




# openheart Young athlete's growing heart: sex differences in cardiac adaptation to exercise training during adolescence

Marianne Inngjerdingen Forså <sup>1,2</sup>, Anders W Bjerring,<sup>1,2</sup> Kristina H Haugaa,<sup>1,2</sup> Marit Kristine Smedsrud,<sup>1,3</sup> Sebastian I Sarvari,<sup>1</sup> Hege W Landgraff,<sup>4</sup> Jostein Hallén <sup>4</sup>, Thor Edvardsen <sup>1,2</sup>

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## ABSTRACT

**Background** Athlete's heart is a condition of exercise-induced cardiac remodelling. Adult male endurance athletes more often remodel beyond reference values. The impact of sex on remodelling through adolescence remains unclear. Paediatric reference values do not account for patient sex or exercise history. We aimed to study the effect of sex on cardiac remodelling throughout adolescence.

**Methods** We recruited 76 male (M) and female (F) 12-year-old cross-country skiers in a longitudinal cohort study. Echocardiography was performed and analysed according to guidelines at age 12 (48 M, 28 F), 15 (34 M, 14 F) and 18 (23 M, 11 F). Repeated echocardiographic measurements were analysed by linear mixed model regression.

**Results** Males displayed greater indexed left ventricular end-diastolic volumes (LV EDVi) from age 12 (M  $81 \pm 7$  vs F  $76 \pm 7$ , mL/m<sup>2</sup>,  $p < 0.01$ ), and progressed further until follow-up at age 18 (M  $2.3 \pm 9.7$  vs F  $-3.9 \pm 4.5$   $\Delta$ mL/m<sup>2</sup>,  $p < 0.01$ ). LV EDVi remained above adult upper reference values in both groups. Males increased LV Mass Index from age 12 to 18 (M  $33 \pm 27$  vs F  $4 \pm 19$ ,  $\Delta$ g/m<sup>2</sup>,  $p < 0.01$ ). Males displayed LV mass above paediatric reference values at ages 15 and 18. A subset of males (35%) and females (25%) displayed wall thickness above paediatric reference values at age 12. Cardiac function was normal. There was no sex difference in exercise hours.

**Conclusion** Sex-related differences in athlete's heart were evident from age 12, and progressed throughout adolescence. Remodelling beyond reference values was more frequent than previously reported, particularly affecting males. Age, sex and exercise history may assist clinicians in distinguishing exercise-induced remodelling from pathology in adolescents.

## INTRODUCTION

Extensive exercise training may induce morphological changes known as the athlete's heart. Hallmarks of athlete's heart are chamber dilatation and wall thickening.<sup>1,2</sup> The presentation of athlete's heart varies between different sports disciplines, most pronounced in endurance sports practitioners.<sup>2,3</sup> Previous reports from our group

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Exercise induces cardiac remodelling, with established sex differences in adults. The impact of sex on adolescent athlete's heart is unclear.

### WHAT THIS STUDY ADDS

⇒ Sex differences in exercise-related cardiac remodelling were evident from early adolescence, and progressed through pubertal years. Remodelling beyond reference values was found in male and female athletes from early adolescence, and more frequent in males from mid-adolescence.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinicians should take into consideration patient sex and exercise history when evaluating adolescents' hearts.

indicate that features of athlete's heart can appear as early as late childhood, and evolve throughout adolescence.<sup>4</sup> Remodelling has been reported to be modest compared with adults.<sup>5-7</sup>

The impact of sex on adult athlete's heart is well described.<sup>2</sup> Adult male athletes more often develop chamber sizes and wall thickness at levels defined as pathological in non-athletes, even when compared with females practising same sport.<sup>2,8</sup> While adult reference values are sex-specific, sex was not regarded clinically important in echocardiographic reference values from the Paediatric Heart Network.<sup>9,10</sup> However, exercise data were not evaluated in these recommendations. Sex differences are described in cross-sectional studies on mid-adolescent athlete's heart.<sup>5-7</sup> Few studies compare males and females practising the same sport, therefore, the impact of different exercise exposure might bias the impact of sex on cardiac remodelling in adolescence.<sup>5,11</sup> There is also a paucity of longitudinal data comparing males and females through pubertal years. Hence, the



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<sup>1</sup>ProCardio Center for Innovation, Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway

<sup>2</sup>Institute of Clinical Medicine, University of Oslo, Oslo, Norway

<sup>3</sup>Department of Paediatric Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway

<sup>4</sup>Department of Physical Performance, Norwegian School of Sports Sciences, Oslo, Norway

### Correspondence to

Dr Thor Edvardsen; thor.edvardsen@medisin.uio.no

pattern of physiological remodelling and evolvement of sex differences in adolescent athlete's heart remains unclear. It is essential to determine whether hypertrophy in a highly trained athlete is an expression of benign, physiological adaptation to exercise or rather a pathological process. Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and arrhythmogenic cardiomyopathy (AC) are examples of conditions that may mimic athlete's heart.<sup>12,13</sup> They are all associated with increased risk for sudden cardiac death.<sup>2,14</sup>

This study aimed to explore development of sex differences in adolescent athlete's heart, and the cardiac remodelling over time. We hypothesised that sex differences in cardiac remodelling increase with age, and that male athletes develop greater morphological changes compared with female athletes.

