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Sex-related differences in left ventricular structure in early adolescent non-professional athletes

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Sex-related differences in left ventricular structure in early adolescent non-professional athletes / Pela', Giovanna Maria; Crocamo, Antonio; LI CALZI, Mauro; Gianfreda, Marina; Gioia, MARGHERITA ILARIA; Visioli, Francesco; Pattoneri, Paolo; Corradi, Domenico; Goldoni, Matteo; Montanari, Alberto. - In: EUROPEAN JOURNAL OF PREVENTIVE CARDIOLOGY. - ISSN 2047-4873. - 23:7(2016), pp. 777-784. [10.1177/2047487315608826]

Availability:

This version is available at: 11381/2796479 since: 2021-10-26T11:55:04Z

Publisher:

SAGE Publications Inc.

Published

DOI:10.1177/2047487315608826

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note finali coverpage

(Article begins on next page)

European Journal of Preventive Cardiology

Sex-related differences in left ventricular structure in early adolescent non-professional athletes --Manuscript Draft--

Manuscript Number:	EJPC-D-15-00344R1
Full Title:	Sex-related differences in left ventricular structure in early adolescent non-professional athletes
Article Type:	Original Scientific Paper
Section/Category:	Sports cardiology
Keywords:	athlete's heart; echocardiography; left ventricular mass; left ventricular geometry; pre-participation screening process.
Corresponding Author:	Giovanna Pela', Ph.D., M.D. University Hospital Parma Parma, ITALY
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University Hospital Parma
Corresponding Author's Secondary Institution:	
First Author:	Giovanna Pela', Ph.D., M.D.
First Author Secondary Information:	
Order of Authors:	Giovanna Pela', Ph.D., M.D. Antonio Crocamo, MD Mauro Li Calzi, MD Marina Gianfreda, MD Margherita Ilaria Gioia, MD Francesco Visioli, MD Paolo Pattoneri, PhD, MD Domenico Corradi, MD Matteo Goldoni, MD Alberto Montanari, MD
Order of Authors Secondary Information:	
Manuscript Region of Origin:	Europe
Abstract:	<p>Background: Professional athletes exhibit lower left ventricular (LV) wall thicknesses, diameters and mass (in females), with less frequent training-related ECG changes, as compared with controls.</p> <p>Methods: We studied the association of sex with LV structure in trained early adolescents. 206 adolescent Caucasian athletes (mean age 13.8+1.6, range 11.8-16.9 years), 158 males (M) and 48 females (F), with similar degree of training underwent ECG and echocardiographic measurements of LV diameters, thicknesses, and mass (LVM), with relative wall thickness (RWT) as the remodelling index.</p> <p>Results: As compared with F, M exhibited greater maximal wall thickness (MWT: M=8.7+1.2 vs F=7.9+0.8) and indexed LVM (100±18 gr/m² vs. 79±12, p<0.001), without differences in RWT (M=0.35+0.04 vs. F=0.34+0.04) and with higher prevalence of ECG-based LV hypertrophy (LVH), sinus bradycardia, and ST-elevation. An ANCOVA analysis, using age, body surface area, systolic blood pressure, heart rate and sex as the covariates, reported that sex is a strong predictor of LVM, MWT, LV</p>

diastolic diameter, and ECG-based LVH. In a binary logistic regression model analysis sex, like LVM, predicted ST-segment elevation.

Conclusions: Our results suggest that, in early adolescence, female athletes have lower LVM and thicknesses compared with males, without geometrical differences. Therefore, sex, independent of age, is a strong determinant of structural parameters also in early adolescent athletes. These data indicate that sex-specific parameters are needed in the pre-participation cardiovascular screening of adolescent athletes.

RE: EJPC-D-15-00344, entitled "Sex-related differences in left ventricular structure in early adolescent non-professional athletes"

Dear Prof. Pela',

The reviewers have returned their comments on your manuscript and have found a few areas where they believe the manuscript can be improved. Please find their comments listed below. We anticipate that you will easily be able to answer the points raised by the reviewers.

If you are willing to revise the manuscript, please include with your revised submission an itemized, point-by-point response to the comments of the reviewers.

Please observe the word limit when revising your manuscript. For an Original Scientific paper, this is 5000 words total, with each table or figure reducing that word count by 250. For other article types (review papers, short report, etc.) please consult the Instructions for Authors on the website, for more specific details.

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With kind regards,

Rosemary Allpress
Managing Editor
European Journal of Preventive Cardiology

September 4th, 2015

Rosemary Allpress
Managing Editor
European Journal of Preventive Cardiology

Dear Managing Editor,

Many thanks for your rapid and thorough evaluation of our manuscript. The revised paper (revisions in red) include two citations to papers recently published in EJPC. As indicated in the specific responses to the reviewers, we added more detailed information about the sport disciplines in which subjects were engaged. We know that soccer and volleyball should be computed together, but soccer is the most popular sport in Italy. Yet, it is unusual for girls do practice this type of sport activity.

Unfortunately, we were unable to provide data about actual conditioning because athletes did not perform cardiopulmonary exercise tests when we screened them. This is a consequence of the observational nature of the study, which was designed and performed in athletes referred to our Sport Medicine Service and Laboratory of Clinical Physiology for pre-participation screening, which is specifically required in Italy at any level of competitive sport activity, regardless of age.

