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Effect of fitness on cardiac structure and function in overweight and obesity (the FATCOR study)

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Abstract *Background and aims:* Obesity is associated with reduced left ventricular (LV) systolic myocardial function. We aimed to explore by means of a cross-sectional study whether this effect is offset in the presence of good fitness.
Methods and results: We studied clinical and echocardiographic data from 469 overweight (body mass index [BMI] >27 kg/m^2) and obese (BMI ≥30 kg/m^2) women and men without known cardiovascular (CV) disease in the FAT associated CardiOvasculaR dysfunction (FATCOR) study. The participants were grouped according to obesity and sex- and age adjusted peak oxygen uptake, obtained by ergospirometry. LV systolic myocardial function was assessed by peak systolic global longitudinal strain (GLS) measured by speckle tracking echocardiography. The association of fitness with GLS was tested in logistic regression analyses and reported as odds ratio (OR) with 95% confidence interval (CI).

In the total study population, participants were 47 years old, 60% were women, and mean BMI was 32.0 kg/m^2. GLS did not differ between fit and unfit subjects within the overweight and obese groups (both $p > 0.05$), but the overweight fit group had higher GLS (more negative value) compared to the obese unfit group (-20.1 ± 2.6 vs. -19.0 ± 3.0, $p < 0.05$). In obese subjects, fitness was associated with higher GLS (OR 0.88 [95% CI 0.79–0.99, $p < 0.05$) in multivariable logistic regression analysis, independent of significant associations with higher arterial stiffness and lower fat percentage (all $p < 0.05$). In the overweight group, fitness was not significantly associated with GLS.
Conclusion: In obesity, fitness was independently associated with higher GLS, while no association was found in overweight.
Clinical trial registration: URL: http://www.clinicaltrials.gov NCT02805478.

Introduction

Overweight and obesity have been associated with increased left ventricular (LV) mass and presence of reduced LV systolic function [1,2]. LV systolic function has traditionally been assessed by LV ejection fraction (EF) [3]. However, use of newer methods like global longitudinal strain (GLS) from speckle tracking echocardiography has

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enabled detection of reduced LV systolic myocardial function when EF is still within the normal range [4–7].

In a population based cohort without hypertension or known cardiovascular (CV) disease, Dalen et al. demonstrated that for every 5 kg/m^2 increase in body mass index (BMI), GLS was reduced by 5% [7]. Furthermore, a small study exploring LV function in relation to fitness in obese adolescents, found good fitness to be associated with higher GLS [8]. However, the effect of fitness on LV myocardial function measured by GLS has not been explored in larger cohort studies of overweight and obese adults free from CV disease. This was the aim of the present study.

Methods

Study population

The current analysis used data from the FAT associated CardiOvascular dysfunction (FATCOR) study, which was conducted from 2009 to 2017 at Haukeland University Hospital, Bergen, Norway. Inclusion and exclusion criteria for the study have been published previously [9,10]. In short: the FATCOR study included 620 women and men aged 30–65 years with a BMI >27.0 kg/m^2 free from any cardiovascular symptom. Exclusion criteria were previous myocardial infarction, gastrointestinal disorder, severe psychiatric illness or inability to communicate in the Norwegian language. The participants were recruited by a general practitioner center with a particular research interest in obesity. A technically satisfactory maximal ergospirometry and echocardiograms suitable for speckle tracking echocardiography were obtained in 469 (76%) participants (Fig. 1). The FATCOR study was conducted in accordance with the Declaration of Helsinki and with approval from the Regional Ethics Committee. Written informed consent was obtained from all participants.