## METHODS

We recruited male and female 12-year-old cross-country skiers from South-Eastern Norway. They were members of athletic clubs and defined as athletes due to participation in organised trainings and competitions. They were followed from 2013 with examinations every third year until 2019. The participants underwent echocardiography and cardiopulmonary testing at ages 12, 15 and 18. They filled out questionnaires on exercise duration, frequency, intensity and sports discipline at all examinations, and were interviewed by an experienced observer to ensure correct categorisation of exercise data. Due to the playful nature of the 12-year-old athletes' exercise regime, endurance and non-endurance exercise was collected as one unit. Exercise was divided into endurance exercise, like

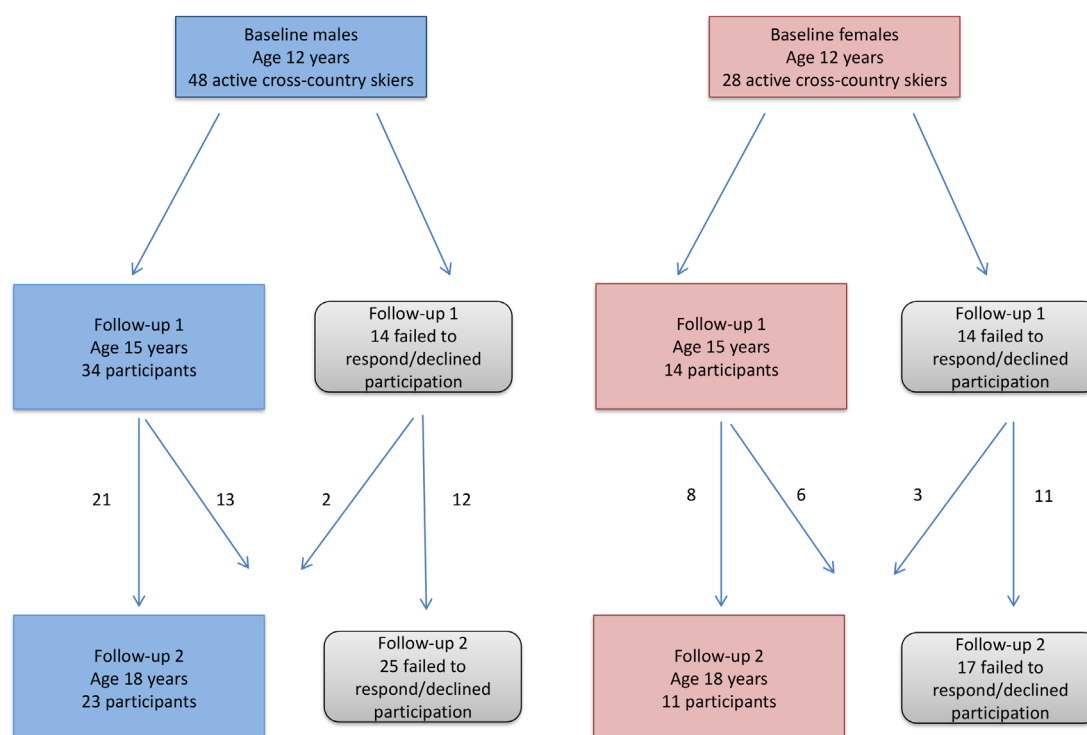
running, biking or skiing, and non-endurance exercise at age 15 and 18. The latter included strength, tactical or technical exercise. We collected data on prior illness and family history of cardiac disease.

Strengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist for cohort reporting was completed.<sup>15</sup> The corresponding author had full access to all data in the study and takes responsibility for its integrity and the data analysis.

## Echocardiography

All examinations were performed on a Vivid E9/E95 machine (GE, Vingmed, Horten, Norway). Measurements and analyses were performed by one single, blinded observer (Echopac; GE, Vingmed). Images were obtained from parasternal long-axis, short-axis, apical four-chamber, three-chamber, two-chamber and subcostal views. All measurements, including global longitudinal strain (GLS) by speckle-tracking strain ( $63 \pm 11$  Hz), were assessed from two-dimensional echocardiography, in accordance with recommendations of the European Society of Cardiovascular Imaging.<sup>16</sup> Chamber sizes and mass were indexed to body surface area (BSA). Left ventricular (LV) ejection fraction (EF) was measured by the biplane Simpson's method. Two-dimensional LV mass was calculated by using Devereux' formula.<sup>17</sup> Relative wall thickness (RWT) was calculated as  $((2 \times \text{LV posterior wall thickness}) / \text{LV internal diameter})$  at end-diastole. Detailed description was given in a recent publication from the same study cohort.<sup>4</sup>

Echocardiographic Z-scores were used to normalise the sizes of cardiovascular structures for body size in growing



**Figure 1** Flow chart. Number of male (blue panel) and female (red panel) participants at baseline, first and second follow-up.

