31.12	37.24	43.75	48.19	52.40	57.76
	LVEF	60.99	62.15	63.18	64.38	66.43	68.79	71.24	73.51	74.91	76.14	77.59
	RWT	0.22	0.23	0.23	0.24	0.25	0.26	0.27	0.28	0.29	0.29	0.30
6 (*n*: 20)	LVM	30.84	32.66	34.31	36.31	39.91	44.36	49.29	54.18	57.35	60.24	63.79
	LVMI	38.54	40.49	42.25	44.36	48.14	52.73	57.75	62.66	65.81	68.66	72.14
	LVMI$^{2.7}$	17.30	18.86	20.31	22.12	25.52	29.92	35.07	40.45	44.07	47.46	51.74
	LVEF	60.17	61.32	62.33	63.51	65.52	67.85	70.25	72.48	73.85	75.06	76.49
	RWT	0.22	0.23	0.23	0.24	0.25	0.26	0.28	0.29	0.30	0.31	0.31
7 (*n*: 20)	LVM	35.92	38.17	40.21	42.71	47.22	52.82	59.07	65.32	69.37	73.09	77.67
	LVMI	39.32	41.42	43.31	45.61	49.71	54.71	60.22	65.63	69.11	72.27	76.13
	LVMI$^{2.7}$	17.68	19.12	20.45	22.10	25.16	29.06	33.56	38.20	41.28	44.15	47.75
	LVEF	59.57	60.70	61.68	62.84	64.82	67.10	69.47	71.65	73.00	74.19	75.59
	RWT	0.22	0.23	0.24	0.24	0.26	0.27	0.29	0.30	0.31	0.32	0.33
8 (*n*: 20)	LVM	40.58	43.25	45.68	48.66	54.06	60.80	68.37	75.96	80.91	85.47	91.08
	LVMI	39.98	42.21	44.22	46.66	51.03	56.39	62.32	68.16	71.92	75.34	79.54
	LVMI$^{2.7}$	17.96	19.30	20.54	22.07	24.88	28.44	32.50	36.63	39.36	41.89	45.04
	LVEF	59.11	60.22	61.19	62.33	64.27	66.51	68.82	70.97	72.29	73.45	74.83
	RWT	0.22	0.23	0.24	0.24	0.26	0.27	0.29	0.31	0.32	0.33	0.34
9 (*n*: 20)	LVM	44.80	47.87	50.67	54.11	60.36	68.20	77.04	85.96	91.78	97.16	103.81
	LVMI	40.56	42.89	45.00	47.57	52.17	57.83	64.11	70.32	74.32	77.98	82.46
	LVMI$^{2.7}$	18.14	19.42	20.59	22.04	24.68	27.99	31.75	35.55	38.04	40.34	43.20
	LVEF	58.77	59.85	60.80	61.92	63.83	66.02	68.29	70.40	71.69	72.83	74.17
	RWT	0.22	0.23	0.24	0.25	0.26	0.28	0.30	0.32	0.33	0.34	0.35
10 (*n*: 20)	LVM	48.57	52.00	55.15	59.02	66.08	74.95	85.01	95.18	101.86	108.02	115.66
	LVMI	41.06	43.48	45.68	48.35	53.15	59.07	65.65	72.17	76.39	80.25	84.98
	LVMI$^{2.7}$	18.24	19.48	20.61	22.00	24.52	27.67	31.24	34.82	37.16	39.32	41.98
	LVEF	58.51	59.57	60.51	61.60	63.47	65.62	67.85	69.91	71.17	72.28	73.60
	RWT	0.22	0.23	0.24	0.25	0.26	0.28	0.30	0.32	0.33	0.34	0.36
11 (*n*: 20)	LVM	51.88	55.65	59.12	63.38	71.18	81.02	92.22	103.58	111.05	117.96	126.54
	LVMI	41.51	44.00	46.27	49.03	54.00	60.14	66.98	73.77	78.17	82.20	87.14
	LVMI$^{2.7}$	18.29	19.50	20.60	21.95	24.41	27.46	30.91	34.36	36.61	38.68	41.24
	LVEF	58.32	59.36	60.28	61.35	63.18	65.29	67.47	69.48	70.72	71.81	73.10
	RWT	0.22	0.23	0.24	0.25	0.27	0.29	0.31	0.33	0.34	0.35	0.36
12 (*n*: 21)	LVM	54.74	58.82	62.57	67.20	75.68	86.40	98.64	111.10	119.30	126.91	136.37
	LVMI	41.90	44.46	46.79	49.62	54.74	61.07	68.12	75.15	79.70	83.87	89.00
	LVMI$^{2.7}$	18.29	19.48	20.57	21.91	24.32	27.34	30.72	34.12	36.33	38.36	40.87
	LVEF	58.18	59.21	60.11	61.16	62.95	65.01	67.14	69.12	70.32	71.39	72.65
	RWT	0.23	0.23	0.24	0.25	0.27	0.29	0.31	0.33	0.34	0.36	0.37
13 (*n*: 20)	LVM	57.18	61.53	65.54	70.48	79.57	91.09	104.27	117.72	126.60	134.84	145.11
	LVMI	42.25	44.87	47.25	50.14	55.38	61.87	69.11	76.33	81.01	85.30	90.58
	LVMI$^{2.7}$	18.24	19.43	20.52	21.85	24.27	27.28	30.66	34.06	36.27	38.30	40.80
	LVEF	58.10	59.10	59.98	61.01	62.77	64.79	66.87	68.79	69.97	71.02	72.24
	RWT	0.23	0.24	0.24	0.25	0.27	0.29	0.31	0.34	0.35	0.36	0.38

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Table 4 (continued)