Cardiovascular risk assessment

All participants completed a standardized questionnaire reporting their medical history and use of any medication. Clinic blood pressure (BP) was measured in accordance with guidelines using an Omron M4 sphygmomanometer (Omron Healthcare Co. Ltd., Hoofdorp, Netherlands) with an appropriately sized cuff [11]. BP was measured in triplets with 1-min intervals after 5 min initial rest in the sitting position, and the average of the 2 last measurements were taken as the clinic BP. Pulse pressure was calculated as the difference between clinic systolic and diastolic BP. A Diasys Integra II apparatus (Novacor, Cedex, France) was used for 24-h ambulatory blood pressure monitoring, as previously described [10]. An average 24-h systolic BP $\geq$ 130 mmHg and/or 24-h diastolic BP $\geq$ 80 mmHg was considered elevated [10,11]. Hypertension was considered present if the 24-h ambulatory BP was elevated or the participants reported use of antihypertensive medication [10].

Tetrapolar bioelectric impedance analysis (Tanita-TBF-300A, Tanita Corporation of America, Arlington Heights, USA) was used for body composition analysis. Overweight (BMI 25.0–29.9 kg/m^2) and obesity (BMI $\geq$30.0 kg/m^2) was defined as described by the World Health Organization [12].

Metabolic syndrome was diagnosed by the American Heart Association/National Heart, Lung and Blood Institute criteria and was considered present in the individual participant if 3 of the 5 following criteria were present: 1) Increased waist circumference ($\geq$88 cm in women and $\geq$102 cm in men), 2) elevated triglycerides ($\geq$1.7 mmol/L), 3) low high-density lipoprotein cholesterol (<1.3 mmol/L in women and <1.03 mmol/L in men), 4) systolic BP $\geq$ 130 mmHg and/or diastolic BP $\geq$ 85 mmHg and/or use of antihypertensive medication or 5) elevated fasting blood glucose $\geq$5.6 mmol/L and/or use of antidiabetic medication [13]. In accordance with the criteria from the American Diabetes Association [14], diabetes mellitus was recognized from fasting blood glucose $\geq$7 mmol/L, 2-h blood glucose $\geq$11.1 mmol/L after a 75-g oral glucose test, or a glycated hemoglobin A_{1c} $\geq$ 6.5%. Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [15].

Conventional echocardiography

Echocardiography was performed with a GE Vivid E9 scanner (GE Vingmed Ultrasound, Horten, Norway) following a standardized imaging protocol, as previously described [10]. The images were analyzed using Image Arena software version 4.4 (TomTec Imaging Systems

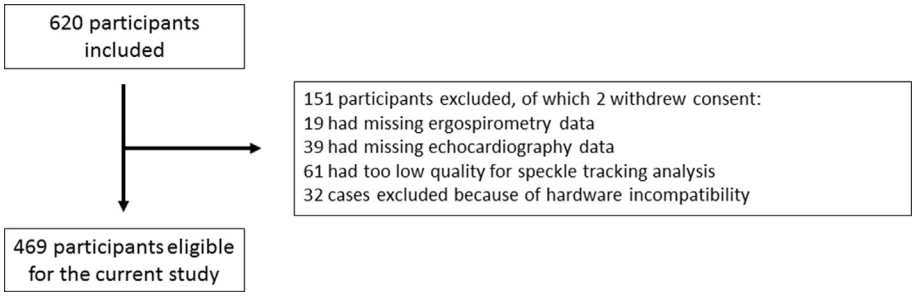

Figure 1 Flow chart of FATCOR study population.

GmbH, Unterschleissheim, Germany) in the Echocardiography Core Laboratory at the University of Bergen, Bergen, Norway. As recommended for clinical trials [16], the initial image analyses were quality assured by proof reading by a single expert reader (EG).

The joint American Society of Echocardiography and the European Association of Cardiovascular Imaging guidelines for chamber quantification were applied for quantitative echocardiography analyses [17]. LV mass was indexed for height$^{2.7}$ as recommended in obesity [18]. Relative wall thickness calculated as 2 x posterior wall thickness/LV internal diameter at end-diastole [17]. EF was calculated using the biplane methods of discs (modified Simpson's rule), and considered reduced if <54% in women and <52% in men [17]. Arterial stiffness was assessed by pulse pressure/stroke volume index which was calculated as pulse pressure/Doppler stroke volume and indexed for height$^{2.04}$.