**Table 1** Basic characteristics in male and female athletes at baseline, first and second follow-up

	Baseline 12 years old		First follow-up 15 years old		Second follow-up 18 years old	
	Male	Female	Male	Female	Male	Female
	(n=48)	(n=28)	(n=34)	(n=14)	(n=23)	(n=11)
Age, years	12.1±0.2	12.1±0.2	15.3±0.3	15.2±0.2	18.4±0.3	18.3±0.2
Height, cm	151±7	154±7	174±10	170±9	184±8	171±7*
Weight, kg	40±5	42±6	59±9	56±7	74±8	65±10*
BSA, m <sup>2</sup>	1.3±0.1	1.4±0.1	1.7±0.2	1.6±0.1	2.0±0.1	1.8±0.1*
BMI, kg/m <sup>2</sup>	17.4±1.5	17.6±1.7	19.4±1.7	19.4±1.9	21.6±1.6	22.1±3.1
Resting HR, bpm	71±12	72±11	61±9	64±10	54±9	58±8
Exercise, hour/wk	7.1±2.5	6.9±2.1	10.0±3.7	9.0±4.1	11.9±4.3	11.1±3.6
Endurance exercise hour/wk	NA	NA	5.7±3.5	4.9±2.6	8.0±5.1	6.6±3.0
Cardiopulmonary exercise test parameters						
VO <sub>2</sub> max mL/min	2545±336	2583±330	3704±626	2931±388*	4906±695	3399±416*
VO <sub>2</sub> max indexed, mL/min/kg	65.1±6.3	57.9±4.9*	64.2±5.7	52.4±6.0*	67.1±6.7	52.9±5.0*
RER	1.05±0.05	1.08±0.05*	1.10±0.05	1.12±0.09	1.11±0.05	1.13±0.07

Observed values expressed as mean±SD. P values for baseline values are calculated using the Student's t-test. P values for follow-ups by linear mixed model regression analysis.

\*Significant difference between male and female group, p≤0.01.

BMI, body mass index; bpm, beats per minute; BSA, body surface area; HR, heart rate; NA, not available; RER, peak respiratory exchange ratio; VO<sub>2</sub> max, maximal oxygen uptake per minute.

children.<sup>9</sup> A BSA-adjusted dimension plus 2 times the standard deviation (ie, Z-score >2) was considered above the upper reference value.

### Cardiopulmonary exercise testing

An incremental exercise test to exhaustion was used to measure maximal oxygen uptake (VO<sub>2</sub> max) (Woodway Elg 70, Weil am Rhein, Germany).<sup>18</sup> The test was terminated when the participant was unable to complete the desired workload. Continuous measurements of oxygen uptake were performed with an automated system (Oxycon Pro, Jaeger-Toennis, Hochberg, Germany).

### Statistical analysis

Data were analysed and presented as observed values at each time point, with numbers, mean±SD and percentages (age 12, age 15 and age 18). Delta values were reported for changes from baseline to each follow-up. Between-group differences at baseline were assessed by the Student's t-test (continuous variables). Repeated echocardiographic measurements were analysed by linear mixed model regression with random slope and intercept.

Linear mixed model regression analysis were used to assess the impact of sex and exercise on each variable. Exercise was defined as the total, cumulative number of exercise hours (per 1000) since baseline. Fixed effects were total hours of exercise, sex and the interaction of these. Reproducibility was expressed as intraclass correlation coefficient (ICC). Statistical analyses were performed using STATA V.15.0 (StataCorp).

## RESULTS

Seventy-six participants were included at age 12, 48 males and 28 females (figure 1). All were active cross-country skiers and in early pubertal age at inclusion. They reported 7±2 hours of exercise per week at age 12, increasing to 12±4 hours of exercise per week at age 18, with no intersex difference at any time point (table 1). Endurance exercise represented more than 50% of total hours exercised in both groups at age 15 and 18. Sex difference in height, weight and BSA first became evident at age 18.

Twenty-four of 34 male participants reported still being active cross-country skiers at age 15, while 9 of 14 female participants still competed. Sixteen of 23 male participants were active cross-country skiers at age 18, while 5 of 11 female participants still competed. The remaining participants were active at a recreational level or shifted to competing in a different sport. All reported minimum 3 hours of total weekly exercise.

### Cardiac morphology

#### Cardiac chambers

Both male and female athletes showed indexed biventricular chamber sizes close to or above upper reference value for the adult population at all time points (table 2, graphical abstract online supplemental figure 1, figure 2).<sup>16</sup> The 12-year-old male athletes had greater chamber sizes than female athletes when indexing for BSA. This was evident for both LV end-systolic volume (LV ESVi) and end-diastolic volume (LV EDVi), right

**Table 2** Cardiac morphology and function in male and female adolescent athletes at baseline, first and second follow-up