Once again, thank you for your kind assistance, we look forward to hearing from you soon.

Sincerely Yours

Prof. Giovanna Pelà

RE: EJPC-D-15-00344, entitled "Sex-related differences in left ventricular structure in early adolescent non-professional athletes"

Reviewer Comments:

Reviewer #1:

The potentially interesting and important manuscript describes differences in left ventricular structure between male and female caucasian adolescent athletes. More than 150 male and around 50 female athletes with a mean age of 13.8 years were investigated for a set of cardiovascular parameters. The major finding of the study is the difference of LVM including lower LV thicknesses and diameters between male and female without alteration of the ventricular structure. It is concluded from the data that sex becomes a strong determinant of structural and functional parameters of athletes' heart from the early adolescence and sex- and age- specific parameters are needed to discriminate in the guidelines for pre participation cardiovascular screening evaluation. The study is well done from cardiovascular screening side but has substantial limitation for the documentation of training-/sport-level and aerobic fitness. These limitations reduce the potential impact of study.

Specific comments:

1. More detailed information should be given for the sport load. It seems from distinct importance for the interpretation of the data to give not only the time per week of training. It is important to know more about the intensity of the training load.

Response: Unfortunately, detailed quantification of physical activity, training levels, and performance was not feasible in our observational study in amateur-level athletes, who greatly differ from elite, professional athletes precisely because of the lack of such measurements during their routine training. Nonetheless, the detailed, questionnaire-based survey of training - which is being often employed - reliably estimates the exercise load in amateur athletes. See Methods, page 7, lines 114 to 115 (see ref 14) .

2. It would also be interesting to compare the training time per week with the LVM and the other parameter of the left ventricular structure.

Response: Training time was not significantly related with LVM and other parameters (data not shown). It should be noted that this parameter had low variability because the training programs are quite similar in adolescents regardless the type of sport in males and females.

3. Specific and detailed information about the sport disciplines should be given.

Response: Good point. Information about sport disciplines is now added to the Methods section (page 7, lines 107 to 113).

4. It would be preferable to have also data of the aerobic capacity of the young athletes

Response: We agree, but, unfortunately, we are unable to provide data about actual conditioning because athletes did not perform cardiopulmonary exercise tests. This is a consequence of the observational nature of the study, which was designed and performed in athletes referred to our Sport Medicine Service and Laboratory of Clinical Physiology for pre-participation screening, which is specifically required in Italy at any level of competitive sport activity, regardless of age.

Reviewer #2:

In the paper of Pelà et al. 206 adolescent Caucasian athletes (158 males -M and 48 females -F), with similar degree of training underwent ECG and echocardiographic measurements of LV diameters, thicknesses, and mass (LVM), with relative wall thickness (RWT) as the remodelling index.

Authors found that M exhibited greater maximal wall thickness, indexed LVM, without differences in RWT and with higher prevalence of ECG-based LV hypertrophy (LVH), sinus bradycardia, and ST-elevation. At ANCOVA analysis, using age, body surface area, systolic blood pressure, heart rate and sex as the covariates, sex resulted a strong predictor of LVM, MWT, LV diastolic diameter, and ECG-based LVH. In a binary logistic regression model analysis sex, like LVM, predicted ST-trait elevation. I believe that the paper is well written and study results clearly explained. Moreover, the specific focus on early adolescence, may add relevant information to previous studies performed in later ages.

My only concern, as reported by authors in the study limitation, is that males and females recruited in this cohort, practice different sports (soccer and volleyball), which cannot be considered the same.

Response: Indeed, soccer and volleyball should not be computed together, but soccer is the most popular sport in Italy, yet girls rarely engage in this type of sport activity.

Furthermore, we only know the average time of training but no information was given about the actual conditioning. It would have been of interest to have had a cardiopulmonary exercise test to correct for this relevant factor. This is particularly important as no control group of sedentary adolescent is incorporated in the analysis.

Response: This was also of concern to Referee 1. We agree, but, unfortunately, we are unable to provide data about actual conditioning because athletes did not perform cardiopulmonary exercise tests. This is a consequence of the observational nature of the study, which was designed and performed in athletes referred to our Sport Medicine Service and Laboratory of Clinical Physiology for pre-participation screening, which is specifically required in Italy at any level of competitive sport activity, regardless of age.

In addition, I do believe that a plasma sampling of sexual hormones would have been of interest.

Response: This is a good point. However, blood collection and cardiopulmonary exercise test are not routinely included during the screenings for fitness and we cannot provide such data. We will incorporate these measurements/tests in future investigations.

I would finally suggest to check for multicollinearity at ANCOVA analysis.

Response: All of the variables included as predictors in the models had R values (Pearson's correlation test) below 0.5. Furthermore, multicollinearity was tested in a multiple regression model, which gives mathematically the same significances of ANCOVA, looking at the VIF (Variance Inflation Factor) values, always below 2. A cut-off value of 10 is usually considered to assess multicollinearity. (*Kutner M.H.,Nachtsheim C.J., Neter J., 2004. Applied Linear regression models, 4th ed., McGraw-Hill*).

We now expand on this in the Methods section (see page 10, lines 162 to 164).