Speckle tracking echocardiography

Speckle tracking echocardiography was done offline on a workstation equipped with EchoPac BT 202 (GE Vingmed Ultrasound, Horten, Norway) by a single investigator (NP) and proof read by a single experienced reader (SS). Peak systolic longitudinal strain was assessed in the apical 2-, 3- and 4-chamber views using automated function imaging with an adequate frame rate and analyzed as recommended by GE. The endocardial border was traced automatically and end-systole was defined by aortic valve closure. After software processing the quality of tracking was assessed visually, and if the tracking was poor the segment was excluded. GLS was calculated as the average peak systolic longitudinal strain in the 17 LV segments [17]. GLS was considered abnormal if $>-18.5\%$ in women and $>-16.9\%$ in men [19]. Mean frame rate was 62 ± 8 frames/s.

Assessment of cardiorespiratory fitness

Ergospirometry with breath-to-breath measurement of respiratory exchange ratio, peak oxygen uptake (VO_{2max}) and metabolic equivalents (MET) was performed on a treadmill (Schiller CS-200, Schiller AG, Baar, Switzerland) using a standardized, incremental protocol (Chronotropic Assessment Exercise Protocol) suited for obese subjects [9]. In 5 cases testing was aborted due to chest pain. However, these participants were included in the present analysis as all 5 reached a sufficient respiratory exchange ratio (≥1.2), indicating satisfactory effort. All other participants exercised on the treadmill until exhaustion. Cardiopulmonary fitness was determined by sex- and age-specific cut-off values of peak oxygen uptake [20]. Following these criteria, if the individual participants achieved a peak oxygen uptake that classified them to have at least good fitness, they were considered fit [20].

Statistics

The IBM SPSS Statistics software version 25 (IBM, Armonk, New York, USA) was used for data management and statistical analysis. The participants were divided into 4 groups characterized by absence or presence of fitness and obesity: overweight fit, overweight unfit, obese fit and obese unfit groups, respectively. Data are presented as mean ± standard deviation for continuous variables and as percentages for categorical variables. One-way analysis of variance with Sidak's post hoc test was used for group comparison of continuous variables, and a general linear model with Sidak's post hoc test was used for group comparison of categorical variables. Uni- and multivariable logistic regression analyses were used to identify the covariables of fitness in overweight and obese groups separately. These results are reported as odds ratio (OR) and associated 95% confidence intervals (CI). A p-value of <0.05 was considered statistical significant in all analyses.

Results

Clinical characteristics in relation to fitness

In overweight subjects, the fit group had lower serum triglyceride levels ($p < 0.05$), but did not differ in age, BP, body fat percentage, waist circumference or prevalences of hypertension, diabetes or metabolic syndrome compared to the unfit group (all $p > 0.05$) (Table 1). In obese subjects, the fit group was older and had lower body fat percentage and waist circumference compared to the unfit group (all $p < 0.05$), while the prevalences of hypertension, diabetes and metabolic syndrome did not differ (all $p > 0.05$) (Table 1).

Cardiac function in relation to fitness

In overweight subjects, LV mass index and systolic function by EF and GLS did not differ between fit and unfit groups (all $p > 0.05$) (Table 2) (Fig. 2). In obese subjects, EF was higher in the fit group ($p < 0.05$), while LV mass index and GLS did not differ (all $p > 0.05$) (Table 2) (Fig. 2). However, GLS was higher (more negative value) in the overweight fit group compared to the obese unfit group ($p < 0.05$) (Table 2) (Fig. 2). EF was higher in the obese fit compared to the overweight fit ($p < 0.05$), but did not differ between the unfit groups ($p > 0.05$) (Table 2) (Fig. 2).

