Left ventricular morphology and function in adolescents: relations to fitness and fatness

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ABSTRACT

Background: Obesity in childhood predisposes individuals to cardiovascular disease and increased risk of premature all-cause mortality. The aim of this study was to determine differences in LV morphology and function in obese and healthy-weight adolescents. Furthermore, relationships between LV outcomes, cardiorespiratory fitness (CRF) and adiposity were explored.

Methods: LV morphology was assessed using magnetic resonance imaging (MRI) in 20 adolescents (11 healthy-weight [BMI equivalent to 18kg/m^2–25 kg/m^2] and 9 obese [BMI equivalent to ≥30 kg/m^2]); 13.3±1.1 years, 45% female, Tanner puberty stage 3 [2–4]) using magnetic resonance imaging (MRI). Global longitudinal strain (GLS), strain rate (SR) and traditional echocardiographic indices were used to assess LV function. CRF (peak oxygen consumption), percent body fat (dual-energy x-ray absorptiometry), abdominal adipose tissue (MRI), and blood biochemistry markers were also evaluated.

Results: Adolescents with obesity showed significantly poorer LV function compared to healthy-weight adolescents ($P<0.05$) indicated by higher GLS (+6.29 %) and SR in systole (+0.17 s^{-1}), and lower SR in early diastole (-0.61 s^{-1}), and tissue Doppler velocities (S' -2.7 cm/s; e' -2.3 cm/s; A' -1.1 cm/s). There were no group differences in LV morphology when indexed to fat free mass ($P>0.05$). Moderate to strong associations between myocardial contractility and relaxation, adiposity and cardiorespiratory fitness were noted in all participants ($r=0.46–0.71$, $P<0.05$).

Conclusion: Obesity in adolescence is associated with altered LV systolic and diastolic function. The notable relationship between LV function, CRF and adiposity highlights the potential utility of multidisciplinary lifestyle interventions to treat diminished LV function in this population.

INTRODUCTION

Paediatric obesity, which affects approximately 17% of children and adolescents worldwide [1], is likely to persist into young adulthood and adversely impacts multiple cardiovascular risk factors [2]. In fact, adiposity in paediatric life is a consistent predictor of increased left ventricular mass (LVM) in young adults [3].

Left ventricular hypertrophy (LVH), which manifests as increased LVM, has been established as a strong predictor of heart failure events and may increase the risk of sudden cardiac death in adults [4]. Obese adolescents have significantly greater absolute and relative LVM compared to healthy-weight adolescents, when assessed through magnetic resonance imaging (MRI) [5,6] and echocardiography [7,8]. However, previous investigations normalised cardiac structure using traditional anthropometric indices (height), which is problematic when comparing populations with starkly contrasting body composition [9]. Normalising LVM to fat free mass (FFM) appears to increase sensitivity for detection of LVH in adults [10]. To date, the effect of paediatric obesity on FFM-indexed LVM, quantified by MRI, is unknown.

Paediatric obesity is associated with subclinical alterations in left ventricular (LV) systolic and diastolic function [9,11]. Specifically, obese children have significantly lower longitudinal, circumferential and radial strain, and strain rates compared to healthy-weight children [12-14]. Global longitudinal strain (GLS) and strain rate (SR) provide diagnostic information on both ventricular deformation and deformation rate thereby offering an accurate non-invasive assessment of cardiac contractility and relaxation [15]. To date, one previous investigation has compared speckle-tracking derived GLS and SR throughout the cardiac cycle, between obese and healthy-weight adolescents [13]. However, these data were not accompanied by comprehensive measurements of LV morphology.

Furthermore, the mechanisms that underlie altered left ventricular function and structure in paediatric obesity are uncertain. There is minimal evidence attributing diminished LV function and altered LV structure to either obesity per se [9,11], associated co-morbidities including insulin resistance [16] or cardiorespiratory deconditioning [17].

Therefore, the aims of this investigation were to compare 1) cardiac MRI-derived outcomes of LV morphology, and 2) speckle tracking echocardiography-derived GLS and SR in systole, early and late diastole, between obese and healthy-weight adolescents. We also wanted to determine the associations between LV measures, adiposity and metabolic co-morbidities, and cardiorespiratory fitness (CRF).