Age (years)	Variable	1th	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
14 (*n*: 21)	LVM	59.20	63.79	68.02	73.25	82.87	95.10	109.13	123.46	132.95	141.76	152.75
	LVMI	42.57	45.23	47.65	50.60	55.94	62.56	69.95	77.33	82.13	86.52	91.93
	$LVMI^{2.7}$	18.16	19.36	20.46	21.80	24.24	27.28	30.71	34.14	36.39	38.45	41.00
	LVEF	58.05	59.03	59.90	60.90	62.62	64.60	66.63	68.51	69.66	70.68	71.88
	RWT	0.23	0.24	0.25	0.26	0.27	0.30	0.32	0.34	0.35	0.37	0.38
15 (*n*: 20)	LVM	60.84	65.63	70.06	75.52	85.61	98.45	113.22	128.34	138.36	147.68	159.31
	LVMI	42.85	45.55	48.00	51.00	56.42	63.15	70.68	78.19	83.07	87.55	93.07
	$LVMI^{2.7}$	18.05	19.27	20.38	21.75	24.23	27.34	30.84	34.37	36.67	38.79	41.41
	LVEF	58.04	59.00	59.84	60.83	62.51	64.44	66.43	68.26	69.39	70.38	71.55
	RWT	0.23	0.24	0.25	0.26	0.28	0.30	0.32	0.34	0.36	0.37	0.38
16 (*n*: 21)	LVM	62.12	67.08	71.66	77.34	87.82	101.18	116.58	132.38	142.86	152.62	164.80
	LVMI	43.10	45.83	48.32	51.35	56.84	63.66	71.29	78.91	83.86	88.41	94.01
	$LVMI^{2.7}$	17.91	19.15	20.29	21.69	24.24	27.44	31.05	34.70	37.09	39.30	42.03
	LVEF	58.06	59.00	59.82	60.79	62.43	64.31	66.25	68.04	69.14	70.10	71.24
	RWT	0.23	0.24	0.25	0.26	0.28	0.30	0.32	0.35	0.36	0.37	0.39
17 (*n*: 21)	LVM	63.06	68.16	72.87	78.72	89.52	103.32	119.25	135.62	146.49	156.62	169.28
	LVMI	43.33	46.08	48.59	51.66	57.20	64.09	71.80	79.51	84.52	89.12	94.79
	$LVMI^{2.7}$	17.75	19.03	20.19	21.63	24.26	27.57	31.34	35.15	37.65	39.96	42.84
	LVEF	58.10	59.02	59.83	60.77	62.37	64.21	66.10	67.85	68.91	69.85	70.96
	RWT	0.23	0.24	0.25	0.26	0.28	0.30	0.33	0.35	0.36	0.38	0.39
18 (*n*: 20)	LVM	63.69	68.90	73.72	79.69	90.75	104.91	121.26	138.10	149.29	159.73	172.79
	LVMI	43.53	46.31	48.84	51.92	57.51	64.45	72.22	79.99	85.05	89.69	95.41
	$LVMI^{2.7}$	17.57	18.88	20.09	21.57	24.30	27.75	31.68	35.69	38.33	40.77	43.82
	LVEF	58.17	59.07	59.86	60.78	62.34	64.13	65.98	67.67	68.71	69.63	70.70
	RWT	0.24	0.25	0.25	0.27	0.28	0.30	0.33	0.35	0.36	0.38	0.39
19 (*n*: 20)	LVM	64.03	69.32	74.22	80.29	91.55	105.98	122.67	139.87	151.32	162.01	175.39
	LVMI	43.72	46.51	49.05	52.15	57.77	64.75	72.56	80.38	85.46	90.13	95.88
	$LVMI^{2.7}$	17.38	18.73	19.97	21.51	24.35	27.95	32.09	36.32	39.12	41.72	44.97
	LVEF	58.26	59.14	59.91	60.80	62.33	64.07	65.87	67.52	68.53	69.42	70.47
	RWT	0.24	0.25	0.26	0.27	0.29	0.31	0.33	0.35	0.37	0.38	0.40
20 (*n*: 21)	LVM	64.12	69.46	74.41	80.55	91.95	106.57	123.51	140.99	152.63	163.50	177.12
	LVMI	43.89	46.68	49.23	52.35	57.98	64.99	72.83	80.68	85.78	90.46	96.23
	$LVMI^{2.7}$	17.17	18.56	19.85	21.45	24.41	28.19	32.56	37.05	40.03	42.81	46.29
	LVEF	58.37	59.23	59.97	60.85	62.33	64.03	65.78	67.38	68.37	69.23	70.25
	RWT	0.24	0.25	0.26	0.27	0.29	0.31	0.33	0.35	0.37	0.38	0.40
21 (*n*: 20)	LVM	63.97	69.34	74.32	80.50	91.99	106.73	123.83	141.49	153.27	164.27	178.06
	LVMI	44.03	46.84	49.40	52.51	58.16	65.18	73.04	80.89	86.00	90.69	96.47
	$LVMI^{2.7}$	16.95	18.39	19.73	21.39	24.48	28.46	33.07	37.85	41.04	44.03	47.77
	LVEF	58.49	59.33	60.06	60.91	62.36	64.01	65.70	67.26	68.22	69.05	70.04
	RWT	0.24	0.25	0.26	0.27	0.29	0.31	0.33	0.36	0.37	0.38	0.40
22 (*n*: 20)	LVM	63.61	68.98	73.97	80.17	91.69	106.49	123.67	141.44	153.30	164.38	178.27
	LVMI	44.17	46.98	49.53	52.65	58.30	65.32	73.18	81.03	86.13	90.82	96.59
	$LVMI^{2.7}$	16.72	18.21	19.60	21.33	24.56	28.75	33.64	38.74	42.17	45.38	49.42
	LVEF	58.64	59.45	60.16	60.99	62.39	64.00	65.64	67.16	68.08	68.89	69.85
	RWT	0.25	0.26	0.26	0.27	0.29	0.31	0.34	0.36	0.37	0.38	0.40
23 (*n*: 20)	LVM	63.05	68.42	73.39	79.58	91.09	105.89	123.09	140.88	152.76	163.87	177.81
	LVMI	44.29	47.10	49.65	52.77	58.41	65.42	73.26	81.10	86.19	90.87	96.62
	$LVMI^{2.7}$	16.48	18.02	19.46	21.26	24.65	29.06	34.26	39.72	43.39	46.86	51.24
	LVEF	58.79	59.58	60.27	61.08	62.44	64.00	65.60	67.07	67.96	68.75	69.67
	RWT	0.25	0.26	0.27	0.28	0.29	0.31	0.34	0.36	0.37	0.38	0.40

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Table 4 (continued)