1 **Sex-related differences in left ventricular structure in early**
2 **adolescent non-professional athletes**

3
4 **Giovanna Pelà¹, Antonio Crocamo¹, Mauro Li Calzi¹, Marina Gianfreda¹,**
5 **Margherita Ilaria Gioia¹, Francesco Visioli², Paolo Pattoneri³, Domenico**
6 **Corradi⁴, Matteo Goldoni¹, and Alberto Montanari¹**

7
8
9 *¹Department of Clinical and Experimental Medicine and Laboratory of Clinical*
10 *Physiology, University Medical School and University Hospital of Parma, Parma,*
11 *Italy; ²Department of Molecular Medicine, University of Padova, Padova, Italy*
12 *³AUSL Cardiology Unit, Parma, Italy; ⁴Department of Biomedical,*
13 *Biotechnological, and Translational Sciences (S.Bi.Bi.T.), Unit of Pathology,*
14 *University Medical School and University Hospital of Parma, Parma, Italy.*

15
16 **Corresponding author:** Giovanna Pelà, University Medical School and
17 University Hospital of Parma, Department of Clinical and Experimental Medicine
18 and Laboratory of Clinical Physiology, Via Gramsci 14, 43100 Parma, IT. Tel:
19 +39-0521-033192, Fax: +39-0521-033185, E-mail: giovanna.pela@unipr.it

20 **Word count:3992**

21 **Abstract**

22 **Background:** Professional athletes exhibit lower left ventricular (LV) wall
23 thicknesses, diameters and mass (in females), with less frequent training-related
24 ECG changes, as compared with controls.

25 **Methods:** We studied the association of sex with LV structure in trained early
26 adolescents. 206 adolescent Caucasian athletes (mean age 13.8 ± 1.6 , range 11.8-
27 16.9 years), 158 males (M) and 48 females (F), with similar degree of training
28 underwent ECG and echocardiographic measurements of LV diameters,
29 thicknesses, and mass (LVM), with relative wall thickness (RWT) as the
30 remodelling index.

31 **Results:** As compared with F, M exhibited greater maximal wall thickness
32 (MWT: $M=8.7 \pm 1.2$ vs $F=7.9 \pm 0.8$) and indexed LVM (100 ± 18 gr/m² vs. 79 ± 12 ,
33 $p < 0.001$), without differences in RWT ($M=0.35 \pm 0.04$ vs. $F=0.34 \pm 0.04$) and
34 with higher prevalence of ECG-based LV hypertrophy (LVH), sinus
35 bradycardia, and ST-elevation. An ANCOVA analysis, using age, body surface
36 area, systolic blood pressure, heart rate and sex as the covariates, reported that
37 sex is a strong predictor of LVM, MWT, LV diastolic diameter, and ECG-
38 based LVH. In a binary logistic regression model analysis sex, like LVM,
39 predicted ST-segment elevation.

40 **Conclusions:** Our results suggest that, in early adolescence, female athletes
41 have lower LVM and thicknesses compared with males, without geometrical
42 differences. Therefore, sex, independent of age, is a strong determinant of
43 structural parameters also in early adolescent athletes. These data indicate that
44 sex- specific parameters are needed in the pre-participation cardiovascular
45 screening of adolescent athletes.

46

47 **Key words:** athlete's heart; echocardiography; left ventricular mass; left
48 ventricular geometry; pre-participation screening process.

49 **Introduction**

50 Regular physical training induces structural and electrical cardiac changes,
51 such as left ventricular (LV) hypertrophy and low heart rate, resulting in the so-
52 called “athlete’s heart”.¹⁻³

53 Such changes are thought not only to depend on the type and intensity of exercise,
54 but also to be influenced by other factors such as age, ethnicity, and sex.^{4,5}

55 However, even though the characteristics of cardiac remodelling have been
56 extensively studied in male athletes of different sport disciplines², scant data are
57 available on the prevalence of athlete’s heart in females vs. males. Pelliccia et al.^{6,7}
58 first demonstrated - in a population of mostly adult professional athletes - lower LV
59 thicknesses, diameters, and mass in females, with less frequent training-related
60 ECG changes.⁸ In contrast to male athletes, female maximal wall thickness (MWT)
61 never exceeded the upper normal value of 12 mm, consistent with the notion of no
62 overlapping of LV thicknesses with the pathological range compatible with
63 hypertrophic cardiomyopathy (HCM).^{6,7,9-11}

64 Even fewer studies have been performed to assess sex-related differences in
65 cardiac remodelling in adolescent athletes. Sharma et al.¹² studied a group of 16-years-
66 old trained persons and suggested that sex itself may be an independent determinant of
67 LV adaptation to regular exercise in adolescence, because of lower LV thicknesses and
68 mass in girls vs. boys. Age is a critical determinant of LV diameters, thicknesses, and

69 mass (LVM), which increase from birth to adolescence and youth in both sexes,
70 independent of sport activity. ¹³ In addition, wide between-sex physiological LV
71 structural differences develop in the early adolescence, along with sexual maturation.
72 Within the 12-to-14 years age interval, LVM - only marginally different between boys
73 and girls in the childhood - becomes much greater in males, showing an age-related
74 progressively greater increase which reaches 30% vs. females at the age of 16. ¹³