SUBJECTS AND METHODS

Twenty adolescents aged 12–16 years (9 obese, BMI ≥ percentile curves that pass through 30 kg/m^2 at age 18 and 11 healthy-weight, BMI percentile curves that pass through 18 kg/m^2 – 25 kg/m^2 at age 18) [18] were recruited as part of a multi-centre randomised controlled trial at The University of Queensland, Brisbane, Australia (Clinicaltrials.gov NCT01991106). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by The University of Queensland Human Research Ethics Committee (reference number 2013000539) and The Mater Hospital Human Research Ethics Committee (reference number HREC/13/MHS/119/AM01). Participants' parents or legal guardians approved consent, and participants provided written assent prior to participation. Details of inclusion and exclusion criteria, recruitment methods and physiological assessments have been previously described [19]. In brief, height and weight were measured for calculation of body mass index (BMI) and body surface area (BSA), and participants self-reported their stage of puberty using the Tanner scale [20]. Additional assessments included blood sampling (first visit), a cardiac and abdominal MRI scan and echocardiographic study (second visit), and a maximal exercise test and body

composition scan (third visit). The assessments were completed over a two-week period (maximum) and were separated by at least 24 hours.

Cardiac MRI

LV morphology was quantified using a 1.5T cardiac MRI unit (Siemens Symphony Sonata, Siemens, Erlangen, Germany). Standard scout images were used to locate the orthogonal planes of the heart. A TrueFISP sequence was used to acquire images in a supine position with a posterior phased array spine coil and an anterior phased array body surface coil. For all sequences, the breath-hold times were between 5–15 seconds. End-expiratory ECG triggered short axis plane images (16 slices, repetition time=41.02ms, echo time=1.25ms, flip angle=70 °, field of view=350mm, slice thickness=8mm, bandwidth=930) were then acquired throughout the ventricles covering the base (atrioventricular valve plane) to the apex. Cine images of the four-chamber view were also acquired (repetition time=39.9ms, echo time=1.22ms, flip angle=70 °, field of view=340mm, slice thickness=10mm, bandwidth=930). Data were analysed using specialised commercially available software for assessment of LV morphology (*Syngo*.via, vb10b, Siemens, Erlangen, Germany) and epicardial adipose tissue (EAT) volume (SliceOmatic Version 5.0, Tomovision, Magog, Canada) by trained observers. The laboratory-specific coefficient of variation for repeated cardiac MRI LV morphology outcomes is 1.1– 2.5% (interclass correlation=0.95–0.97).

Short axis cine loops were used to determine end systole, defined as the frame with the smallest ventricular cavity. Contours were drawn around endocardial and epicardial LV borders, including the septum but excluding the papillary muscles. The papillary muscles were added to LV end-systolic volume (LVESV) and LV end-diastolic volume (LVEDV) and from this, stroke volume (SV) and ejection fraction (EF) were calculated. LVM was determined by summing the LVEDV within the epi- and the endocardial borders as

previously described [21], and multiplying the volume by the specific density of the myocardium (1.05g/cc). The four-chamber cine loops were used to determine LV internal diameter at systole and diastole (LVIDs and LVIDd), and interventricular septum thickness (IVST) during end-diastole. LVIDs and LVIDd were measured 1–2 slices (8–16mm) below the valvular leaflets, while IVST was measured approximately 24–36mm below the valvular leaflets [22]. EAT volume was also quantified at end-diastole using short-axis cine loops covering the entire left and right ventricle. EAT cross-sectional area was multiplied by slice thickness to obtain EAT volume, and slice volumes were summed to obtain total EAT volume. Measures of LV structure and EAT volume are presented as absolute values and were also linearly scaled to FFM to create an 'index' which reduces the confounding effects of differing body size [23,24].

Echocardiography

A full resting echocardiographic assessment was conducted by an experienced sonographer using a Vivid 7 or E9 ultrasound machine (GE Vingmed Ultrasound AS, Horten, Norway) using a phased array transducer (GE M3S, 1.5–4 MHz). Participants lay in the left lateral decubitus position and three cine loops from the parasternal and the three standard apical planes (four chamber, two chamber and long axis) were recorded in grey-scale harmonic mode and colour tissue Doppler imaging (apical views). To optimize image quality, the sector depth and width were adjusted for each participant, resulting in a mean B-mode frame rate of at least 55 frames/second. To determine the timing of cardiac events, tissue Doppler velocity curves (sample volume at the basal septum) were conducted immediately before acquisition of short-axis images, which minimised changes in heart rate. Aortic valve closure (AVC) was defined at the end of the negative spike after ejection [25]. The images were digitally stored on a hard drive for offline analysis. EchoPAC (Version 112, GE Medical

Systems, Milwaukee, WI, USA) was used for echocardiographic analysis by a trained investigator and a cardiologist.

Standard Doppler and Tissue Doppler

LV standard Doppler echocardiographic indices were measured from parasternal and apical views. Peak early (E) and late (A) mitral inflow velocities were measured using pulsed-wave Doppler imaging at the leaflet tips. Peak mitral annular systolic (S'), early (e') and late (A') diastolic tissue velocities were measured through pulsed-wave Doppler mode and are presented as mean values of the four sites (septal, lateral, anterior and inferior). The ratio between E and A, and, E and e' was calculated to determine LV filling and LV filling pressure, respectively.