Covariables of fitness in overweight and obese subjects

In overweight subjects, being fit was significantly associated with lower serum level of triglycerides ($p < 0.05$), and tended to be associated with lower body fat percentage ($p = 0.059$) in univariable analyses, while no associations with measures of LV systolic function was found (Table 3). In multivariable logistic regression analysis, being fit and overweight was associated with a lower body fat percentage and with lower serum level of triglycerides (both $p < 0.05$) (Table 3).

In obese subjects, fitness was associated with higher GLS, EF, LV mass index and pulse pressure stroke volume index, and with lower body fat percentage in univariable logistic regression analyses (all $p < 0.05$) (Table 3). Fitness

Table 1 Clinical characteristic of the total study population in fit and unfit groups.

Variable	Overweight		Obese		p
	Fit (n = 77)	Unfit (n = 99)	Fit (n = 43)	Unfit (n = 250)	
Women (%)	58	62	61	60	0.980
Age (years)	49 ± 10*	48 ± 9	52 ± 8*	46 ± 9	<0.001
Height (cm)	172 ± 9	172 ± 9	170 ± 10	173 ± 9	0.053
Weight (kg)	83 ± 9*†	84 ± 9*†	93 ± 12*	104 ± 15	<0.001
Body mass index (kg/m^2)	28.1 ± 1.3	28.5 ± 1.0	32.2 ± 1.6	34.6 ± 3.8	NA
Waist circumference (cm)	98 ± 8*†	100 ± 7*†	108 ± 8*	113 ± 11	<0.001
Fat percentage (%)	33 ± 8*	35 ± 7*	36 ± 7*	40 ± 8	<0.001
Muscle mass (kg)	55 ± 11	53 ± 10*	57 ± 11	59 ± 12	<0.001
Estimated GFR (ml/min/1.73 m^2)	93 ± 14	97 ± 13	93 ± 10	98 ± 13	0.016
Total cholesterol (mmol/L)	5.3 ± 1.0	5.6 ± 1.1*	5.6 ± 0.9	5.3 ± 1.0	0.030
LDL cholesterol (mmol/L)	3.5 ± 0.8	3.8 ± 0.9	3.7 ± 0.9	3.6 ± 0.9	0.092
HDL cholesterol (mmol/L)	1.4 ± 0.3	1.3 ± 0.4	1.3 ± 0.3	1.3 ± 0.3	0.358
Triglycerides (mmol/L)	1.2 ± 0.6*‡	1.5 ± 0.9	1.5 ± 0.9	1.5 ± 0.8	0.016
Fasting blood glucose (mmol/L)	5.1 ± 0.6	5.4 ± 1.2	5.5 ± 0.9	5.3 ± 0.9	0.094
HbA_{1c} (%)	5.5 ± 0.4	5.6 ± 0.6	5.6 ± 0.5	5.6 ± 0.5	0.679
Diabetes mellitus (%)	4	9	14	8	0.280
Metabolic syndrome (%)	27*†	45	54	52	0.001
Current smoking (%)	11	19	5	13	0.146
Clinic systolic blood pressure (mmHg)	129 ± 16	128 ± 18	134 ± 19	130 ± 15	0.233
Clinic diastolic blood pressure (mmHg)	81 ± 9	81 ± 10	83 ± 9	83 ± 10	0.222
Heart rate (beats/minute)	64 ± 10*	67 ± 11	69 ± 10	68 ± 10	0.005
Clinic pulse pressure (mmHg)	48 ± 11	47 ± 13	52 ± 14*	47 ± 10	0.054
24-h systolic blood pressure (mmHg)	118 ± 10*	119 ± 12*	122 ± 11	123 ± 13	0.005
24-h diastolic blood pressure (mmHg)	79 ± 7	78 ± 8*	78 ± 7	81 ± 8	0.005
Hypertension (%)	46*	51*	64	67	0.002
VO_{2max} (ml/kg/min)	38.7 ± 7.9	29.6 ± 5.7	36.0 ± 7.0	28.0 ± 5.7	NA
MET	10.9 ± 2.3	8.4 ± 1.7	10.1 ± 2.0	7.9 ± 1.7	NA

GFR, glomerular filtration rate; HDL, high-density lipoprotein; HbA_{1c}, glycosylated hemoglobin; MET, metabolic equivalent. *$p < 0.05$ vs obese unfit, †$p < 0.05$ vs obese fit and ‡$p < 0.05$ vs overweight unfit in post-hoc analysis.

remained independently associated with higher GLS in obese subjects also in multivariable analysis (Table 3).