75 In short, the appearance of *between-sex* differences in LV parameters in
76 adolescent athletes may not only reflect, as generally thought ¹², sex-related different
77 responses of LV to training, but also the physiological age-dependent divergence in LV
78 parameters in the early adolescence. Furthermore, in the 12-to-14 years age interval,
79 sex-related differences in body size are much less pronounced than in 16-years-old
80 people, thus limiting the specific influence of anthropometric characteristics on LV. ¹³
81 It may be thus of interest to study LV parameters in adolescent athletes of both sexes
82 within their trans-pubertal age. For this purpose, we investigated ECG- and ECHO-
83 findings in 206 adolescent female (F) and male (M) amateur-level endurance athletes,
84 practising sports in local, non-professional tournaments. Of note, their age averaged
85 13.8 ± 1.6 years (range 11.8-to-16.9), which is approximately 2-years earlier than that of
86 participants in the only previous study in adolescent athletes of both sexes. ¹²

87 Our aims were 1): to determine whether and to what extent between-sex
88 differences in LV thicknesses and mass already were detectable in amateur-level

89 athletes within the early, trans-pubertal phase of adolescence; 2): to contribute
90 defining age- and sex-specific cardiac parameters at the pre-participation
91 cardiovascular screening of adolescents, in an effort to differentiate athlete's heart
92 from structural cardiac diseases such HCM, which may cause sudden death in the
93 youth.⁹

94

95

96 **Methods**

97 *Participants*

98 This study was approved by the Medical Ethical Committee of Parma. Written
99 informed consent was obtained from the parents of athletes.

100 Between 2006 and March 2014, we consecutively selected 206 Caucasian
101 amateur level adolescent athletes (158 M and 48 F) from within the adolescent athletes
102 referred to the sport pre-participation screening in the Parma AUSL Sport Medicine
103 Service and Laboratory of Clinical Physiology (Parma, Italy). Screening criteria were:
104 age lower than 17 years (range 11.8-16.9 years; average 13.8 ± 1.6 SD), Caucasian
105 ethnicity, absence of symptoms, structurally normal heart, and blood pressure (BP)
106 within the normal range. All participants competed in local, amateur-level leagues of
107 different endurance disciplines. Soccer was by far most prevalent sport activity in M
108 (102/158, 65% total), who also participated in other disciplines including basketball
109 (n=13), athletics (n=9), judo (n=3), rugby (n=7), baseball (n=3), handball (n=2),
110 volleyball (4), cycling (n=4), karate (n=2), tennis (n=3), triathlon (n=2), fencing (n=1),
111 and water polo (n=3). Girls predominantly played volleyball (n=21), but also
112 gymnastics (n=4), athletics (n=6), soccer (n=2), basketball (n=5), swimming (n= 2),
113 softball (n=4), judo (n=1), rugby (n=1), kick boxing (n=1), and skating (n=1).

114 A 9-item Physical Activity Questionnaire for Adolescents (PAQ-A) was used
115 to assess the type, intensity, and duration of sport activity.¹⁴ All evaluations were

116 performed during periods of intensive training, with physical examinations and 12-
117 lead resting ECG and 2-D ECHO. BP was assessed on two occasions, with three
118 consecutive measurements (OMRON 705 IT).

119

120 *ECG*

121 Twelve-lead, 25 mm/second, supine-position ECGs were interpreted¹⁵ by three
122 investigators (GP, ML, AC) blinded to the type of subject. Heart rate (HR), QRS-axis,
123 PR-interval, QRS-duration, and corrected QT-interval were measured. S1+R5 in
124 precordial leads were calculated using the Sokolow-Lyon voltage criteria (positive if \geq
125 35mm) to define the presence of LV hypertrophy (LVH). Prevalence of Q-waves (\geq
126 2mm in depth in ≥ 2 adjacent leads), presence and shape (concave or domed) of ST-
127 segment elevation (≥ 1 mm in ≥ 2 adjacent leads), prevalence of inverted T-waves (≥ 2
128 mm in depth in ≥ 2 adjacent leads, excluding aVR and III), were also assessed.

129

130 *Transthoracic ECHO*

131 M-mode, two-dimensional, and Doppler ECHO were performed by one
132 ultrasonography-experienced cardiologist (GP), using commercially available, multi-
133 hertz sector, 2-4 MHz probe-equipped machines (Aspen, Siemens Acuson, Mountain
134 View, California, USA; Vivid S5, GE Healthcare, USA). With the subject set in the

135 left lateral position, images based on three consecutive heart cycles were obtained
136 from standard projections.