Myocardial Speckle Tracking

GLS and SR measurements were obtained from three wall segments: basal, midwall, and apical using three apical views (4 chamber, 2 chamber and apical long axis). In all orientations, frame rates were maximised and ranged from 50–120 frames/second. All images were optimised using gain, compression, and dynamic range to enhance myocardial definition. For analysis of GLS, one cardiac cycle from the apical long-axis images with a well-defined late-systolic endocardial border was selected for analysis. Regions of interest of the left ventricle were adjusted to include most of the myocardium, but not the pericardium. The endocardial borders at end-systole were manually traced and subsequently tracked by the software. In cases where the software or the observer identified poor tracking quality, the region of interest was re-adjusted until acceptable tracking quality was obtained. Segments that continued to display poor tracking quality were discarded. Default spatial and temporal smoothing was applied. Myocardial deformation was determined from continuous frame-by-frame tracking of the 'kernels' and GLS and SR were calculated from the displacement and rate of displacement. Mid-myocardial values for all available planes were averaged to provide GLS, and SR values in systole, early diastole and late diastole.

Cardiorespiratory fitness

Participants completed a maximal exercise treadmill test with continuous breath-by-breath respiratory gas analysis (Metamax 3B, Cortex Biophysik GmbH, Leipzig, Germany) and a facemask system (Hans Rudolph, KS, USA). Calibration procedures have been outlined elsewhere [19]. After three minutes of rest, participants completed a four-minute warm up at 4km/h while they were familiarized with treadmill walking. Thereafter, treadmill inclination was increased by 2% each minute to a maximum gradient of 12–16%. Following this, treadmill speed was increased by 1km/h each minute until volitional exhaustion. Heart rate was measured continuously during the test by radio telemetry (Polar, Polar Electro, Kempele, Finland). Peak oxygen uptake ($\dot{V}O_{2peak}$) was calculated as the average of the two highest 30-second values attained.

Abdominal adipose tissue and whole body composition

MRI images were obtained using a 1.5T MRI unit (Siemens Symphony Sonata) as previously detailed [19]. In summary, 14x8mm axial slices centred over the umbilicus were acquired during breath hold. MRI scans were anonymised and analysed by a single investigator using SliceOmatic (Version 5.0, Tomovision, Magog, Canada). The average subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) cross-sectional area (CSA), and total SAT and VAT volumes were calculated. Average SAT and VAT CSA, and total SAT and VAT volumes were summed to quantify total abdominal adipose tissue (TAAT) CSA and volume. Intra-observer SAT and VAT analysis coefficient of variation was 0.7% and 3.6%, respectively.

Total body fat percentage, total fat mass and total fat free mass was determined using dual-energy x-ray absorptiometry (Discovery DXA System, Hologic QDR Series, Massachusetts, USA).

Biochemical analyses

Detailed serum and plasma collection procedures have been outlined elsewhere [19]. Samples were analysed for fasting lipids and triglycerides, fasting glucose and HbA1c (Rx Daytona Plus, Randox Laboratories, Crumblin, County Amtrim, UK), and C peptide (electrochemiluminescence immunoassay [ECLIA], Cobas e411 immunoassay analyzer, Roche Diagnostics, Indianapolis, IN, USA). The Homeostatic Model Assessment was used to calculated insulin resistance (HOMA-IR), beta cell function (HOMA-B) and insulin sensitivity (HOMA-S) via the HOMA2 calculator (Version 2.2.3, University of Oxford, Oxford, United Kingdom) [26]. Basal disposition index (DI) was calculated as $Basal\ DI = \frac{HOMA-B}{HOMA-IR}$ to determine beta cell function at steady state allowing comparison between varying degrees of IR. The coefficients of variation were as follows: total cholesterol (1.0%), high-density lipoprotein (1.0%), triglycerides (1.4%), fasting glucose (0.6%), C peptide (0.8%) and HbA1c (2.7%).

Statistical analysis

Data are expressed as mean ± SD if continuous and normally distributed, or median (IQR) and percentages if categorical or non-normally distributed. Normality of data was assessed through visual examination of histograms and quantified using the Shapiro-Wilk test. A non-parametric test was used if the assumption of normality continued to be violated following data transformation. Independent t-tests or Mann-Whitney U tests, and χ^2 tests were used compare outcomes between healthy-weight and obese adolescents. Hedges' g effect sizes were calculated to further quantify between-group differences and were interpreted as follows: small effect (0.20), small-to-medium effect (0.20–0.50), medium-to-large effect (0.50 – 0.80) and large-to-very large effect (0.80–1.30) [27]. Effect sizes for non-normally distributed outcomes were calculated using the following equation: $r = \frac{Z\ statistic}{\sqrt{n}}$ and interpreted using the aforementioned thresholds. Univariate linear regression modelling was

to determine the association between LV function and structure, adipose tissue, insulin resistance and CRF outcomes in all adolescents. The strength of the r value was interpreted as weak (r≤0.1), moderate (r=0.3–0.5) or strong (r>0.5) [28]. SPSS Statistics (Version 24.0, IBM, Armonk, NY, USA) was used to perform the statistical analyses. All statistical tests with P value < 0.05 were considered significant.