Age (years)	Variable	1th	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
24 (*n*: 21)	LVM	62.33	67.66	72.61	78.77	90.22	104.96	122.11	139.87	151.72	162.82	176.75
	LVMI	44.40	47.20	49.75	52.86	58.49	65.48	73.30	81.10	86.17	90.83	96.56
	$LVMI^{2.7}$	16.24	17.83	19.32	21.20	24.75	29.40	34.93	40.77	44.73	48.48	53.23
	LVEF	58.96	59.73	60.40	61.18	62.51	64.02	65.56	66.98	67.85	68.61	69.51
	RWT	0.25	0.26	0.27	0.28	0.30	0.32	0.34	0.36	0.37	0.39	0.40
(b) Males (*n*: 683)												
5 (*n*: 22)	LVM	15.91	17.95	19.91	22.43	27.38	34.19	42.69	52.11	58.72	65.13	73.47
	LVMI	29.15	31.85	34.38	37.53	43.46	51.18	60.26	69.77	76.18	82.22	89.84
	$LVMI^{2.7}$	18.86	20.55	22.13	24.10	27.78	32.54	38.13	43.95	47.86	51.53	56.15
	LVEF	61.18	62.15	62.99	63.98	65.67	67.60	69.58	71.41	72.54	73.52	74.69
	RWT	0.20	0.21	0.22	0.23	0.25	0.27	0.29	0.32	0.33	0.34	0.36
6 (*n*: 22)	LVM	22.03	24.60	27.06	30.19	36.26	44.46	54.51	65.46	73.05	80.34	89.73
	LVMI	32.76	35.53	38.09	41.28	47.20	54.80	63.62	72.75	78.83	84.52	91.65
	$LVMI^{2.7}$	19.25	20.82	22.28	24.08	27.41	31.67	36.59	41.66	45.02	48.16	52.09
	LVEF	60.37	61.39	62.29	63.33	65.12	67.17	69.29	71.25	72.44	73.50	74.75
	RWT	0.21	0.22	0.22	0.23	0.25	0.27	0.30	0.32	0.34	0.35	0.37
7 (*n*: 24)	LVM	28.60	31.71	34.64	38.36	45.48	54.98	66.47	78.80	87.27	95.34	105.68
	LVMI	36.00	38.81	41.40	44.61	50.51	58.02	66.65	75.48	81.32	86.76	93.53
	$LVMI^{2.7}$	19.60	21.08	22.44	24.12	27.21	31.12	35.59	40.14	43.15	45.94	49.41
	LVEF	59.76	60.82	61.75	62.83	64.69	66.82	69.02	71.06	72.31	73.41	74.71
	RWT	0.21	0.22	0.23	0.24	0.26	0.28	0.30	0.33	0.34	0.35	0.37
8 (*n*: 23)	LVM	35.45	39.06	42.45	46.72	54.83	65.55	78.35	91.95	101.22	110.00	121.18
	LVMI	38.90	41.75	44.37	47.59	53.50	60.94	69.43	78.04	83.71	88.96	95.48
	$LVMI^{2.7}$	19.89	21.31	22.61	24.21	27.12	30.79	34.95	39.16	41.93	44.48	47.65
	LVEF	59.30	60.38	61.33	62.44	64.33	66.51	68.76	70.85	72.13	73.26	74.60
	RWT	0.21	0.22	0.23	0.24	0.26	0.28	0.31	0.33	0.34	0.36	0.37
9 (*n*: 24)	LVM	42.40	46.48	50.30	55.10	64.14	75.98	90.01	104.78	114.77	124.21	136.16
	LVMI	41.51	44.40	47.04	50.28	56.20	63.61	72.01	80.48	86.02	91.14	97.48
	$LVMI^{2.7}$	20.16	21.54	22.79	24.33	27.13	30.63	34.58	38.56	41.16	43.56	46.53
	LVEF	58.95	60.04	61.00	62.12	64.03	66.24	68.52	70.63	71.93	73.08	74.43
	RWT	0.22	0.23	0.24	0.25	0.26	0.29	0.31	0.33	0.35	0.36	0.37
10 (*n*: 23)	LVM	49.30	53.83	58.06	63.35	73.27	86.16	101.32	117.17	127.85	137.89	150.56
	LVMI	43.85	46.78	49.45	52.72	58.66	66.07	74.42	82.81	88.28	93.32	99.54
	$LVMI^{2.7}$	20.41	21.75	22.98	24.48	27.20	30.60	34.42	38.25	40.75	43.05	45.88
	LVEF	58.68	59.78	60.74	61.86	63.78	66.00	68.29	70.41	71.71	72.86	74.22
	RWT	0.22	0.23	0.24	0.25	0.27	0.29	0.31	0.33	0.35	0.36	0.38
11 (*n*: 25)	LVM	56.04	60.99	65.60	71.35	82.09	95.96	112.18	129.06	140.37	150.98	164.33
	LVMI	45.96	48.92	51.63	54.93	60.91	68.35	76.70	85.06	90.50	95.50	101.66
	$LVMI^{2.7}$	20.63	21.96	23.17	24.65	27.34	30.67	34.42	38.17	40.61	42.85	45.61
	LVEF	58.48	59.58	60.53	61.65	63.57	65.78	68.06	70.17	71.47	72.62	73.98
	RWT	0.23	0.24	0.24	0.25	0.27	0.29	0.31	0.34	0.35	0.36	0.38
12 (*n*: 27)	LVM	62.51	67.86	72.83	79.01	90.51	105.32	122.54	140.38	152.30	163.45	177.44
	LVMI	47.84	50.85	53.59	56.94	62.98	70.48	78.88	87.25	92.70	97.69	103.84
	$LVMI^{2.7}$	20.83	22.16	23.37	24.85	27.52	30.84	34.56	38.27	40.69	42.91	45.64
	LVEF	58.34	59.43	60.37	61.49	63.39	65.57	67.84	69.94	71.22	72.36	73.70
	RWT	0.23	0.24	0.25	0.26	0.27	0.29	0.32	0.34	0.35	0.36	0.38

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Table 4 (continued)

Age (years)	Variable	1th	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
13 (*n*: 32)	LVM	68.63	74.36	79.66	86.25	98.48	114.16	132.33	151.09	163.59	175.26	189.89
	LVMI	49.52	52.59	55.37	58.76	64.89	72.48	80.95	89.40	94.87	99.90	106.07
	LVMI$^{2.7}$	21.02	22.36	23.57	25.06	27.74	31.07	34.81	38.54	40.96	43.19	45.93
	LVEF	58.25	59.32	60.25	61.35	63.23	65.39	67.62	69.69	70.96	72.08	73.41
	RWT	0.23	0.24	0.25	0.26	0.28	0.30	0.32	0.34	0.35	0.36	0.38
14 (*n*: 36)	LVM	74.34	80.42	86.04	93.02	105.93	122.44	141.53	161.17	174.23	186.42	201.66
	LVMI	51.02	54.14	56.97	60.42	66.65	74.36	82.95	91.50	97.04	102.12	108.36
	LVMI$^{2.7}$	21.20	22.55	23.78	25.28	28.00	31.38	35.16	38.94	41.40	43.65	46.43
	LVEF	58.19	59.25	60.17	61.25	63.10	65.22	67.41	69.45	70.69	71.79	73.09
	RWT	0.24	0.25	0.25	0.26	0.28	0.30	0.32	0.34	0.35	0.36	0.38
15 (*n*: 54)	LVM	79.61	86.01	91.93	99.27	112.83	130.14	150.10	170.60	184.21	196.89	212.74
	LVMI	52.35	55.53	58.42	61.94	68.28	76.13	84.87	93.57	99.20	104.36	110.70
	LVMI$^{2.7}$	21.37	22.74	23.99	25.52	28.29	31.74	35.60	39.46	41.98	44.29	47.14
	LVEF	58.17	59.21	60.11	61.17	62.98	65.06	67.21	69.20	70.42	71.49	72.76
	RWT	0.24	0.25	0.26	0.26	0.28	0.30	0.32	0.34	0.35	0.36	0.38
16 (*n*: 60)	LVM	84.38	91.10	97.30	104.98	119.16	137.22	158.03	179.37	193.52	206.70	223.15
	LVMI	53.52	56.77	59.72	63.31	69.79	77.80	86.73	95.61	101.37	106.63	113.11
	LVMI$^{2.7}$	21.53	22.93	24.21	25.78	28.61	32.15	36.12	40.10	42.69	45.08	48.02
	LVEF	58.18	59.19	60.08	61.11	62.88	64.91	67.01	68.94	70.13	71.18	72.42
	RWT	0.24	0.25	0.26	0.27	0.28	0.30	0.32	0.34	0.35	0.36	0.38
17 (*n*: 56)	LVM	88.66	95.67	102.13	110.13	124.89	143.69	165.32	187.48	202.17	215.83	232.88
	LVMI	54.54	57.87	60.88	64.56	71.19	79.39	88.54	97.64	103.53	108.93	115.57
	LVMI$^{2.7}$	21.67	23.11	24.43	26.04	28.96	32.61	36.72	40.84	43.54	46.01	49.07
	LVEF	58.22	59.20	60.06	61.07	62.79	64.77	66.81	68.69	69.84	70.86	72.06
	RWT	0.24	0.25	0.26	0.27	0.28	0.30	0.32	0.34	0.35	0.36	0.38
18 (*n*: 50)	LVM	92.42	99.70	106.42	114.72	130.04	149.54	171.97	194.93	210.15	224.30	241.96
	LVMI	55.43	58.83	61.93	65.69	72.49	80.91	90.29	99.64	105.70	111.26	118.09
	LVMI$^{2.7}$	21.82	23.30	24.65	26.31	29.34	33.12	37.39	41.69	44.49	47.08	50.28
	LVEF	58.27	59.23	60.07	61.05	62.72	64.64	66.61	68.43	69.55	70.53	71.69
	RWT	0.25	0.26	0.26	0.27	0.29	0.30	0.32	0.34	0.35	0.36	0.37
19 (*n*: 38)	LVM	95.67	103.20	110.15	118.75	134.60	154.77	177.98	201.74	217.47	232.12	250.38
	LVMI	56.20	59.68	62.85	66.72	73.70	82.35	92.01	101.64	107.89	113.62	120.66
	LVMI$^{2.7}$	21.95	23.48	24.88	26.60	29.74	33.67	38.13	42.62	45.57	48.29	51.65
	LVEF	58.35	59.28	60.09	61.04	62.66	64.51	66.42	68.18	69.25	70.20	71.32
	RWT	0.25	0.26	0.27	0.27	0.29	0.31	0.32	0.34	0.35	0.36	0.37
20 (*n*: 40)	LVM	98.42	106.18	113.35	122.22	138.58	159.40	183.36	207.90	224.16	239.29	258.17
	LVMI	56.84	60.42	63.67	67.64	74.82	83.72	93.68	103.62	110.08	116.01	123.30
	LVMI$^{2.7}$	22.08	23.66	25.11	26.90	30.16	34.26	38.93	43.65	46.75	49.62	53.18
	LVEF	58.45	59.35	60.13	61.05	62.61	64.39	66.23	67.92	68.95	69.86	70.94
	RWT	0.25	0.26	0.27	0.28	0.29	0.31	0.32	0.34	0.35	0.36	0.37
21 (*n*: 37)	LVM	100.67	108.65	116.02	125.15	141.99	163.44	188.13	213.45	230.23	245.85	265.35
	LVMI	57.38	61.05	64.39	68.47	75.86	85.03	95.32	105.60	112.29	118.44	126.00
	LVMI$^{2.7}$	22.20	23.84	25.35	27.20	30.60	34.90	39.80	44.77	48.05	51.09	54.86
	LVEF	58.56	59.43	60.18	61.06	62.56	64.28	66.04	67.66	68.65	69.52	70.55
	RWT	0.26	0.26	0.27	0.28	0.29	0.31	0.33	0.34	0.35	0.36	0.37
22 (*n*: 29)	LVM	102.44	110.63	118.19	127.55	144.85	166.90	192.32	218.40	235.69	251.80	271.92
	LVMI	57.82	61.58	65.02	69.21	76.82	86.29	96.92	107.58	114.52	120.90	128.77
	LVMI$^{2.7}$	22.32	24.02	25.58	27.52	31.07	35.57	40.73	45.98	49.46	52.68	56.69
	LVEF	58.69	59.52	60.25	61.09	62.53	64.17	65.85	67.40	68.34	69.17	70.15
	RWT	0.26	0.27	0.27	0.28	0.29	0.31	0.33	0.34	0.35	0.36	0.37