137 Interventricular septal (SWT) and posterior wall (PWT) thicknesses were
138 measured at the parasternal long-axis view according to the Penn convention and the
139 greatest measure was considered as the maximal wall thickness (MWT), with systolic
140 (ESD) and diastolic (EDD) LV diameters measured in the same projection.^{16,17} RWT
141 was calculated as: $(\text{SWT} + \text{PWT}) / \text{EDD}$, using the 0.42 cut-off to define eccentric
142 (≤ 0.42) or concentric (≥ 0.42) remodelling.¹⁸ Penn convention-based LVM also was
143 normalized - when necessary - to body surface area (BSA) or to height^{2,7}, an estimate
144 of lean body mass (LBM).^{18,19} Simpson's biplane rule-based end-diastolic and
145 systolic LV volumes and ejection fraction (EF) were calculated, while Fractional
146 Shortening (FS) was: $[(\text{EDD} - \text{ESD}) / \text{EDD}] \times 100$. Blood flow across the mitral valve
147 was monitored using the pulsed-Doppler technique in the apical four-chamber view,
148 with the sample volume placed at the tip of the valve. The blood flow profile contains
149 diastolic E and A waves and peak flow velocity and its time-integral were measured
150 for each wave. The intra-observer percent variability for MWT was < 3.5 as
151 previously reported.²⁰

152

153 *Statistical analyses*

154 Data are expressed as means \pm SD after testing for normality (Kolmogoroff-
155 Smirnoff) and sex as univariate factor was assessed by means of two-tailed Student's *t*
156 test (SPSS 20.0 software package, IBM, Armonk, New York, USA), χ -square, or
157 Fisher F-test, when appropriate. ANCOVA, calculating also marginal means, was used
158 to analyze sex differences in ECHO-based variables (LVM, MWT, EDD) and ECG-
159 based LVH using age, HR, BSA, and systolic BP as covariates. Dichotomous ECG
160 variable such as ST elevation and inverted T wave were analysed with a binary logistic
161 regression model including as covariates sex, age, HR, BSA, systolic BP, LVM and
162 EDD. **Multicollinearity among predictors was excluded from all multivariate models**
163 **(correlation coefficients between couples of variables were always < 0.5 and VIF –**
164 **Variance Inflation Factor < 2).**
165 A 2-tailed p value < 0.05 was considered as significant.

166

167

168 **Results**

169 All athletes engaged in organized, sport-specific training for approximately 2.5
170 hours twice a week and participated (usually during weekends) in one amateur-level
171 local competition. Total sport load was approximately eight hours/week in both
172 groups. M and F had similar age and body mass index (BMI), but height, weight and
173 BSA were higher in M than in F (Table 1).

174 Systolic and diastolic BP were significantly lower, but HR was higher in F
175 compared with M (Table 1).

176

177 *ECG Findings*

178 The prevalence of LVH and high S1+R5 voltages was greater in M, as were
179 those of ST-elevation and sinus bradycardia, with similar PR and QRS duration; QRS-
180 axis; QT-interval; prevalence of enlarged left atrium; and inverted T-waves in the two
181 groups (Table 2). Pathological Q-waves were not observed in any athlete. The
182 ANCOVA analysis revealed that S1+R5 voltage-based LVH was strongly and
183 independently predicted by sex only ($p < 0.01$). In the binary logistic regression model
184 analysis, sex and LVM significantly predicted ST-segment elevation ($p < 0.05$ for both),
185 without any effects of other physiological variables. Negative T wave was only
186 determined by age ($p < 0.01$).

187

188 *Left Ventricular Dimensions and Geometry*

189 M exhibited greater SWT, PWT, MWT, and LVM compared with F (Table 3).
190 Normalization of LVM for BSA, weight, height, or LBM did not abolish the
191 differences we observed between sexes.

192 LV cavity size, as assessed by diameters and volumes, was lower in F
193 compared to M whilst the two groups did not differ for their geometry, as evaluated by
194 RWT (Table 3).

195 Figure 1 shows that frequency distribution of LVM (A), MWT (B), and EDD
196 (C) was distinctly right-shifted for M, with the upper limit for MWT that never
197 exceeded 10 mm in F (range 6.1 to 9.6 mm) and 13 in M (range 6.5 to 12.3 mm).

198 Systolic function, as assessed by FS and EF, was slightly higher (FS: 40 ± 6 %
199 vs 38 ± 5 , $p = \text{ns}$; EF: 68 ± 6 % vs 67 ± 6 , $p = 0.07$) and stroke volume was significantly
200 lower (60 ± 12 ml vs. 72 ± 17 , $p < 0.001$) in F compared with M, without differences in
201 diastolic function (data not shown).

202 The ANCOVA-analysed association of LVM, indexed LVM, MWT, and EDD
203 (the dependent variables) with age, BSA, systolic BP, HR, and sex (the independent
204 variables) showed that sex is a strong independent predictor of all structural ECHO-
205 parameters (for all $p < 0.001$) with similar effects of BSA. Systolic BP was
206 significantly related to MWT and indexed values of LVM (for all $p < 0.05$), with HR

207 being a predictor of absolute and indexed LVM (for both $p < 0.01$) and MWT ($p < 0.05$)

208 without any predicting correlation computed for EDD.