RESULTS

Comparison of obese and healthy-weight adolescents

Table 1 illustrates clinical, CRF, body composition and blood biochemistry of obese (n=9) and healthy-weight adolescents (n=11). There were no between-group differences for age, sex, and Tanner stages of puberty. As expected, obese adolescents exhibited key characteristics of obesity including increased weight, BMI, BSA, percent body fat and fat mass compared to healthy-weight adolescents (P<0.001 between groups for all outcomes). Greater abdominal SAT, VAT and TAAT volume was also noted in obese versus healthy-weight adolescents (P<0.001 for all outcomes). Increased cardiac adiposity was noted among obese adolescents as indicated by greater absolute and indexed EAT volumes around the left and right ventricle compared to healthy-weight adolescents (P≤0.001). Obese adolescents had significantly lower CRF than healthy-weight adolescents, even when $\dot{V}O_{2peak}$ was normalised to fat free mass (FFM) (P<0.001). Adolescent obesity was also associated with greater insulin resistance (HOMA IR, P=0.003).

There was no difference in FFM-indexed LV structure between obese and healthy-weight adolescents **(Table 2)**. However, the two groups exhibited contrasting LV function **(Table 3)**. Obese adolescents had significantly higher GLS (P<0.001) and systolic SR (P=0.037), accompanied by reduced early diastolic SR (P=0.001), S' (P=0.003), e' (P=0.045), A' (P=0.041), and A (P=0.022) with medium to very large group differences noted (ES=0.5–1.9).

Associations of LV function and structure

GLS showed moderate to strong associations with total body fat percent (r=0.54, P=0.015), abdominal adipose tissue (r=0.67–0.71, P≤0.001). Systolic strain rate was moderately associated with abdominal adipose tissue (r=0.50, P=0.030) while strain rate in early diastole was strongly associated with total body fat percent (r=0.64, P=0.002), abdominal adipose tissue (r=0.72, P<0.001). Both GLS and strain rate in early diastole were strongly associated with $\dot{V}O_{2peak}$ (r=0.54, P=0.015 and r=0.58, P=0.008, respectively).

DISCUSSION

To the best of our knowledge, this is the first study to illustrate that while paediatric obesity results in impaired global longitudinal strain and strain rate, there are no differences in MRI-derived, FFM-indexed LV morphology compared to healthy-weight adolescents. These findings are consistent with pathological adult models including the early disease states of hypertension [29], ischaemia [30] and Type 2 Diabetes Mellitus (T2DM) [31]. Additionally, we found that reduced myocardial contractility and relaxation were strongly associated with total body and abdominal adiposity and insulin resistance while enhanced contractility and relaxation had a strong relationship with CRF.

While our finding that obese adolescents have diminished LV function compared to healthy-weight counterparts is consistent with earlier work, the observation that obese adolescents have normal MRI-quantified LV morphology has not been reported. Previously, two studies found no significant differences in echocardiographic-derived absolute LVM [32] or indexed LVM (g/height) [32,33] between obese and healthy-weight children. However, allometric indexation of LVM ($height^{1.85}$ in males and $height^{1.72}$ in females) did elicit a significant difference [32]. Several echocardiographic studies suggest that obese children have increased LVM compared to healthy-weight children, however these findings are likely due to suboptimal indexation techniques [7,8,11,13,16]. Furthermore, although

echocardiography is more commonly utilised for cardiac assessment, MRI provides superior accuracy when assessing cardiac volumes and masses [34]. Nevertheless, two MRI studies reported significantly greater absolute and height-adjusted LVM in obese versus healthy-weight adolescents [5,6] which is in direct contrast to our findings and likely due to different indexation techniques. The method of indexation and imaging methodology used is critical in determining the influence of adiposity on LV morphology and should be considered.

We normalised LVM to dual-energy x-ray absorptiometry (DXA)-derived FFM to accurately compare our study populations in accordance with current recommendations [Rowland:2007ti; 23] as at least 75 % of LVM variance is explained by FFM in children [24]. The majority of previous comparisons between healthy-weight and obese paediatric populations indexed cardiac morphology outcomes to height although there were no significant different between groups, which may have misconstrued findings [7,8,11,13,16]. Additional error may be introduced when comparing populations with a wide age distribution as FFM increases variably between males and females during puberty [35]. While we acknowledge that DXA-derived FFM may be difficult to obtain, LVM indexed to $BSA^{1.5}$ in the absence of FFM data may be more appropriate [23] and caution should be applied during data interpretation.