	Baseline 12 years old		First follow-up 15 years old		Second follow-up 18 years old	
	Male	Female	Male	Female	Male	Female
	(n=48)	(n=28)	(n=34)	(n=14)	(n=23)	(n=11)
LA volume/BSA, mL/m <sup>2</sup>	28.4±6.4	25.2±4.8	32.5±7.3	29.4±6.7	39.6±8.4	29.1±4.2*
IVSd, mm	7.8±0.9	7.9±0.8	8.3±1.0	7.3±1.0*	9.5±1.3	8.0±1.1*
LVPWd, mm	7.2±1.0	7.2±0.7	8.1±1.1	7.1±1.2*	9.4±1.3	7.8±0.6*
LVIDd, mm	42±0.3	40±0.3	51±0.4	47±0.3*	55±0.5	48±0.5*
LVIDd/BSA, mm/m <sup>2</sup>	2.1±0.3	1.9±0.3	3.0±0.2	2.9±0.2	2.8±0.2	2.7±0.2
LV EDV, mL	106±14	103±15	147±29	118±13*	166±26	124±17*
LV EDV/BSA, mL/m <sup>2</sup>	81±7	76±7*	86±12	72±6*	85±9	70±6*
LV ESV, mL	45±7	43±7	63±13	51±7*	64±16	50±8*
LV ESV/BSA, mL/m <sup>2</sup>	34±4	32±4*	37±7	31±4*	32±6	29±3
LVM, g	92±18	87±13	147±36	106±24*	204±50	126±25*
LVM/BSA, g/m <sup>2</sup>	70±13	65±9	85±16	65±14*	103±22	72±13*
RV EDA, cm <sup>2</sup>	17.2±2.8	16.8±2.7	23.5±4.5	18.8±3.1*	26.8±4.4	20.3±2.5*
RV EDA/BSA, cm <sup>2</sup> /m <sup>2</sup>	15.3±3.1	13.6±2.2*	13.7±2.3	11.5±1.7*	13.6±2.1	11.6±1.1*
RV ESA, cm <sup>2</sup>	10.7±2.0	9.9±1.6	14.3±2.9	11.5±10.3*	15.3±2.5	11.7±2.0*
RV ESA/BSA, cm <sup>2</sup> /m <sup>2</sup>	8.9±1.9	7.8±1.4*	8.3±1.5	7.0±1.1*	7.8±1.1	6.6±1.0*
RWT	0.35±0.05	0.36±0.05	0.32±0.04	0.31±0.05	0.34±0.06	0.33±0.03
Z-scores						
IVSd, Z-score	1.4±1.0	1.4±0.8	1.0±0.8	0.2±0.8*	1.7±1.0	0.7±1.1*
LVPWd, Z-score	0.8±0.9	0.9±0.7	1.0±0.8	0.2±1.1*	1.7±1.1	0.6±0.6*
LVIDd, Z-score	-0.4±0.9	-0.9±0.8	0.4±0.8	-0.4±0.7*	0.7±0.9	-0.4±0.9*
LV EDV, Z-score	1.2±0.5	0.7±0.7*	1.1±0.8	0.1±0.5*	0.7±0.6	-0.1±0.5*
LVM, Z-score	1.5±1.4	0.9±1.1	2.6±1.5	0.6±1.3*	3.9±1.9	1.2±1.5*
LV systolic function						
LV EF, %	58±3	58±4	57±3	57±2	62±5	60±3
LV GLS, %	22.9±2.1	21.8±1.5*	22.4±1.9	21.7±2.4	20.7±1.6	20.6±1.3
LV diastolic function						
Mitral E velocity, cm/s	0.95±0.12	0.96±0.11	0.98±0.17	1.00±0.12	0.86±0.14	0.86±0.10
Mitral A velocity, cm/s	0.46±0.12	0.47±0.10	0.44±0.10	0.43±0.07	0.41±0.08	0.43±0.11
Mitral E/A ratio	2.2±0.5	2.1±0.4	2.3±0.6	2.4±0.7	2.1±0.5	2.1±0.7
E/e' ratio	7.0±1.3	7.0±1.1	7.1±1.5	7.1±1.5	6.0±0.9	6.2±0.9

Observed values are expressed as mean±SD. P values at baseline are calculated using the Student's t-test. P values for follow-ups are calculated by linear mixed model regression analysis. Z-scores are calculated by parameterz.com calculator, and values are number of standard deviations above estimated mean for the given BSA, -2-2 is normal range.

\*Significant difference between male and female group, p≤0.01.

BSA, body surface area; EDA, end-diastolic area; EDV, end-diastolic volume; EF, ejection fraction; ESA, end-systolic area; ESV, end-systolic volume; GLS, global longitudinal strain; IVSd, interventricular septum thickness in end-diastole; LA, left atrium; LV, left ventricle; LVIDd, left ventricular internal diameter in end-diastole; LVM, left ventricular mass; LVPWd, left ventricular posterior wall thickness in end-diastole; RV, right ventricular; RWT, relative wall thickness.

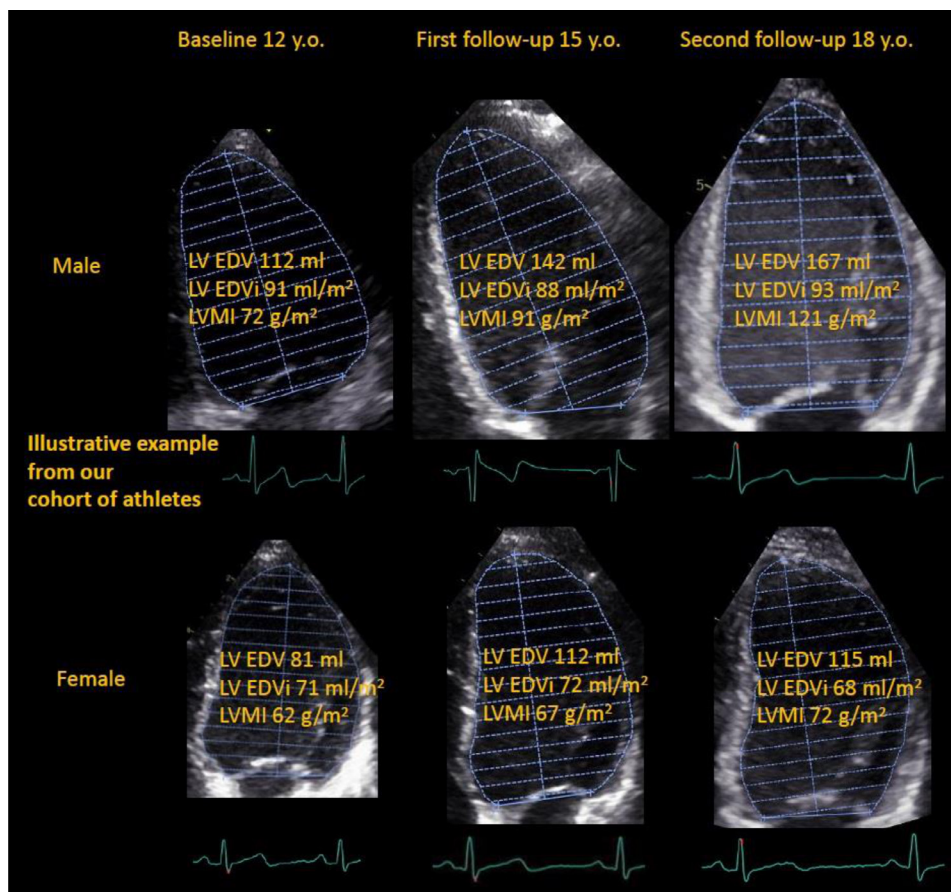
ventricular end-diastolic area (RV) and end-systolic area (RV ESAi).