Discussion

The present study focused on whether fitness may offset the obesity associated LV systolic myocardial dysfunction. Epicardial fat accumulation is increased in obesity, and like other visceral fat tissue, it is metabolically active [21]. It is well demonstrated that epicardial fat stimulates reactive fibrosis in the myocardium by a number of mechanisms, subsequently leading to reduced myocardial function [2,21]. Additionally, epicardial fat may infiltrate the myocardium, resulting in myocardial steatosis [22]. Previous studies have documented the association of obesity with lower LV systolic chamber and myocardial function [1,5,6,23]. The present study adds to this by demonstrating that among obese subjects without known CV disease, having at least good fitness was associated with higher LV myocardial function assessed by GLS, particularly related to a lower body fat percentage, while no impact was found on myocardial function in overweight subjects. Additionally, we show that although average EF and GLS were within normal range, the prevalence of abnormal GLS was much higher than abnormal EF, indicating that GLS is a more sensitive tool for detection of subclinical systolic dysfunction.

Fitness, obesity and myocardial function

In a small study of 9 obese adolescents, Dias et al. observed a strong univariable association between fitness and higher GLS [8]. However, due to a low number of observations, the finding could not be further explored in multivariable analyses [8]. The present study expands their finding by showing that having at least good fitness is independently associated with higher GLS in obese adults. In contrast, Share et al. did not find an independent association between physical activity and GLS in a small cross sectional study of young women with abdominal adiposity [24]. In a study of 142 healthy subjects with increased BMI but free from hypertension and diabetes, Wong et al. found that LV myocardial function, evaluated by tissue Doppler strain, became progressively poorer with increasing BMI, while no association between LV myocardial function and exercise capacity measured by peak oxygen uptake was found [25]. Our larger study expands previous knowledge by showing that the negative LV myocardial effects of excess body fat are evident even in less selective obese subjects. The findings suggest that obesity-associated LV myocardial dysfunction may be modified by fitness through reductions in body fat mass percentage.

We recently identified higher pulse pressure, a crude measure of arterial stiffness, as a key confounder of

Table 2 Echocardiographic characteristics of total study population and in fit and unfit groups.

Variables	Overweight		Obese		p
	Fit (n = 77)	Unfit (n = 99)	Fit (n = 43)	Unfit (n = 250)	
Interventricular septal thickness end-diastole (cm)	1.07 ± 0.22	1.04 ± 0.22†	1.16 ± 0.21	1.11 ± 0.23	0.014
Left ventricular diameter end-diastole (cm)	4.94 ± 0.49	4.87 ± 0.40	4.91 ± 0.47	5.00 ± 0.48	0.083
Posterior wall thickness end-diastole (cm)	0.81 ± 0.16	0.81 ± 0.14	0.88 ± 0.15	0.85 ± 0.17	0.049
Left ventricular mass index (g/m$^{2.7}$)	38.5 ± 9.2†	36.4 ± 7.6*†	43.2 ± 6.4	40.0 ± 9.4	<0.001
Relative wall thickness (ratio)	0.33 ± 0.07	0.34 ± 0.07	0.36 ± 0.08	0.34 ± 0.08	0.187
Ejection fraction (%)	61 ± 5	62 ± 5	64 ± 5*§	62 ± 5	0.014
Reduced ejection fraction (%)	1	2	2	5	0.271
Global longitudinal strain (%)	−20.1 ± 2.6*	−19.7 ± 2.8	−20.0 ± 2.5	−19.0 ± 3.0	0.005
Reduced global longitudinal strain (%)	16*	24	19	30	0.040
Pulse pressure/stroke volume index (mm Hg/mL·m$^{2.04}$)	1.05 ± 0.88	0.84 ± 0.87†	1.44 ± 0.76	0.93 ± 0.83†	0.001

*p < 0.05 vs. obese unfit; †p < 0.05 vs. obese fit and §p < 0.05 vs. overweight fit in post-hoc analysis.