Our study found that obese adolescents had altered myocardial contractility characterised by reduced GLS and SR in systole in comparison to healthy-weight adolescents. These findings are consistent with previous comparisons of obese and healthy-weight adolescents using both 2D-STE and tissue Doppler imaging-derived GLS and SR [8,11-14,36] as well as 3D-wall motion tracking echocardiography [33]. However, when assessed using cardiac MRI, obese adolescents showed similar systolic SR to healthy-weight counterparts [6]. This discrepancy is likely due to the significantly lower temporal resolution and therefore sensitivity of cardiac MRI compared to echocardiography to identify functional

differences [37]. The finding that obese adolescents have reduced systolic function is further supported by impaired S' in obese adolescents compared to healthy-weight controls reported in this study and previous work [8,12,14,33]. We also report altered diastolic function via reduced SR in early diastole and significantly lower e', in obese versus healthy-weight adolescents, which is consistent with echocardiographic [12,13,32] and cardiac MRI findings [6]. Current evidence suggests that SR in late diastole appears intact among adolescents with obesity [6,13]. Together, it appears that paediatric obesity is associated with altered systolic function and a certain degree of diastolic impairment compared to the non-obese state. Our findings closely resemble the early disease states of intrinsic (hypertension [29] and ischaemia [30]) and extrinsic (T2DM [31]) cardiomyopathies. Patients with early diabetic cardiomyopathy show significantly reduced myocardial contractility [38] that is further amplified in co-existence with LVH [38]. Indeed, reduced longitudinal function in the absence of ischaemia or LVH may occur with preserved EF and SV due to compensatory increased radial contractility [39]. While we did not assess radial contractility per se, this is likely preserved in paediatric obesity, thereby permitting normal EF [11,36]. Obesity-related comorbidities, including insulin resistance, lead to maladaptation in fatty acid metabolism, glucose uptake, protein synthesis, cardiac collagen content and mitochondrial function [9,16,40], which could deleteriously impact myocyte function and compliance [16]. Our findings were in agreement with these mechanistic underpinnings whereby obese adolescents exhibited greater insulin resistance and reduced basal DI, increased quantities of epicardial adipose tissue, and sub-optimal LV function.

Among our study population, myocardial contractility and relaxation was significantly associated with adiposity, insulin resistance and CRF. Adolescents with increased total body and abdominal adiposity, and insulin resistance exhibited reduced GLS and SR in systole and early diastole. On the contrary, adolescents with greater relative CRF had enhanced GLS and

SR in systole. Myocardial deformation/rate, BMI and duration of obesity were previously found to be significantly associated (r = 0.19 – 0.60) in two studies of obese children [33,41]. The deleterious effect of adiposity on LV function is further illustrated through weight-loss studies in morbidly obese adolescents. In these individuals, bariatric surgery-induced weight loss [42] or a low carbohydrate-diet induced weight loss [43] significantly improved LV diastolic function. Although significant weight loss (8 – 34 %) in obese adolescents [42,43] may be effective for improving diastolic function, achieving and maintaining weight loss without regular exercise is often difficult [44]. Even in the absence of weight loss, exercise may elicit improvements in LV function [45] by increasing cardiac compliance and the contribution of early filling flow to total diastolic filling. Exercise can increase the elastic recoil generated during systole, causing a more rapid untwist during the isovolumic relaxation period [46]. The increased untwisting and active myocardial relaxation generates active suction of the blood from the atria [47] resulting in a rapid decrease in LV pressure and promotes early LV filling [48]. In fact, the untwisting mechanics appear to contribute most to early rather than late diastolic LV filling [49]. Given the associations between adiposity, CRF and LV function, our group is currently investigating the effects of a multi-disciplinary lifestyle approach (exercise training combined with a nutrition intervention) on cardiac function in children and adolescents with obesity. We hypothesise that this intervention will maximise the beneficial effects on cardiac function by stimulating a decrease in adiposity and concomitant increases in CRF [19].

Limitations of the present investigation include the cross-sectional study design and a small sample size. We were unable to conduct multivariate linear regression analyses due to the reduced number of observations. This was a sub-study of a larger multi-centre randomised controlled trial [19] and cardiac MRI investigations were limited to one centre. Furthermore,

this outcome measure was confined to participants older than 12 years due to the difficulty of consecutive breath-holds required for the MRI protocol.

In conclusion, our study demonstrated that although FFM-indexed LV structure is similar between obese and healthy-weight adolescents, obese adolescents exhibit subclinical reductions in myocardial indices of contractility and relaxation. The strong association between LV function, fitness and adiposity advocates for lifestyle interventions to ameliorate reduced cardiac function in paediatric obesity.