LV EDVi and ESVi increase was greater in males from ages 12 to 15 (table 3). From similar indexed left atrial volumes (LAVI) at age 12, only male athletes increased LAVI from ages 12 to 15 and further to age 18.

#### LV mass and wall thickness

Both groups demonstrated indexed left ventricular mass (LVMI) within reference values at time of inclusion. Only

males increased their LVMI, and reached upper reference value for adults at age 18 (table 3).<sup>16</sup> Sex differences in LVMI were evident from age 15 (table 2, graphical abstract (online supplemental figure 1)). Normal LV geometry was the dominating pattern in both groups. Concentric remodelling was found in 4/48 males (8%) and 4/28 females (14%) at age 12. Chamber dilatation exceeded relative wall thickening by mid-adolescence, and RWT was normalised at age 15. From then, only



**Figure 2** Illustration of typical sex differences in LV remodelling in adolescent athletes by echocardiography. Typical LV remodelling (at end-diastole) from apical four-chamber view in a male (upper row) and a female (lower row) adolescent athlete. The male athlete displays greater increase in LV EDV, LV EDVi and LVMI compared with the female from age 12 (first column), to age 15 (second column) and age 18 (third column). EDV(i), end-diastolic volume (indexed); LV, left ventricular; LVMI; LV mass indexed.

males demonstrated concentric and eccentric remodeling at the last follow-up. Concentric hypertrophy was not found.

#### Z-scores

Males had larger Z-scores for LV EDV from age 12 (table 2). Additional sex differences in interventricular septum thickness (IVSd), LV posterior wall thickness (LVPWd) and LV mass (LVM) was evident from age 15. The male group demonstrated LVM above paediatric reference values (Z-score >2) at ages 15 and 18 (table 2, figure 3). Wall thickness was within reference values on group levels at all time points. However, 17/48 males (35%) and 7/28 females (25%) demonstrated Z-scores >2 for IVSd and/or LVPWd at age 12. IVSd was most frequently enlarged (13 males, 5 females). Only three males had Z-scores >2 for IVSd and/or LVPWd at age 15. By age 18, 13/23 males (56%) and 3/11 females (27%) had Z-scores >2 for IVSd and/or LVPWd.

#### Cardiac function

Both groups had normal cardiac function throughout the study period, evaluated by EF, GLS and diastolic function (table 2).

#### Effect of exercise

Both groups reported the same amount of exercise, but morphological changes were more pronounced in males (tables 2 and 3). We estimated the effect of exercise on parameters of importance for athlete's heart by linear mixed model analysis. Male adolescent athletes increased their LVMI by 7.4g more than females for every 1000 hour of exercise. Likewise, for every 1000 hours of exercise males increased LAVI by 1.8mL more than females, and LV EDVi by 4.0mL more than females.

#### Cardiopulmonary exercise testing

Male athletes had greater absolute values of  $\text{VO}_2$  max at time of inclusion (table 1), and the increase was greater in males at all time points. Both groups had moderate to strong correlations between  $\text{VO}_2$  max and LV EDV (age 12 male  $R=0.67$ ,  $p<0.001$ , female  $R=0.65$ ,  $p<0.001$ , age 15 male  $R=0.85$ ,  $p<0.001$ , female  $R=0.86$ ,  $p<0.001$ , age 18 male  $R=0.71$ ,  $p<0.001$ , female  $R=0.80$ ,  $p<0.01$ ). We found a strong correlation between  $\text{VO}_2$  max and LVM in males at ages 15 and 18 ( $R=0.84$ ,  $p<0.001$  and  $R=0.87$ ,  $p<0.001$ ), while there was no significant correlation in females. At age 12, the correlation was weak to moderate

**Table 3** Changes in echocardiographic parameters in male and female athletes from baseline to first follow-up, first to second follow-up and baseline to second follow-up