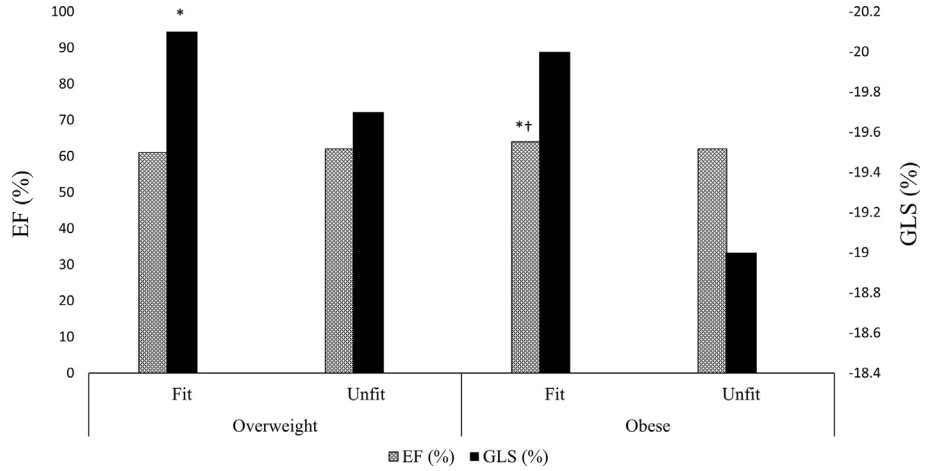

Figure 2 LV systolic myocardial and chamber function in fit and unfit groups. EF, ejection fraction; GLS, global longitudinal strain. *p < 0.05 vs. unfit obese; †p < 0.05 vs overweight fit.

prevalent subclinical cardiac disease in the FATCOR cohort, including presence of a dilated left atrium, concentric LV geometry and LV hypertrophy [10]. Both observational and cross-sectional data have suggested higher directly measured peak oxygen uptake to be associated with lower arterial stiffness, measured by pulse wave velocity [26,27]. From this it has been concluded that good fitness may slow age-related increase in arterial stiffness and that fitness impacts arterial stiffness more than BMI, in particular in younger subjects without obesity and hypertension [26,27]. Adding to this, the present analysis in middle-aged subjects identified a positive association of fitness with higher GLS despite presence of higher arterial stiffness in the obese group. There is also compelling evidence that fitness reduces the incidence of CV events and mortality [28–30]. In a large meta-analysis Nocon et al. found that physical activity was associated with a 35% lower risk of CV mortality, and that risk reduction was present both when physical activity was quantified by questionnaires and by exercise testing [30]. In another meta-analysis Kodama et al. suggested that when maximal aerobic capacity quantified by metabolic equivalents (METs) reaches

Table 3 Covariables of fitness in overweight and obese subjects in uni- and multivariable logistic regression analyses.

Variable	Overweight subjects		Obese	
	Univariable	Adjusted	Univariable	Adjusted
Global longitudinal strain (%)	0.93 (0.84–1.05)	n.a.	0.87 (0.77–0.99)*	0.88 (0.79–0.99)*
Ejection fraction (%)	0.95 (0 90–1.07)	n.a.	1.09 (1.03–1.17)*	n.a.
Triglycerides (mmol/L)	0.49 (0.29–0.80)*	0.50 (0.30–0.84)*		
Fat percentage (%)	0.96 (0.93–1.00)	0.96 (0.92–1.00)*	0.94 (0.90–0.98)*	0.93 (0.89–0.98)*
PP/SVi (mmHg/mL·m$^{2.04}$)			1.04 (1.01–1.07)*	2.07 (1.28–3.32)*
Left ventricular mass index (g/m$^{2.7}$)			1.04 (1.00–1.07)*	n.a.