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Table 4 (continued)

Age (years)	Variable	1th	2.5th	5th	10th	25th	50th	75th	90th	95th	97.5th	99th
23 (*n*: 30)	LVM	103.76	112.13	119.87	129.45	147.18	169.81	195.93	222.76	240.57	257.17	277.92
	LVMI	58.17	62.03	65.55	69.87	77.71	87.49	98.50	109.55	116.76	123.40	131.60
	$LVMI^{2.7}$	22.43	24.20	25.82	27.84	31.55	36.28	41.72	47.29	50.97	54.40	58.69
	LVEF	58.84	59.63	60.32	61.13	62.50	64.06	65.67	67.14	68.04	68.82	69.75
	RWT	0.26	0.27	0.27	0.28	0.29	0.31	0.33	0.34	0.35	0.36	0.37
24 (*n*: 31)	LVM	104.64	113.18	121.08	130.88	149.01	172.20	198.99	226.56	244.88	261.98	283.35
	LVMI	58.42	62.39	66.01	70.45	78.54	88.64	100.05	111.53	119.03	125.94	134.49
	$LVMI^{2.7}$	22.54	24.37	26.07	28.17	32.06	37.03	42.77	48.68	52.60	56.26	60.84
	LVEF	59.00	59.75	60.41	61.18	62.48	63.96	65.48	66.88	67.73	68.47	69.35
	RWT	0.26	0.27	0.28	0.28	0.30	0.31	0.33	0.34	0.35	0.36	0.37