	Baseline to first follow-up (12–15 years old)		First to second follow-up (15–18 years old)		Baseline to second follow-up (12–18 years old)	
	Male	Female	Male	Female	Male	Female
	(n=34)	(n=12)	(n=21)	(n=7)	(n=23)	(n=10)
LA volume/BSA, $\Delta\text{mL}/\text{m}^2$	3.8 $\pm$ 8.0*	4.9 $\pm$ 5.7	6.6 $\pm$ 10.2*	1.6 $\pm$ 7.2	11.1 $\pm$ 9.0*	6.1 $\pm$ 5.4
IVSd, $\Delta\text{mm}$	0.4 $\pm$ 1.2	-0.6 $\pm$ 1.4†	1.2 $\pm$ 1.2*	1.1 $\pm$ 1.9	1.6 $\pm$ 1.7	-0.2 $\pm$ 1.5†
LVIDd, $\Delta\text{mm}$	9.0 $\pm$ 4.9*	6.5 $\pm$ 3.0*	3.3 $\pm$ 4.7*	2.6 $\pm$ 1.5	13.1 $\pm$ 5.7*	8.3 $\pm$ 4.4*
LVPWd, $\Delta\text{mm}$	1.1 $\pm$ 1.4*	-0.2 $\pm$ 1.4†	1.1 $\pm$ 1.1*	1.4 $\pm$ 1.0	2.0 $\pm$ 1.8	0.3 $\pm$ 1.2†
LVIDd/BSA, $\Delta\text{mm}/\text{m}^2$	0.9 $\pm$ 0.3*	0.9 $\pm$ 0.2*	-0.2 $\pm$ 0.2*	-0.0 $\pm$ 0.1	0.7 $\pm$ 0.3	0.8 $\pm$ 0.3
LV EDV, $\Delta\text{mL}$	42 $\pm$ 23*	15 $\pm$ 25*†	13 $\pm$ 16*	1 $\pm$ 12	57 $\pm$ 20*	25 $\pm$ 11*†
LV EDV/BSA, $\Delta\text{mL}/\text{m}^2$	4.6 $\pm$ 12.4*	-5.4 $\pm$ 14.2†	-2.6 $\pm$ 9.6	-4.4 $\pm$ 6.3	2.3 $\pm$ 9.7	-3.9 $\pm$ 4.5†
LV ESV, $\Delta\text{mL}$	19 $\pm$ 12*	12 $\pm$ 9*†	1 $\pm$ 10	-3 $\pm$ 6	18 $\pm$ 13*	10 $\pm$ 6*
LV ESV/BSA, $\Delta\text{mL}/\text{m}^2$	2.8 $\pm$ 6.6*	1.2 $\pm$ 4.5	-4.8 $\pm$ 5.1*	-3.6 $\pm$ 2.7	-2.0 $\pm$ 6.3	-1.8 $\pm$ 3.8
LVM, $\Delta\text{g}$	55 $\pm$ 36*	18 $\pm$ 30†	49 $\pm$ 33*	35 $\pm$ 23*	107 $\pm$ 51*	35 $\pm$ 32*†
LVM/BSA, $\Delta\text{g}/\text{m}^2$	14 $\pm$ 21*	-2 $\pm$ 20†	16 $\pm$ 16*	17 $\pm$ 13	33 $\pm$ 27*	4 $\pm$ 19†
RV EDA/BSA, $\Delta\text{cm}^2/\text{m}^2$	-2.6 $\pm$ 2.7*	-3.0 $\pm$ 2.9*	-0.3 $\pm$ 2.4	-1.1 $\pm$ 1.2	-1.7 $\pm$ 3.4*	-2.9 $\pm$ 3.2*
RV ESA/BSA, $\Delta\text{cm}^2/\text{m}^2$	-1.1 $\pm$ 2.0	-1.6 $\pm$ 1.4	-0.7 $\pm$ 1.3	1.1 $\pm$ 0.8	-0.9 $\pm$ 1.9*	-1.7 $\pm$ 2.2*

Observed values expressed as mean $\pm$ SD. P values are calculated using linear mixed model regression analysis.

\*Significant increase between follow-ups,  $p\leq 0.01$ .

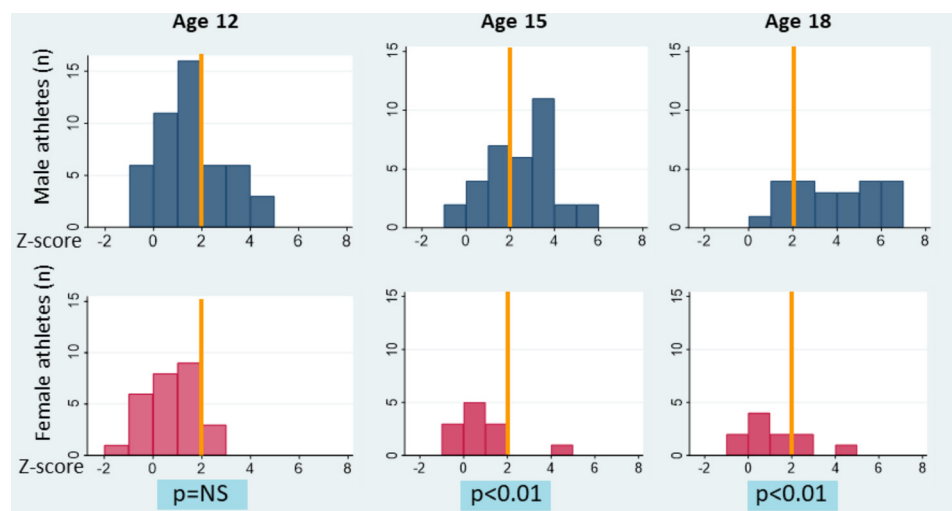
†Significant difference between male and female group,  $p\leq 0.01$ .

BSA, body surface area; EDA, end-diastolic area; EDV, end-diastolic volume; ESA, end-systolic area; ESV, end-systolic volume; IVSd, interventricular septum thickness in end-diastole; LA, left atrium; LV, left ventricle; LVIDd, left ventricular internal diameter in end-diastole; LVM, left ventricular mass; LVPWd, left ventricular posterior wall thickness in end-diastole; RV, right ventricle.

in both groups (male  $R=0.32$ ,  $p<0.05$ , female  $R=0.44$ ,  $p<0.05$ ). The correlation between LAVI and  $\text{VO}_2$  max was only significant in males, and stronger at age 15 ( $R=0.69$ ,  $p<0.001$ ) and 18 ( $R=0.67$ ,  $p<0.001$ ).