PP/SVi, pulse pressure/stroke volume index; n.a., variable not included in model.
*p < 0.05.

at least 8 METs and 6 METs in middle-aged men and women, respectively, a substantial reduction in risk of CV events and mortality is achieved [29]. In the present cohort we found that the average METs exceeded these sex-specific cut-offs in all groups, but apart from the association between fitness and higher GLS in the obese group, we could not find that fitness had a positive impact on powerful predictors of CV disease like prevalence of hypertension and higher LV mass in the obese groups.

Covariables of myocardial function

Elevated serum triglyceride level is a component of atherogenic dyslipidemia and common in subjects with metabolic syndrome. However, Wang et al. found lower LV myocardial function measured by GLS regardless of presence of metabolic syndrome in obese subjects, when compared to normal weight subjects [6]. In the present study the prevalence of metabolic syndrome was similar in fit and unfit obese subjects, but significantly lower in the fit overweight group that also had significantly higher GLS compared to obese unfit subjects.

When adipose tissue reaches its maximum storage capacity for free fatty acids, the surplus will be deposited in other tissues including the myocardium [31]. Cardiac steatosis has been linked to myocardial dysfunction both in animal models [31,32] and humans [33,34]. Szczepaniak et al. quantified myocardial triglyceride content by magnetic resonance spectroscopy, and found that subjects with the highest levels of myocardial triglycerides had the lowest myocardial contractile function as well as increased LV mass [35]. Keeping in mind that cardiac function is normally the main limiting factor of peak oxygen uptake [36], presence of myocardial steatosis in the FATCOR cohort may offer a possible mechanistic explanation to the independent associations found between fitness and lower body fat percentage in both overweight and obese groups. Additionally, the absence of an association between fitness and LV systolic function in the overweight group suggests the presence of a threshold related to the amount of body fat for when myocardial steatosis leads to alterations in the myocardium that might depress cardiac function.

Limitations

The current study has some limitations. Due to the cross-sectional design, cause–effect relationships could not be explored. As the FATCOR participants were characterized by middle-age, obesity and absence of known CV disease, generalization of the results to less selective cohorts must be done with caution. Due to missing data 151 participants had to be excluded from the current analysis. This might have introduced a selection bias, however, the excluded participants had comparable age and BMI to the included participants. Missing ergospirometry was caused by participants not showing up for testing, despite repeated invitations. Missing data on speckle tracking echocardiography was caused by poor image quality. The bioimpedance analysis was performed with a foot-foot system, which can cause fat-free mass to be somewhat underestimated in subjects with increased BMI, as well as give some underestimation of body fat in males and overestimation of body fat in females [37,38]. Duration of obesity and measured fitness level was unknown in the current study. If and how menopause impacts arterial stiffness and myocardial function remains unclear [39,40]. This was not explored in the FATCOR study as data on prevalence of menopause and menopausal age were not recorded.

Conclusion

In conclusion, in the FATCOR cohort, including overweight and obese subjects without known CV disease, fitness was associated with higher LV myocardial function in obese subjects, while no impact was found in those with overweight. Overall, these results highlight the value of including GLS in evaluation of subclinical LV systolic dysfunction in obesity.

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Conflicts of interest

None.

Authors' contributions

HH, EE and EG contributed to conception and design. SS contributed to conception. HH, HM, KM, EE, MTL and EG contributed to acquisition, analysis and interpretation. NP contributed to analysis. SS contributed to acquisition. HH, EE, HM, SS, NP and EG drafted the manuscript. All authors critically revised the manuscript, gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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