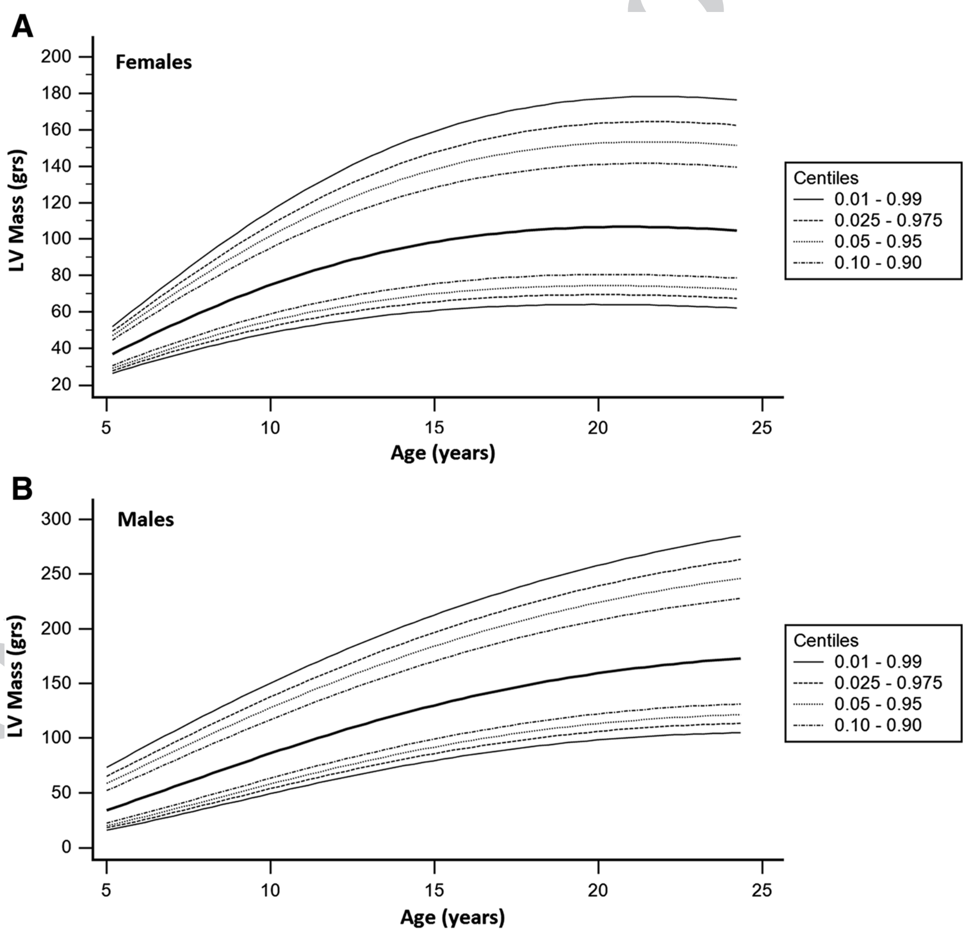
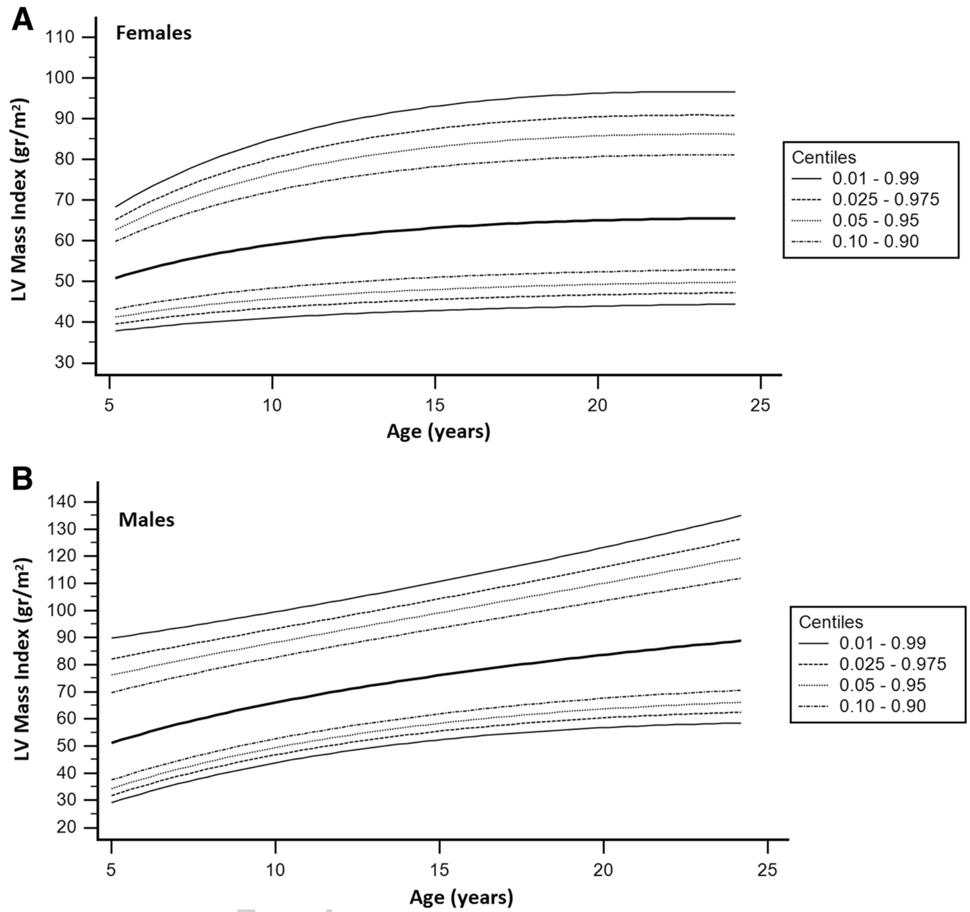


Fig. 1 Age-specific percentiles of left ventricular mass (g) in females (**a**) and males (**b**)

When LVM was indexed according BSA and height$^{2.7}$ the values were 72.44 ± 14.57 g/m^2 and 31.09 ± 6.34 g/m$^{2.7}$. Even corrected by BSA and height males presented higher values of LVMI and $LVMI^{2.7}$ (32.81 ± 6.17 and 28.24 ± 5.54, respectively) (Table 1). Age-specific (5 year RIs) percentile analyses for LVMI corresponding to males and females are shown in Table 4. Similarly, in the *supplementary materials*, Tables S4 and S5 show the RIs for LVMI, defined for each year of age. Figure 2a and b show the LVMI-age percentiles for females and males, respectively.

Age-specific (5 year intervals, RIs) percentile analyses for $LVMI^{2.7}$ corresponding to males and females are shown in Table 4. In the *supplementary materials*, Tables S6 and S7 show the RIs for $LVMI^{2.7}$, defined for each year of age. Figure 3a and b show the $LVMI^{2.7}$-age percentiles for females and males, respectively.

Fig. 2 Age-specific percentiles *of left ventricular mass* index (g/m^2) in females (**a**) and males (**b**)



LVEF percentiles corresponding to 5 year age intervals were generated for females and males (Table 4). A similar analysis was done for each year of age (from 5 to 24 years old), as seen in Tables S8 and S9 for females and males, respectively (*supplementary material*). Figure 4a and b show the LVEF-age percentiles for females and males, respectively.

Finally, LVRWT percentiles corresponding to 5 year age intervals were generated (Table 4). A similar analysis was done for each year of age (from 5 to 24 years old), as seen in Tables S10 and S11 (*supplementary material*). Figure 5a and b show the LVRWT age percentiles for females and males, respectively.

Discussion

To our knowledge, this study represent the first South-American registry concerns the RIs and percentile curves of LVM (and derived indexes), LVRWT and LVEF in healthy children and adolescents (5–24 years old) obtained from a population-based study. From our study the most relevant findings are as follows:

First, *in children and adolescents, the elaboration of RIs for the main recommended parameters for the assessment of LV geometry, LV function and TOI requires the consideration of sex-specific tables and percentile curves*, since in general terms, for equal age, boys have higher levels of LVM (grs), LVMI (g/m^2), LVMI (gr/m$^{2.7}$) and LVEF than girls (Table 3).

In this regard, although previous studies have clearly shown that the levels of LVM, LVMI vary between boys and girls [14], there are different publications in which single cut points are proposed without considering sex differences [7] or studies in which sex has not been considered when analyzing these parameters as indicators of LVH in children and adolescents [29]. There have been numerous studies showing the relationship between gender and LVM. These data show that females have a lower prevalence of LVH than men for any given level of BP [30]. Goble et al. reported that in pre-adolescent children, LVM is directly related to weight and male sex and inversely related to resting heart rate and body fat, and suggest that body size, and in particular lean body mass, explains much of the variability in cardiac growth seen in children [31]. Existing studies show controversial results with respect to sex-related differences in LVM corrected by the lean body mass [15, 32]. Considering the lack