209

210

211 **Discussion**

212 The foremost result of the present study is that adolescent male athletes have
213 significantly greater LV mass, thicknesses, and cavity size compared with age-
214 matched female athletes with comparable degree of training. LV structure is, hence,
215 very different according to the sex also in adolescent athletes, similar to adult elite
216 athletes^{6,7}. This is consistent with the significantly lower (in females vs males) EDD,
217 MWT, and LVM found in a large group of adolescent athletes by Sharma et al.¹², who
218 first indicated sex as an important determinant of LV adaptation to exercise in the
219 adolescence. However, participants in the present study (aged 13.8 ± 1.6 years) were
220 substantially younger than those of Sharma et al.¹² (the age of whom averaged 16
221 years); thus, our data indicate that sex-related differences in LV structure can be
222 detected even in early adolescence. The approximately two-year age difference vs. the
223 study of Sharma et al.¹² may be important, because population studies¹³ indicate that
224 the age-related physiological LVM growth curves, which can be superimposed before
225 puberty, diverge from the 12-to-14 years interval. Indeed, markedly greater LVM
226 growth in males, start to be seen close to pubertal development. Sexual
227 characterization, mostly triggered by the increase of testosterone in boys vs.
228 oestrogens in girls, is indeed thought to exert differential growth effects on the
229 myocardium, stimulating a greater increase in the size of myocytes in males, in turn

230 contributing to the appearance - in the trans-pubertal age - of sex-related differences in
231 cardiac structures.²¹

232 Sex-dependent phenotype maturation is similar in both sexes as shown by large
233 increases in height, weight, BSA, and LBM; however, such changes are much more
234 pronounced in males than in females.¹³ Because body size is a strong physiological-,
235 sex-, and age-independent determinant of LV structure^{13,22}, the marked anthropometric
236 differences between the sex subgroups recorded in our study could partially explain
237 the greater LVM observed in males. However, as the 24% greater absolute LVM in
238 males vs females was essentially maintained after normalizing LVM for any
239 anthropometric variable, sex *per se* appears to be an independent strong predictor of
240 LVM in the trans-pubertal phases of adolescence, as also indicated by the ANCOVA
241 analysis.

242 In addition to the physiological training-independent, age-related, between-sex
243 divergence in cardiac growth curves, the higher LVM of male trans-pubertal athletes
244 could reflect the contribution of other factors, namely sex-related different heart
245 responses of LV to physical activity training.^{4,5} However, because female and male
246 sedentary control groups were not tested in the present investigation and in previous
247 echocardiographic studies in adult or adolescent athletes^{6,7,12}, this issue remains
248 unresolved. Yet, a recent MR study in adult athletes reported similar LV hypertrophic

249 changes to training in females vs. males, consistent with the lack of any sex-specific
250 LVM response to exercise.²³

251 Other factors potentially involved in LV remodeling in athletes were different
252 between the males and females of our cohort, including a slightly higher BP and a
253 lower HR seen in males. Both parameters were predictive of LVM (according to the
254 ANCOVA analysis), although to a much lesser extent when compared with sex and
255 body size. A lower HR in athletes is generally thought to reflect a higher training
256 intensity²⁴, which could also have been facilitated in the male subgroup as suggested
257 by the markedly greater LBM. In brief, some differences in the level of physical
258 activity might have played some roles in cardiac remodeling. Hemodynamic loads
259 could also have affected LVM in adolescent male athletes, similar to what has been
260 previously observed in adult athletes^{25,26} and as indicated by the association of LVM
261 with systolic BP. However, the association of systolic BP and HR with LVM were
262 much weaker than those of sex and body size, consistent with the hypothesis that
263 cardiac workloads strongly influence LVM variability in the adulthood but not in the
264 adolescence.²²

265 Similar to LVM, LV diameters and thicknesses were greater in the male
266 subgroup, with sex and body size strongly and independently predicting EDD and
267 MWT. Conversely, EDD and MWT were poorly predicted by systolic BP and HR.
268 MWT has been proposed as a diagnostic tool in adolescent and adult athletes

269 undergoing pre-participation screening, to discriminate between training-related LV
270 thickening and pathological LVH and to contribute preventing the HCM-related
271 sudden death in athletes. As showed in Figure 1, the frequency distribution of MWT
272 was right-shifted in males, with upper limits not exceeding 13 mm in males and 10
273 mm in females, which were significantly lower than those reported by Sharma et al.¹²
274 in 16- years old athletes (11 mm in females vs 14 mm in males). Our data are
275 consistent with the sex-related difference in the age-dependent LV growth curve and
276 also indicate the need of sex-specific MWT-based criteria to improve the pre-
277 participation assessment of early adolescent athletes.

278 RWT-based LV geometry study did not show between-sex differences,
279 consistent with similar growth-related increases in LV chamber dimensions and wall
280 thicknesses in both sexes. Furthermore, RWT was 0.35 in males and 0.34 in females,
281 similar to that we found in white, male early adolescent athletes.²⁰ RWT in male black
282 counterparts was 0.44, consistent with a concentric remodeling pattern linked to
283 African ethnicity, as opposed to a sex-independent, eccentric-type LV remodeling in
284 Caucasian people.²⁰ **An even more pronounced eccentric LV remodelling in Japanese**
285 **football players suggests a varied spectrum of LV remodelling patterns across various**
286 **ethnicities.**²⁷

287 Concerning the exercise-related ECG changes, increased S1+R5 voltages and
288 prevalence of ST elevation, sinus bradycardia, and positive LVH criteria were less

289 frequent in females, with sex strongly and independently predicting ECG-based LVH
290 and ST-segment elevation, which also was related to the ECHO-based LVM. Therefore,
291 sex is a determinant not only of structural, but also of electrical LV remodeling in early
292 adolescent athletes.

