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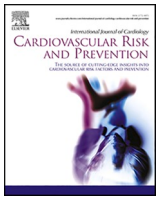

The impact of body mass index on cardiac structure and function in a cohort of obese patients without traditional cardiovascular risk factors

Henry H.L. Chen [a,b,c], Aditya Bhat [a,d], Gary C.H. Gan [a,c,d,e], Shaun Khanna [a,c], Golo Ahlenstiel [c], Kazuaki Negishi [b,f], Timothy C. Tan [a,b,c,d,e,*]

[a] Department of Cardiology, Blacktown Hospital, Sydney, NSW, 2148, Australia
[b] University of Sydney, Camperdown, NSW, 2006, Australia
[c] Blacktown Clinical School, Western Sydney University, NSW, 2148, Australia
[d] University of New South Wales, NSW, 2052, Australia
[e] Department of Cardiology, Westmead Hospital, Sydney, NSW, 2145, Australia
[f] Department of Cardiology, Nepean Hospital, Sydney, NSW, 2753, Australia

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ABSTRACT

Background: Obesity has been linked with alterations in hemodynamic, autonomic, and hormonal pathways in the body, leading to a spectrum of cardiovascular changes. We sought to evaluate the effects of obesity on structural and functional changes of the heart in the absence of cardiac disease and associated risk factors.
Methods: We identified healthy outpatients without any cardiovascular disease or risk factors from our institution's echocardiography database (2017–2020). Patients were stratified by body mass index (BMI; normal: 18.5–25 kg/m^2; overweight: 25–30 kg/m^2; class 1 obesity: 30–35 kg/m^2; class 2 obesity: 35–40 kg/m^2; class 3 obesity: >40 kg/m^2). Traditional and advanced echocardiographic parameters of cardiac chamber size and function including left ventricular global longitudinal strain (LV-GLS), left atrial reservoir strain (LASr), and right ventricular free wall strain (RV-FWS) were examined. The optimal cut-off BMI for discriminating LV-GLS (>-17.5%), LASr (<23%), and RV-FWS (>-23%) impairment was calculated using ROC curves.
Results: 307 patients were assessed (41.5 ± 13.3yrs; 36.5%male; LVEF 61.3 ± 4.8%). No significant differences in indexed chamber volumes or LVEF were appreciated across BMI groups ($p > 0.05$ for all). LV-GLS, LASr, and RV-FWS were all significant on one-way ANOVA for differences from the group mean (all $p < 0.01$). Jonckheere-Terpstra test confirmed a significant trend of lower absolute LV-GLS, LASr and RV-FWS values across the rising BMI groups. On ROC curve analysis, a BMI value of 29.9 kg/m^2, 35.1 kg/m^2, and 37.3 kg/m^2 were associated with LASr (AUC: 0.75), RV-FWS (AUC: 0.72), and LV-GLS (AUC: 0.75) impairment respectively.
Conclusion: Obesity is linked with subclinical reduction of cardiac function in otherwise healthy subjects without cardiovascular risk factors, with reduction of left atrial function occurring at lower BMI, followed by the right and left ventricular function.

1. Introduction

Obesity represents a contemporary public health crisis in Western society, affecting 39.6% of adults and 18.5% of children and adolescents in the United States [1]. This sobering statistic is compounded by its health effects, namely an increase in chronic disease, including cardiovascular disease, hypertension, diabetes mellitus, and malignancy [2]. Much of the deleterious health effects of obesity have been attributed to the development of associated cardio-metabolic risk factors, however obesity has been independently associated with a poor prognosis. It has been attributed as the causative etiology for one in five deaths and carries a significant economic burden, approximating $147 billion in healthcare spending in 2008 [3,4].

Obesity has been linked to alterations in hemodynamic, autonomic, and hormonal pathways in the body, leading to a spectrum of cardiovascular changes, from subclinical structural cardiac alterations to development of clinical cardiac failure. Much of these changes are caused by alterations in myocardial load dynamics and affected by coexistent disease states such as hypertension, diabetes mellitus, obstructive sleep apnoea, and ischemic heart disease [5,6]. Although recent studies have examined the effect of obesity on metabolically

* Corresponding author. Department of Cardiology, Blacktown Hospital, 18 Blacktown Road, Blacktown, NSW, 2148, Australia.
E-mail address: timothy.tan9@gmail.com (T.C. Tan).

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Abbreviations:

LV	Left ventricle
GLS	Global longitudinal strain
LA	Left atrium
RV	Right ventricle
BMI	Body mass index
LV-GLS	Left ventricular global longitudinal strain
LASr	Left atrial reservoir strain
RV-FWS	Right ventricular free wall strain
LVEF	Left ventricular ejection fraction
BSA	Body surface area
RV-FAC	Right ventricular fractional area change

healthy patients and found an association with subclinical cardiac impairment, there is a paucity of information on cardiac function in obese patients without both cardiac and metabolic risk factors [7,8].