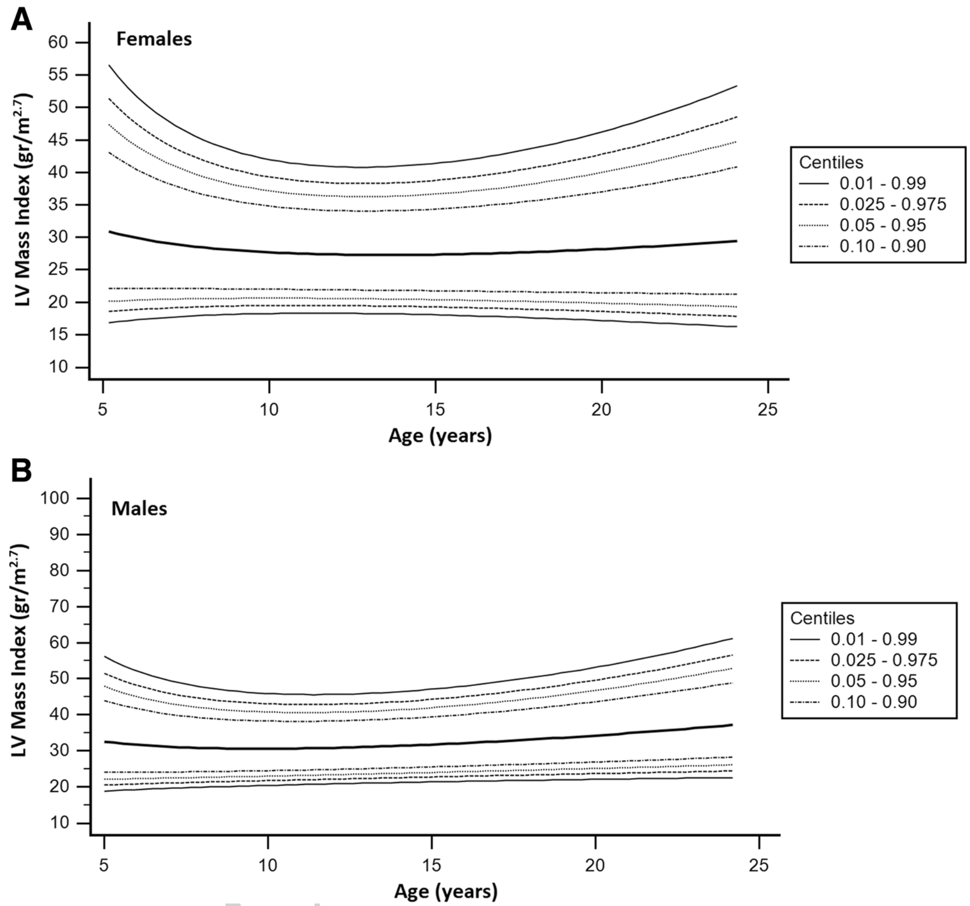


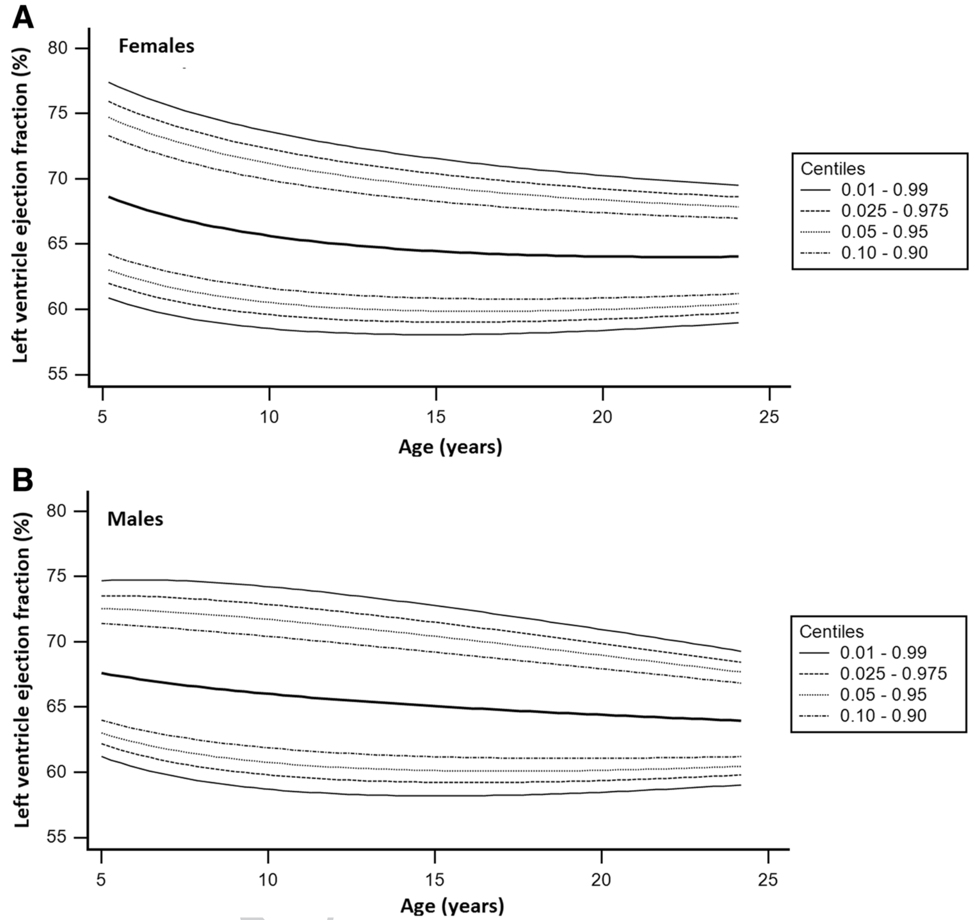
Fig. 3 Age-specific percentiles of left ventricular mass index (gs/m$^{2.7}$) in females (**a**) and males (**b**)

of a definitive answer to the question of whether the relation between lean body mass and LVM differs by sex, it is prudent to use sex-specific RIs. In Argentina, Escudero et al. reported in young non-hypertensive subjects that the difference in LVM between women and men was partially explained (16%) by sex differences in BP, supporting an early effect of BP on cardiac mass even in the absence of hypertension [33].

Second, *the RIs found for the analyzed South-American population showed a high similarity and a potential complementarity with those previously reported by Khoury et al. in North-American population (2009)*. Similarity, this characteristic is reflected in the shape of the curves with a surprising overlap in the clinically relevant percentiles (95th) for both boys and girls between 5 and 18 years old (Fig. 6). Complementarity, given that the Khoury et al. reports RIs for some ages lower than those reported in this study (0–5 years), while in the present work we report RIs for ages that exceed those reported by Khoury et al. (18–24 years old) [14]. As our results show (Table 4; Fig. 6), even having reached adulthood (18 years old), the values of LVM continue to be age-dependent; therefore requiring age-related RIs even in young adults. On the other hand, note that both the values reported in our study and those reported by Khoury et al. [14] differ significantly with that data reported by Chinali et al. [29] (Fig. 6). Our data have similarities with other studies in terms of mean LVMI [31, 34], and LVMI$^{2.7}$ [14, 15]. However, only the study of Khoury et al. presented the LVMI as sex- and age-related percentiles. These data surge from a retrospective analysis of the database of the Echocardiography Laboratory at Cincinnati Children's Hospital. Since no available database exists in Latin America territory, a comparative analysis with the North-American largest database of LVMI and LVMI$^{2.7}$ [14] was made. As can be seen, LVMI values of the Argentinean population are very similar to those observed in North-American children and adolescents. Moreover, the age-related changes of LVMI$^{2.7}$ showed by both populations are very similar.