293 Prevalence of “juvenile” inverted T waves was low in our study group and only
294 related to age, in agreement with their tapering down in the pubertal age.²⁸

295

296 *Limitations*

297 The main limitation of our study is the small proportion (23 vs 77%) of female
298 athletes in the cohort. This proportion reflects the typically lower participation of girls
299 vs boys in competitions. Indeed, fewer (25 vs 75 %) adolescent female than male
300 athletes usually undergo clinical examinations at the Parma AUSL Sport Medicine
301 Service. This is comparable with the study of Sharma et al.¹². However, all ECHO
302 measurements were performed by one single experienced cardiologist, thus
303 minimizing variability.

304 We did not perform cardiopulmonary test; therefore, we cannot exclude
305 different levels of training in the two groups. We also must take into account that the
306 type of sport such as soccer (more prevalent in male) and volley (more popular among
307 females) might differentially affect LV remodelling in the two groups.

308

309 **Conclusion**

310 In conclusion, our results confirm that, in the early phase of adolescence,
311 between-sex differences in LV structure are already detectable in amateur-level
312 Caucasian athletes, with lower LV thicknesses, mass, and diameters (but not geometry)
313 in female than male athletes. Exercise-related ECG abnormalities also are less
314 prevalent in females. In short, sex becomes a strong determinant of structural and
315 functional parameters of athletes' heart from the early adolescence. Finally, we
316 suggest that sex- and age- specific parameters and guidelines are needed to
317 discriminate physiological and HCM-related pathologic hypertrophy in the pre-
318 participation cardiovascular screening evaluation of non-professional early adolescent
319 athletes.

320

321 **Conflict of interest**

322 The authors declare that there is not conflict of interest.

323

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404

405 **Figure Legend**

406

407 **Figure 1.** Percent distribution of left ventricular mass index (LVM/BSA) (A),
408 maximal wall thickness (MWT) (B), and left ventricular end diastolic diameter
409 (LVEDD) (C) in adolescent male (black bars) and female (white bars), amateur-level
410 athletes. The upper limit for MWT was 12.3 for males and 9.6 for females. None
411 exceed the upper limit of 13 mm.

Table 1. Anthropometry and clinical data in female and male adolescent amateur-level athletes

Parameter	Males (=158)	Females (n=48)	p value
Age (years)	13.8 ± 1.6	13.7 ± 1.4	ns
Height (cm)	1.67 ± 0.11	1.61 ± 0.07	<0.01
Weight (kg)	60 ± 13	52 ± 9	<0.05
BMI (kg/m ²)	20.2 ± 3.0	19.7 ± 2.4	ns
BSA (m ²)	1.62 ± 0.24	1.54 ± 0.15	<0.05
SBP (mmHg)	117 ± 11	112 ± 10	<0.01
DBP (mmHg)	70 ± 7	67 ± 7	< 0.05
HR (beats-per-minute)	71 ± 11	76 ± 11	< 0.01

Data are expressed as mean values ± standard deviation. BMI, Body mass index; BSA, Body surface area; DBP, Diastolic blood pressure; HR, Heart rate; SBP, Systolic blood pressure; F, female athletes; M, male athletes

Table 2. ECG findings in female and male adolescent amateur-level athletes

Parameters	Males	Females	p value
PR interval (ms)	139 ± 23	134 ± 22	NS
QRS complex duration (ms)	83 ± 16	80 ± 12	NS
QT _c interval (ms)	403 ± 36	404 ± 28	NS
QRS axis (°)	64 ± 30	69 ± 26	NS
S ₁ +R ₅ wave voltages (mm)	30 ± 11	22 ± 6	< 0.001
Synus Bradycardia	18 % (26/146)	0 % (0/42)	<0.01
Left Ventricular Hypertrophy (Sokolow-Lyon criteria)	38 % (56/146)	2 % (1/42)	< 0.001
Partial right bundle branch block	38 % (56/146)	33 % (14/42)	NS
ST segment elevation	47 % (69/146)	10 % (4/42)	< 0.001
Inverted T waves	14 % (20/146)	10 % (4/42)	NS
Left Atrial enlargement	3 % (5/146)	10 % (4/42)	NS

Data are expressed as mean values ± standard deviation. Synus bradycardia, heart rate < 60 b.p.m.; F, female; M, male.

Table 3. ECHO-based left ventricular morphology in female and male adolescent amateur-level athletes: sex-related differences.

Parameters	Males	Females	p value
End-diastolic diameter (mm)	47 ± 4	44 ± 3	< 0.001
End-systolic diameter (mm)	29 ± 4	27 ± 4	< 0.001
End-diastolic volume (ml)	109 ± 25	89 ± 17	< 0.001
End-systolic volume (ml)	37 ± 12	28 ± 8	< 0.001
Septal thickness (mm)	8.4 ± 1.2	7.6 ± 0.9	< 0.001
Posterior wall thickness (mm)	8.1 ± 1.2	7.2 ± 0.9	< 0.001
Maximal wall thickness (mm)	8.7 ± 1.2	7.9 ± 0.8	< 0.001
RWT	0.35 ± 0.04	0.34 ± 0.04	ns
Absolute LVM (g)	163 ± 43	122 ± 25	< 0.001
LVM/BSA (g/m ²)	100 ± 18	79 ± 12	< 0.001
LVM/W	2.9 ± 0.5	2.4 ± 0.4	< 0.001
LVM/h	97 ± 22	75 ± 13	< 0.001
LVM/LBM (g/h ^{2.7})	40 ± 8	33 ± 5	< 0.001

Data are expressed as mean values ± standard deviation.