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Table 1. Comparison of clinical, cardiorespiratory fitness, body composition and blood biochemistry characteristics in obese and healthy-weight adolescents.

	Obese (n = 9)	**Healthy-weight (n = 11)**	**P value**	**ES**
Age	13.1 ± 1.0	13.5 ± 1.2	0.431	
Sex (F, %)	67	27	0.078	
Tanner Puberty Stage (1 – 4)	3 (2 – 4)	3 (2 – 4)	0.953	
Height (cm)	165.5 ± 10.2	164.3 ± 8.3	0.777	0.13
Weight (kg)	86.8 ± 11.9	50.1 ± 8.7	<0.001	3.58
Body mass index (kg/m^2)	31.7 ± 3.5	18.5 ± 2.3	<0.001	4.56
Body mass index Z-score	2.19 ± 0.24	-0.23 ± 0.67	<0.001	4.61
Body surface area	2.0 ± 0.2	1.5 ± 0.2	<0.001	2.50
Systolic BP (mmHg)	117 ± 7	107 ± 7	0.009	1.43
Diastolic BP (mmHg)	67 ± 4	60 ± 5	0.005	1.53
Resting HR (beats/min)	76 ± 13	77 ± 9	0.931	0.09
Peak HR (beats/min)	196 ± 9	198 ± 7	0.717	0.25
$\dot{V}O_{2peak}$ (L/min)	2.67 ± 0.66	2.67 ± 0.58	0.995	0.00
$\dot{V}O_{2peak}$ (mL/kg/min)	30.6 ± 5.0	53.5 ± 7.5	<0.001	3.52
$\dot{V}O_{2peak}$ (mL/kg^{FFM}/min)	64.3 ± 6.1	78.8 ± 7.5	<0.001	2.10
Total body fat (%)	47.9 ± 5.0	23.0 ± 6.9	<0.001	4.06
Total fat mass (kg)	39.0 ± 5.5	10.8 ± 4.6	<0.001	0.84
Total fat free mass (kg)	41.1 ± 7.4	33.9 ± 6.0	0.027	1.08
MRI TAAT CSA (cm^2)	555.5 (485.0 –617.7)	77.9 (64.6 – 107.1)	<0.001	0.84
MRI TAAT volume (cm^3)	6299.2 (6114.9 – 6918.5)	873.2 (683.7 – 1199.6)	<0.001	0.84

MRI VAT CSA (cm^2)	63.4 ± 15.2	15.1 ± 5.3	<0.001	4.44
MRI VAT volume (cm^3)	710.6 ± 170.1	169.4 ± 59.5	<0.001	4.44
MRI SAT CSA (cm^2)	505.4 (419.9 – 539.5)	63.1 (49.5 – 88.6)	<0.001	0.84
MRI SAT volume (cm^3)	5790.0 (5357.5 – 6042.1)	707.0 (554.7 – 991.9)	<0.001	0.84
EAT volume (cm^3)	34.8 ± 11.8	16.0 ± 7.1	0.001	1.98
EATi (cm^3/kg_{FFM})	0.85 ± 0.27	0.47 ± 0.18	<0.001	1.69
Cholesterol (mmol/L)	4.05 ± 1.38	4.12 ± 1.02	0.893	0.06
HDL (mmol/L)	1.06 ± 0.17	1.60 ± 0.37	0.002	1.74
LDL (mmol/L)	2.35 ± 0.99	2.19 ± 0.72	0.695	0.19
Triglycerides (mmol/L)	1.38 ± 0.82	0.71 ± 0.27	0.074	1.23
Fasting glucose (mmol/L)	5.20 ± 0.46	5.23 ± 0.28	0.829	0.08
C peptide (nmol/L)	0.99 ± 0.23	0.55 ± 0.13	<0.001	2.52
HbA1c (%)	5.4 ± 0.33	5.3 ± 0.22	0.353	0.39
HOMA-IR	2.2 ± 0.6	1.2 ± 0.3	0.003	2.29
HOMA-B	153.4 ± 43.0	100.4 ± 22.4	0.003	1.67
HOMA-S	48.8 ± 14.2	85.6 ± 23.5	0.002	1.79
Basal DI	71.5 ± 13.8	82.4 ± 11.6	0.091	0.87

ES, effect size; F, female; BP, blood pressure; HR, heart rate; VO_{2peak}, peak oxygen uptake; MRI; magnetic resonance imaging; TAAT; total abdominal adipose tissue; CSA; cross-sectional area; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; EAT, epicardial adipose tissue; EATi, epicardial adipose tissue index; HDL, high-density lipoprotein; LDL, low density lipoprotein; HbA1c, glycated haemoglobin; HOMA-IR,

HOMA of insulin resistance; HOMA-B, HOMA of beta cell function; HOMA-S, HOMA of insulin sensitivity; DI, disposition index