Third, *the use of single cut-off point of LVMI$^{2.7}$proposed by Khoury et al.* [14] *in girls and boys over 9 years old (40 and 45 g/m$^{2.7}$, respectively), would underestimate the diagnosis of LVH, given that: (a) those values are closer to our 99th percentile* (Fig. 6)*, (b) the tendency of the percentile levels of LVMI$^{2.7}$ (75th, 90th, 95th, 99th) to increase gradually over 10–12 years, evidences that a fixed cut-off point would be theoretically inappropriate, generating a pattern of age-dependent sub-diagnosis*. In fact, the differences between the 95th of our population and the proposed single

Fig. 4 Age-specific percentiles of left ventricular ejection fraction (%) in females (**a**) and males (**b**)



cut-off points (40 and 45 g/m$^{2.7}$) show variations with age (Fig. 7). In this way, the age for which greater differences are reached (higher sub-estimate of diagnosis of hypertrophy) are 12.8 years in girls (difference of 3.74 g/m$^{2.7}$) and 11.2 years in boys (difference of 4.39 g/m$^{2.7}$). The differences between the 95th percentile and the fixed cut-off point after these ages show a gradual decrease, reaching values similar at 20 years and 18.4 years for females and males, respectively (Fig. 7). Furthermore, if a fixed cut-off point is used for the LVMI$^{2.7}$ of 51 g/m$^{2.7}$, as suggested by the "Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents" [7], it leads to important differences (age-dependent) in the levels of under diagnosis of LVH (Fig. 7). About this, the differences between the 95th percentile in our population and a fixed cut-off value of 51 g/m$^{2.7}$, could reach 14.74 and 10.39 g/m$^{2.7}$, for girls and boys, respectively (reaching these differences at ages of 12.8 and 11.2 years for girls and boys, respectively) (Fig. 7). Additionally, this fixed cut-off point would determine that at lower and higher ages than those reported above, the levels of underestimation of LVH are drastically reduced (Fig. 7). In summary, although a value of LVMI$^{2.7}$ >51 g/m$^{2.7}$ clearly represents a probable case of LVH, the significant distance between this value and the 95th percentile, in addition to the age-dependence of these differences, highlights the need to have other ways of assessing the LVH.

On the other hand, when analyzing our data according to the fixed cut-off points for LVMI (g/m^2) proposed by Flynn et al. (115 g/m^2 for boys, 95 g/m^2 for girls) [7], it is again evident that the differences vary according to age and sex (Table 4). For example, in a teenager with LVMI value in the 95th percentile according to age and sex, the difference with respect to fixed cut-off point gradually decreases with increasing age (in males this difference is 0 when reaching just 22.2 years old) (Table 4).

Fourth, *our study reports for the first time RIs of the variables used for the diagnosis and follow-up of cardiac TOI obtained in a South American population*. In this regard, to date there were no reports of RIs for these echocardiographic variables in populations of our region. Consequently, physicians had to be guided by RIs obtained from populations of other countries with different ethnic composition [14]. In addition to body mass index, ethnicity contributes to differences in prevalence of LVH. A collaborative study of the International Pediatric Hypertension Association found that

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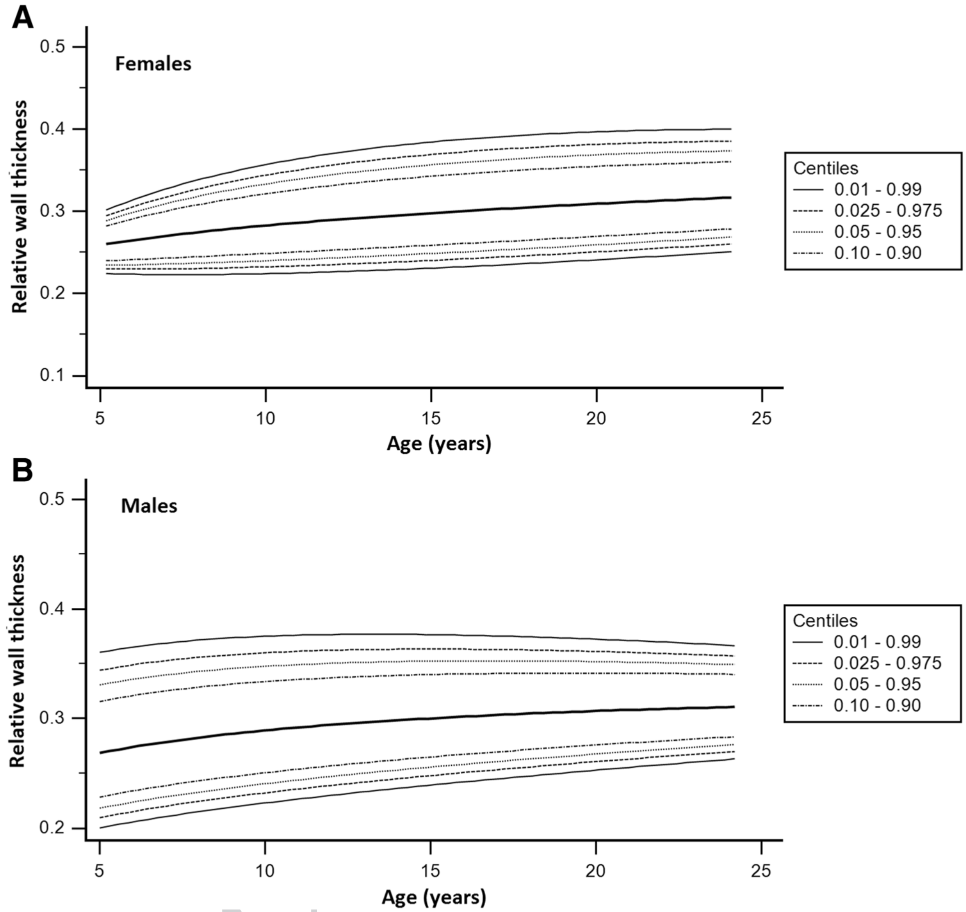

Fig. 5 Age-specific percentiles of left ventricular relative wall thickness in females (**a**) and males (**b**)

LVH and concentric hypertrophy occurred most frequently in hypertensive Hispanic children [35].

The LVRWT allows determining the LV geometry and classification of LV mass increase as either concentric hypertrophy (LVRWT > 0.42) or eccentric hypertrophy (LVRWT ≤ 0.42) [1, 7]. Our data showed that all children and adolescents showed normal LV wall thickness. In this way the average of IVSD and PWD was 7.37 ± 1.04 mm with maximum values of 10 mm. Our values of LVRWT are in accordance with previous works [15, 31, 36].

In our study, subjects presented normal LV function reflected by normal values of LVEF, SV, CO, and E/A ratio (Tables 1, 4, S7 and S8).

Study Limitations

This research used a cross-sectional design; consequently, the age-related changes of LVM (and derived indexes), LVRWT, and LVEF should be interpreted with caution, since it may misestimate the real time-dependent (age-related) change of these markers of TOI of the subjects included in the analyzed population. Although it is difficult, new longitudinal studies are necessary to measure the prognostic impact of cardiac TOI as outcome. In our study protocol, we did not include ethnicity as a study variable. It should be noted that this population has certain characteristics that may not be fully applicable to other races, ethnicities or regions. It can be thought that works of this type would only be of interest to a small portion of the professionals. However, at present, globalization has modified the world population distribution, determining that millions of people do not live in their country of origin and/or that of their parents (i.e., Europeans living in South-America or vice versa). For this reason, it is essential to have information on potential particularities (differentials) that could exist in parameters of cardiovascular structure/function, in native and non-native populations of a given country. In this context, we need works that, by means of precise approaches, allow us to know the cardiovascular characteristics of people with different origins, and very especially to compare populations.