F, female athletes; h, height; LVM, absolute left ventricle mass; LVM/BSA, indexed LVM for body surface area; LVM/LBM, indexed LVM for lean body mass; RWT, relative wall thickness; M, male athletes; W, weight.

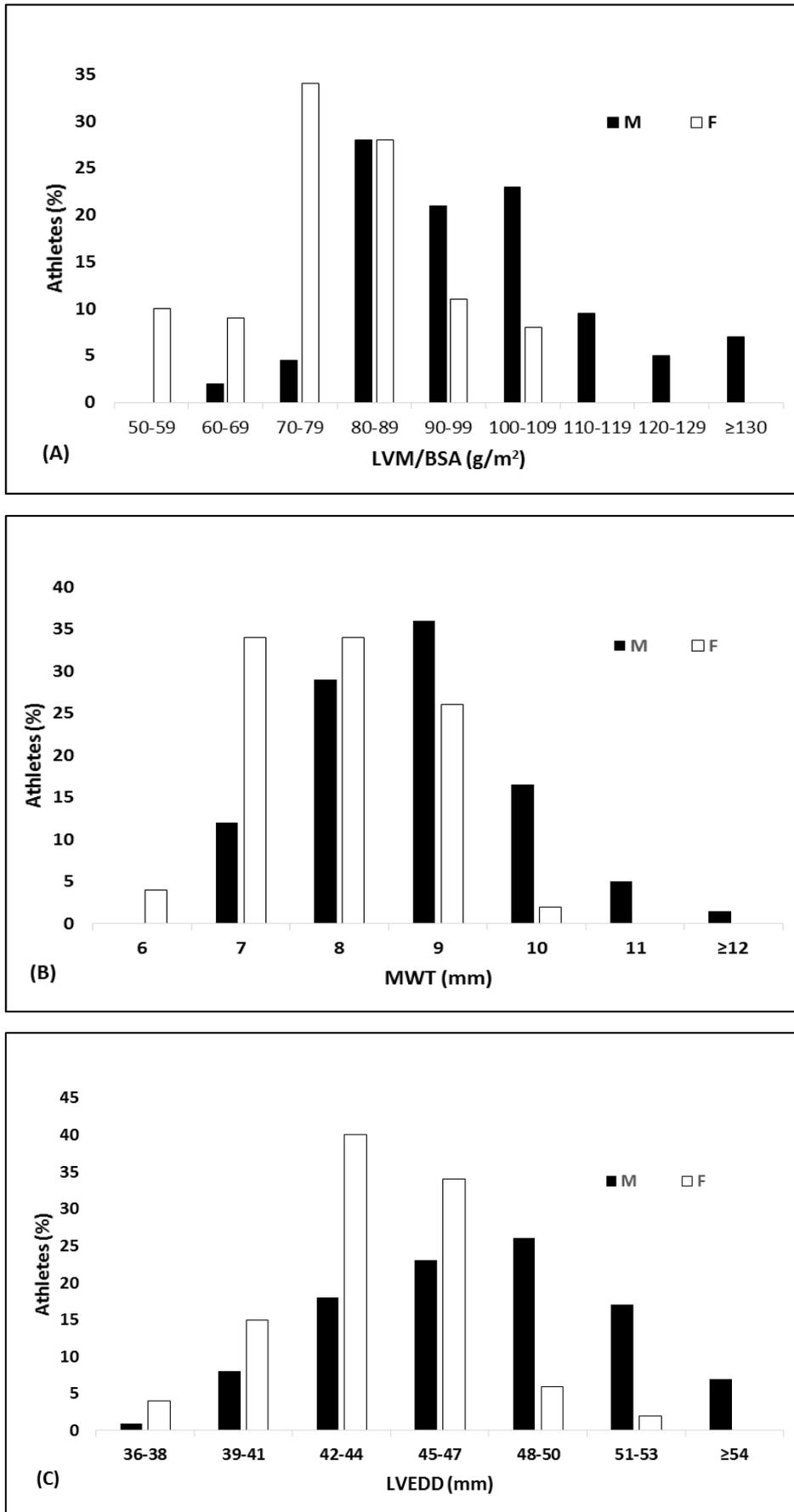


Figure I. The distribution of Left Ventricular Mass Index (LVM/BSA) (A), Maximal Wall Thickness (MWT) (B), and Left Ventricular End Diastolic Diameter (LVEDD) (C) in Males (M) (black bars) and Females (F) (white bars) athletes.

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 CORRESPONDING AUTHOR: PELA'G.
 ADDRESS: UNIVERSITY MEDICAL SCHOOL AND UNIVERSITY HOSPITAL OF PARMA
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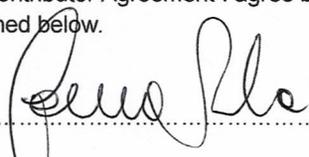
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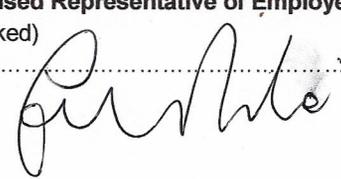
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