Table 2. Cardiac MRI-derived left ventricular structure outcomes for obese and healthy-weight adolescents

	Obese (n = 9)	Healthy-weight (n = 11)	P value	ES
LVM (g)	105.5 (89.8 – 125.2)	90.3 (85.5 – 94.8)	0.112	0.37
LVMi (g/kg_{FFM})	2.7 (2.4 – 2.8)	2.7 (2.6 – 3.1)	0.497	0.16
LVEDV (mL)	175.2 ± 36.8	139.2 ± 24.6	0.018	1.18
LVEDVi (mL/kg_{FFM})	4.3 ± 0.4	4.1 ± 0.3	0.374	0.57
LVESV (mL)	68.2 ± 11.0	52.3 ± 10.6	0.004	1.48
LVESVi (mL/kg_{FFM})	1.7 ± 0.2	1.6 ± 0.3	0.291	0.38
Ejection fraction (%)	60.3 ± 5.8	62.3 ± 5.4	0.445	0.36
Stroke volume (mL)	103.8 (82.3 – 132.1)	83.9 (76.2 – 85.9)	0.112	0.37
Indexed stroke volume (mL/kg_{FFM})	2.57 ± 0.40	2.57 ± 0.26	0.973	0.00
LVM/LVEDV	0.63 ± 0.05	0.67 ± 0.06	0.150	0.72
LVIDd (cm)	5.10 ± 0.38	4.79 ± 0.32	0.060	0.89
LVIDdi (cm/kg_{FFM})	0.13 ± 0.02	0.14 ± 0.02	0.064	0.50
LVIDs (cm)	3.44 ± 0.36	3.06 ± 0.39	0.037	1.01
LVIDsi (cm/kg_{FFM})	0.09 ± 0.01	0.09 ± 0.01	0.330	0.00
IVST (cm)	0.99 ± 0.11	0.90 ± 0.10	0.066	0.86
IVSTi (cm/kg_{FFM})	0.02 ± 0.004	0.03 ± 0.003	0.196	0.57

LVM, left ventricular mass; LVMi, left ventricular mass index; LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume index; LVESV, left ventricular end-systolic volume; LVESVi, left ventricular end-systolic volume index; LVIDd,

left ventricular internal diameter during diastole; LVIDdi, left ventricular internal diameter during diastole index; LVIDs, left ventricular internal diameter during systole; LVIDsi, left ventricular internal diameter during systole index; IVST, interventricular septal thickness; IVSTi, interventricular septal thickness index

Table 3. Differences in systolic and diastolic echocardiographic function between obese and healthy-weight adolescents

	Obese (n = 9)	**Healthy-weight (n = 11)**	**P value**	**ES**
GLS (%)	-15.50 ± 2.72	-21.79 ± 3.60	<0.001	1.94
SR_S (s^{-1})	-0.87 ± 0.15	-1.04 ± 0.18	0.037	1.02
SR_E (s^{-1})	1.76 ± 0.30	2.37 ± 0.36	0.001	0.82
SR_A (s^{-1})	0.52 ± 0.18	0.61 ± 0.17	0.254	0.52
S' (cm/s)	8.9 ± 1.0	11.6 ± 2.2	0.003	1.53
e' (cm/s)	15.8 ± 2.7	18.1 ± 2.1	0.045	0.96
A' (cm/s)	6.3 ± 0.9	7.4 ± 1.2	0.041	1.02
E (cm/s)	83.1 ± 13.6	93.4 ± 13.6	0.112	0.78
E/e'	5.23 ± 1.00	5.33 ± 0.86	0.825	0.11
E/A	2.39 ± 0.68	2.06 ± 0.62	0.259	0.51
A (cm/s)	35.2 ± 9.4	48.3 ± 13.0	0.022	1.14

GLS, global longitudinal strain; SR_s, systolic strain rate; SR_E, early diastolic strain rate; SR_A, late diastolic strain rate; s', peak systolic tissue velocity; e', peak early diastolic tissue velocity; a', peak late diastolic tissue velocity; E, peak early diastolic mitral flow; A, peak late diastolic mitral flow

Table 4. Univariate linear regression showing LV function and morphology associations with adiposity, insulin resistance and cardiorespiratory fitness in all adolescents (n = 20). Unstandardised beta (β) regression coefficients, SE (standard error of β) and 95 % CI of β are presented.