Conclusions

Our data show that in children and adolescents, the interpretation of the LVM (and derived indexes), LVRWT and LVEF RIs requires sex and BSA-related RIs. In particular, the use of single cut-off point of $LVMI^{2.7}$ would

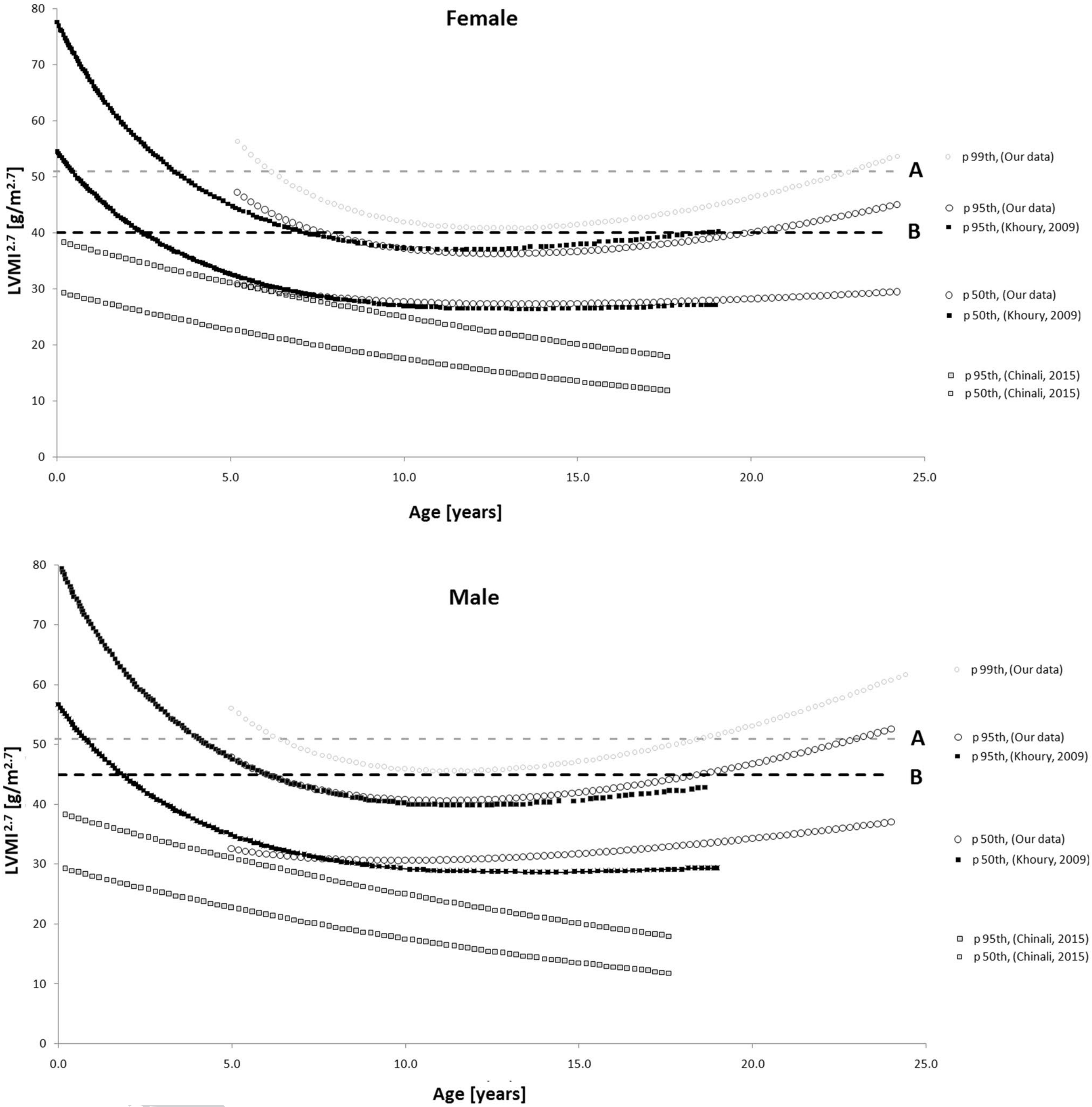

Fig. 6 Age-specific percentiles of left ventricular mass index (LVMI; $g/m^{2.7}$) obtained in our population and those reported from a European [29] and North-American population [14]. 50th, 95th, and 99th percentiles obtained in boys and girls (top and bottom panel, respectively) were represented. Line A: cut-off point to consider severe left ventricular hypertrophy [34]. Line B: threshold to diagnose left ventricular hypertrophy [14, 34]

underestimate the diagnosis of LVH, generating a pattern of age-dependent sub-diagnosis.

This study provides the largest south-american database concerning RIs and percentile curves of LVM, LVRWT, and LVEF as markers of cardiac TOI obtained in healthy children and adolescents non-exposed to CRFs.

Our results show the compatibility of the RIs obtained from our population with those described in the European guidelines. In particular, the RIs found for the analyzed South-American population (Argentina) showed a high similarity and a potential complementarity with those

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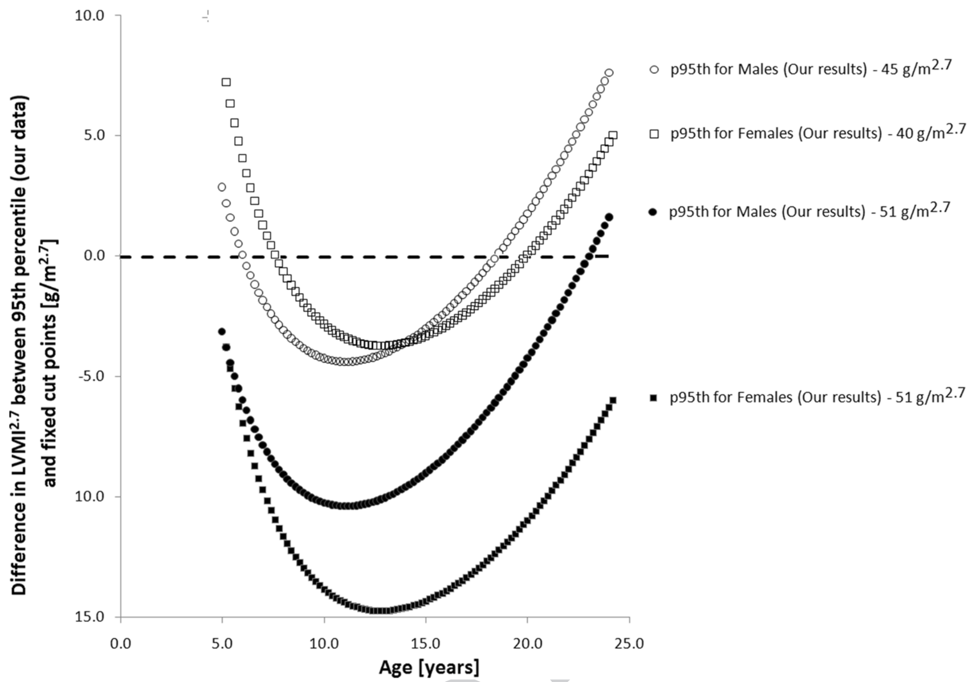

Fig. 7 Difference in left ventricular mass index (LVMI; gr/m$^{2.7}$) between our percentile 95th in girls and boys and fixed cut-off points to diagnose left ventricular hypertrophy (40 g/m$^{2.7}$ and 45 g/m$^{2.7}$ for females and males, respectively; proposed y Khoury et al. [14] or severe left ventricular hypertrophy (51 g/m$^{2.7}$; proposed by Flynn et al. [7, 34])

reported by Khoury et al. in North-American children and adolescents.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict on interest.

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