### Reproducibility

Reproducibility analyses were performed for LV EDV, LV ESV, RV EDA and EF. Interobserver intraclass correlations for LV EDV was 0.96 ( $p<0.001$ ), for LV ESV 0.92 ( $p<0.001$ ), EF 0.73 ( $p=0.03$ ) and RV EDA 0.92 ( $p=0.001$ ). Intraobserver intraclass correlations for LV EDV was 0.99



**Figure 3** Distribution of left ventricular mass (LVM) Z-scores in serial echocardiographic measurements of male and female adolescent athletes at ages 12, 15 and 18. Males in blue (upper row), females in red (lower row). The orange, vertical line demarks Z-score 2. Values to the right of the orange line are above upper reference value. P values comparing male and female group at baseline (age 12) are calculated using the Student's t-test, and not significant (NS). P values for follow-ups (ages 15 and 18) are calculated by linear mixed model regression analysis.

( $p < 0.001$ ), LV ESV 0.97 ( $p < 0.001$ ), EF 0.77 ( $p = 0.02$ ) and RV EDA 0.94 ( $p < 0.001$ ). LV and RV strain intraobserver and interobserver variability analyses was published in a previous study.<sup>19</sup>

## DISCUSSION

The longitudinal design of our study may provide novel insight into the development of sex differences in adolescent athlete's heart. Features of athlete's heart were found in male and female athletes from early adolescence, with progressing sex differences through pubertal years. Both groups demonstrated cardiac remodelling beyond reference values already at age 12. Remodelling beyond reference values was, however, more frequent in males from mid-adolescence. Our findings suggest that sex-related differences in adolescent cardiac remodelling might be more comprehensive than previously reported. They propose a need for a sex-specific approach when evaluating the hearts of adolescent athletes.

### Development of sex differences in cardiac morphology

By examining male and female athletes with similar exercise exposure in early, mid and late adolescence, we were able to compare the development of athlete's heart over time. The significant sex-related differences in patterns of cardiac growth and remodelling were evident also when indexing for BSA. Interestingly, both male and female athletes showed signs of athlete's heart by biventricular enlargement, evident from early to late adolescence. This finding indicates a volumetric effect of exercise in both groups. We found the further chamber dilatation and mass increase to be more pronounced in male athletes, diverging from age 12 (graphical abstract online supplemental figure 1). Volumetric effect of exercise in early adolescence is previously only described in males.<sup>20</sup> Our findings suggest that sex-related differences described in previous cross-sectional studies were developed from early to mid adolescence.<sup>5–7</sup> This is in line with a comprehensive review study of adolescent athlete's heart, where age 14 was proposed as a 'cut-off' for maturational years,<sup>5</sup> corresponding to sex-related differences in remodelling patterns in sports-matched Olympic athletes.<sup>8</sup>

Growing body size during adolescence have a well-described impact on cardiac growth and remodelling in both males and females.<sup>5 21 22</sup> Males display a more rapid LV mass growth rate from age 12, paralleling their rapid increase in body height and weight.<sup>21</sup> Lean body mass increase more in males during puberty, while percentage body fat increase more in females.<sup>22</sup> The relative weight of somatic growth versus exercise training on cardiac remodelling in maturational years is debated, and yet to be fully explored.<sup>23 24</sup> The previously mentioned review paper on adolescent athlete's heart found significant differences in cardiac size between athletes and non-athletes, also when adjusting for age.<sup>5</sup> These differences appeared to exaggerate during maturational years.

However, one limitation was the cross-sectional design in the majority of studies reviewed, permitting causative conclusions to be drawn.

It is likely that pubertal hormonal influences were at least partly responsible for the sex differences in our study group. Androgen receptors mediate cardiac hypertrophy in both male and female cardiac myocytes.<sup>25</sup> Norwegian males enter puberty at 11.7 years, while females enter puberty at 10.4 years.<sup>26 27</sup> Male testosterone levels increase from start of puberty, which coincidence around our baseline examination.<sup>28</sup> One could, therefore, speculate that the pubertal male testosterone boost was the prime mechanism behind the apparently superior effect of exercise on the male heart. However, as our baseline examination took place after average female pubertal onset, we can not estimate the impact of early female maturation on cardiac development. In order to explore the relative weight of somatic growth versus exercise training on cardiac remodelling in maturational years, we need prospective studies. Ideally, a longitudinal study comparing males and females from preadolescence to adult age, with monitoring of physical activity and maturational stage. This inherits important ethical and practical considerations.

### Evaluation of athlete's heart by paediatric reference values

An interesting finding in our study was the amount of male and female athletes with wall thickening above paediatric reference values (Z-score  $> 2$ ) at age 12. The male group even exceeded reference values for LVM at ages 15 and 18. Note that Z-scores should be interpreted with care at age 18, where underlying data are more scarce compared with younger age groups. Nonetheless, findings of increased wall thickness and LVM in a preparticipation screening could lead to considerations about high-intensity sport participation. The challenge lies in separating exercise-induced LV hypertrophy from early stages of pathology, such as HCM, AC or DCM. Recent guidelines for HCM diagnosis suggest a Z-score of  $> 2.5$  as a threshold for identification of early HCM in asymptomatic children without family history.<sup>29</sup> In family screening for HCM a Z-score  $> 2$  is applied. Current reference values for echocardiography in children do not include exercise data, which challenges the interpretation of pathological values in adolescent athletes. Age and sex had only small additional effects on paediatric reference values in a recent review article, and the differences were not considered clinically important.<sup>9 10</sup> This is in contrast to a prior paediatric MRI study, showing sex differences in LV measurements, also after indexing for BSA.<sup>30</sup> We argue that the observed sex-related differences in cardiac morphology could be of clinical significance in adolescent athletes. As our study population is small, larger studies are warranted to establish sex-specific echocardiographic reference values for adolescent athletes. This is important to improve distinguishing of physiological adaptation to exercise from potential pathological processes.