	r value	β	SE	95 % CI	P value
GLS (%)					
Total body fat (%)	0.54	0.172	0.064	0.038– 0.307	**0.015**
VAT volume (cm^3)	0.67	0.010	0.003	0.004 – 0.016	**0.001**
SAT volume (cm^3)	0.71	0.001	0.000	0.001 – 0.002	< **0.001**
TAAT volume (cm^3)	0.71	0.001	0.000	0.001 – 0.002	< **0.001**
EATi (cm^3/kg_{FFM})	0.30	4.660	0.345	-2.588 – 11.908	0.193
HOMA-IR	0.63	4.572	1.393	1.619 – 7.524	**0.005**
Basal DI	0.58	-0.197	0.069	-0.343 – -0.051	**0.011**
VO_{2peak} (mL/kg/min)	0.50	-0.169	0.070	-0.315 – -0.023	**0.026**
VO_{2peak} ($mL/kg^{FFM}/min$)	0.39	-0.175	0.098	-0.381 – 0.030	0.090
SR_S (s^{-1})					
Total body fat (%)	0.28	0.004	0.003	-0.003 – 0.010	0.228
VAT volume (cm^3)	0.36	0.000	0.000	0.000 – 0.001	0.123
SAT volume (cm^3)	0.50	0.000	0.000	0.000 – 0.000	**0.026**
TAAT volume (cm^3)	0.49	0.000	0.000	0.000 – 0.000	**0.030**
EATi (cm^3/kg_{FFM})	0.21	0.130	0.145	-0.175 – 0.436	0.381
HOMA-IR	0.26	0.075	0.071	-0.076 – 0.227	0.307
Basal DI	0.31	-0.004	0.003	-0.011 – 0.003	0.211

VO_{2peak} (mL/kg/min)	0.30	-0.004	0.003	-0.011 – 0.002	0.202
VO_{2peak} (mL/kg^{FFM}/min)	0.29	-0.005	0.004	-0.014 – 0.003	0.210
SR_E (s^{-1})					
Total body fat (%)	0.64	-0.020	0.006	-0.033 – -0.008	**0.002**
VAT volume (cm^3)	0.64	-0.001	0.000	-0.002 – 0.000	**0.002**
SAT volume (cm^3)	0.72	0.000	0.000	0.000 – 0.000	**<0.001**
TAAT volume (cm^3)	0.72	0.000	0.000	0.000 – 0.000	**<0.001**
EATi (cm^3/kg_{FFM})	0.32	-0.491	0.341	-1.208 – 0.226	0.167
HOMA-IR	0.53	-0.376	0.153	-0.700 – -0.053	**0.025**
Basal DI	0.26	0.009	0.008	-0.009 – 0.026	0.305
VO_{2peak} (mL/kg/min)	0.58	0.020	0.007	0.006 – 0.033	**0.008**
VO_{2peak} (mL/kg^{FFM}/min)	0.43	0.019	0.010	-0.001 – 0.039	0.059
SR_A (s^{-1})					
Total body fat (%)	0.29	-0.004	0.003	-0.010 – 0.002	0.214
VAT volume (cm^3)	0.12	0.000	0.000	0.000 – 0.000	0.602
SAT volume (cm^3)	0.32	0.000	0.000	0.000 – 0.000	0.174
TAAT volume (cm^3)	0.30	0.000	0.000	0.000 – 0.000	0.201
EATi (cm^3/kg_{FFM})	0.19	-0.112	0.139	-0.403 – 0.179	0.430
HOMA-IR	0.21	0.059	0.069	-0.086 – 0.205	0.399
Basal DI	0.45	-0.006	0.003	-0.012 – 0.000	0.064
VO_{2peak} (mL/kg/min)	0.59	0.003	0.003	-0.003 – 0.010	0.279
VO_{2peak} (mL/kg^{FFM}/min)	0.17	0.003	0.004	-0.006 – 0.012	0.480

LVMi (g/kg_{FFM})

Total body fat (%)	0.19	-0.004	0.005	-0.014 – 0.006	0.436
VAT volume (cm^3)	0.01	0.000	0.000	0.000 – 0.000	0.960
SAT volume (cm^3)	0.19	0.000	0.000	0.000 – 0.000	0.431
TAAT volume (cm^3)	0.17	0.000	0.000	0.000 – 0.000	0.482
EATi (cm^3/kg_{FFM})	0.04	0.037	0.233	-0.453 – 0.527	0.874
HOMA-IR	0.07	0.032	0.116	-0.214 – 0.277	0.789
Basal DI	0.06	0.001	0.005	-0.010 – 0.013	0.805
VO_{2peak} (mL/kg/min)	0.18	0.004	0.005	-0.007 – 0.015	0.450
VO_{2peak} ($mL/kg^{FFM}/min$)	0.10	0.003	0.007	-0.011 – 0.017	0.674

GLS, global longitudinal strain; SR_s, systolic strain rate; SR_E, early diastolic strain rate; SR_A, late diastolic strain rate; LVMi, left ventricular mass index; BP, blood pressure; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; TAAT, total abdominal adipose tissue; EATi, epicardial adipose tissue index; VO_2peak, peak oxygen uptake; HOMA-IR, HOMA of insulin resistance; DI, disposition index