## Sex differences in exercise effect on cardiac morphology and VO<sub>2</sub>max

The correlation between LVM and LAV to VO<sub>2</sub> max was exclusive to the male group. Growing body size, including cardiac, pulmonary and muscular growth, has been proposed as the most powerful determinants for VO<sub>2</sub> max, but this is highly debated.<sup>31–34</sup> Sex-related differences in determinants of VO<sub>2</sub> max are scarcely described for adolescent athletes. The greater increase in male LV mass and volume supports the hypothesis of cardiac size as a powerful determinant of VO<sub>2</sub> max along with body size. Our male athletes nearly doubled their VO<sub>2</sub> max during the observation period, and the correlation between LVM and VO<sub>2</sub> max might only be evident from a certain LVM level, which females in our study did not reach. Our findings may support that indexing of VO<sub>2</sub> max should be sex-specific.

### Clinical implications

Distinguishing physiological, benign adaptation to exercise from pathological processes with risk for sudden cardiac death is an important challenge for clinicians. Cardiac remodelling was seen already at age 12 and progressed, particularly in males. This indicates that patient sex may be of relevance when evaluating athlete hearts also in adolescents. Our athletes demonstrated normal cardiac function, evaluated by EF, GLS and diastolic function. This is in line with previous studies comparing athlete's heart to cardiomyopathy patients.<sup>2</sup> Increased wall thickness without concomitant ventricular dilatation seems unlikely to represent physiological adaptation to exercise, as does unilateral ventricular dilatation or reduced cardiac function. Female sex and a lack of prior exercise history should raise suspicion of pathology if LVM is above reference values. The association between LV EDV and VO<sub>2</sub> max in both our male and female group supports usefulness of exercise testing in cases where the mechanism behind LV hypertrophy remains unclear. This is already suggested in adult guidelines.<sup>27</sup>

Our study supports an integrated approach where sex, exercise anamnesis and family history of cardiac disease are key elements in the examination of the adolescent athlete's heart.

### Limitations

Reports of exercise, including exercise intensity and duration, are not able to provide complete insight into the performance of each exercise hour. Differences in exercise intensity between the participants cannot be excluded. The smaller number of female participants could potentially limit the ability to detect significant remodelling in this group, particularly at last follow-up due to attrition. We used linear mixed model regression analysis with random slope and intercept to investigate development over time, and account for missing data points. Though we can not exclude selection bias,

we believe our data provide insight into the remodelling patterns of adolescents who continue exercise through adolescence.

The athletes were recruited from the same endurance sport, and findings may not be directly comparable to athletes of other sports. We cannot exclude a change in remodelling pattern if change of sports. Our participants were compared using their chronological age, not maturational level. A complete evaluation of pubertal status was not performed.

### CONCLUSIONS

This longitudinal study may improve our understanding of the development of sex differences in adolescent athlete's heart. Features of athlete's heart were more pronounced in males from early adolescence, with progressing sex differences through pubertal years. While both groups demonstrated cardiac remodelling beyond reference values in early adolescence, this was more frequent in males in mid and late adolescence. Although the study size was limited, our findings suggest that sex-related differences in exercise-induced cardiac remodelling might be more comprehensive than previously reported. Larger studies are warranted to establish sex-specific cardiac reference values for adolescent athletes.

**Twitter** Thor Edvardsen @ThorEdvardsen

**Contributors** MIF, AWB, HWL, KHH, MKS, SIS, JH and TE contributed to the conception or design of the work. All coauthors contributed to the acquisition, analyses or interpretation of data for the work. MIF drafted the manuscript. All coauthors critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy. The corresponding author (TE) had full access to all data in the study and takes responsibility for its integrity and the data analysis. TE acts as the guarantor, and accepts full responsibility for the work and conduct of the study, had access to the data, and controlled the decision to publish.

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#### ORCID iDs

Marianne Inngjerdingen Forså <http://orcid.org/0000-0001-7459-6642>

Jostein Hallén <http://orcid.org/0000-0002-6646-0734>

Thor Edvardsen <http://orcid.org/0000-0002-3800-765X>

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Background

**Athlete's heart: Sex differences in cardiac remodelling increase during adolescence**

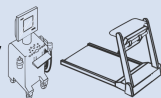
**Longitudinal cohort study**

Cross-country skiers  
 Age 12 (n=78, F 37%)  
 Age 15 (n=48, F 29%)  
 Age 18 (n=34, F 32%)



**Consecutive examinations**

Age 12, 15, 18  
 Echocardiography  
 Exercise test  
 Exercise data



**Males display greater left ventricular remodelling compared to females with similar exercise exposure**



**Figure**

Blue area: Male reference values  
 Purple area: Common reference values  
 Pink area: Female reference values  
 Lang et al (2015), ASE

\*: Significant difference male vs female group,  $P \leq 0.01$ .

Graphical illustrations: smart.servier.com, thenounproject.com