Current advanced echocardiographic techniques provide a more sensitive method of detecting functional changes. Two-dimensional myocardial deformation indices utilising speckle tracking echocardiography allow for detection of subclinical changes in myocardial function not reflected by conventional measures of cardiac function such as ejection fraction. Its prognostic value has been validated in many populations including coronary disease, cardiomyopathies, chemotherapy cardiotoxicity, cardiac resynchronisation therapy, and in valvular disease [9]. In the general population, left ventricular (LV) global longitudinal strain (GLS) impairment has been shown to be an independent and incremental prognosticator for long term cardiovascular morbidity and mortality. [10].

Patients with obesity but without both cardiac and metabolic risk factors are scarce and would serve to illustrate the natural history of the disease process and its effects on the cardiac chambers in isolation. Additionally, in contrast to characterisation of the LV, the impact of obesity on left atrial (LA) and right ventricular (RV) function has not been as well characterised. Hence, the aim of our study was to evaluate the effects of body mass index on structural and functional changes of the LV, LA, and RV in the absence of any cardiac disease and associated risk factors, and to evaluate the stage at which body mass index elevation would begin to affect cardiac structure and function.

2. Materials and methods

2.1. Study population

We retrospectively identified consecutive healthy adults ≥18 years of age, who attended our institution's outpatient echocardiography service between the 1st of January 2017 to 31st of December 2020 with normal LV systolic and diastolic function. A rigorous inclusion criterion was applied to ensure that only patients with no documented or reported history of any cardiovascular disease or associated risk factors, such as hypertension, diabetes mellitus, hyperlipidaemia, ischemic or structural heart disease, arrhythmias, pulmonary disease, obstructive sleep apnoea, malignancies, and systemic inflammatory or chronic conditions including chronic liver disease were included. We excluded patients who were pregnant, trained athletes, those with a history of excessive alcohol intake (≥8 standard drinks per week) or those who were on cardioactive drug treatment. As these may potentially confound echocardiographic assessments of cardiac structure and function.

A rigorous examination of the hospital electronic medical records, medication history, blood pressure recordings and HbA1c level of each of the included patients was also undertaken to ensure that there was no recent or remote history of any potential conditions which may potentially confound the echocardiographic parameters and excluded any patient which did not meet inclusion criteria or had incomplete data. Patients with inadequate echocardiographic image quality for analysis were also excluded (Fig. 1).

Eligible patients were grouped based on body mass index (BMI) using the World Health Organisation classification: normal (BMI 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2), class 1 obesity (BMI 30–34.9 kg/m^2), class 2 obesity (BMI 35–39.9 kg/m^2) and class 3 obesity (BMI ≥40 kg/m^2).

The study protocol was approved by the Western Sydney Local Health District Human Research Ethics Committee (2006-17 QA).

2.2. Transthoracic echocardiography

Transthoracic echocardiography was performed using Philips EPIQ (Bothwell, WA, USA) as well as GE E9 and GE E95 (Boston, Massachusetts, USA) devices in accordance with established clinical practice and measurements in keeping with the American Society of Echocardiography recommendations [11]. In brief, LV volume and ejection fraction were calculated using modified Simpson's biplane method. LA volume was measured at end systole utilising the 2- and 4-chamber views using the biplane method of discs.

Pulse-wave Doppler was performed in the apical 4-chamber view to measure mitral inflow velocities for the assessment of LV filling. These measurements included mitral inflow peak early filling (E-wave) and late diastolic filling (A-wave) velocities, the E/A ratio, deceleration time of early filling velocity, and the isovolemic relaxation time. Utilising pulse-wave tissue Doppler imaging in the apical views, mitral annular velocities were obtained, and derived variables included: peak velocity of early (E) and late (A) filling, deceleration time of the E wave velocity and atrial filling fraction. E/e' and lateral e' were subsequently calculated.

2.3. Speckle-tracking echocardiography

Two-dimensional global longitudinal strain analysis was performed offline using vendor independent computer software (TomTech Image Arena Systems v2.3, Germany). Measurements were performed by two independent investigators blinded to patient demographics, clinical and echocardiographic data. All reported parameters were a mean of measurements from three cardiac cycles.

Briefly, LV longitudinal strain was assessed by tracing the LV endocardium at end systole. LV global longitudinal strain was then calculated as the average of the 18-segments obtained across the three standard apical views. For LA longitudinal strain, the LA endocardium was manually traced in the apical 2- and 4-chamber views at end-systole. LA reservoir strain was measured as the peak strain value at the end of the reservoir phase. Right ventricular strain was evaluated by tracing the RV endocardium in the RV-focused apical view at end-systole. We analysed RV free wall strain which was derived from the average peak systolic strain of the 3 RV free wall segments. The automated software tracked the movement of the LV, LA and RV myocardium throughout the cardiac cycle using R to R gating.

Quantitation of inter- and intra-observer variability of longitudinal strain parameters (LV-GLS, LASr and RV-FWS) was performed in 20% of the population through repeat measurements by a second independent investigator and the original investigator at least one month later. Reproducibility of these measurements were represented by the intra-class correlation coefficient and coefficient of variation.

2.4. Statistical analysis

All statistical analysis was performed using the Statistical Package for Social Sciences software (SPSS Version 22; SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviations and compared using Student's unpaired and paired *t*-test as appropriate. Categorical variables were expressed as numbers and

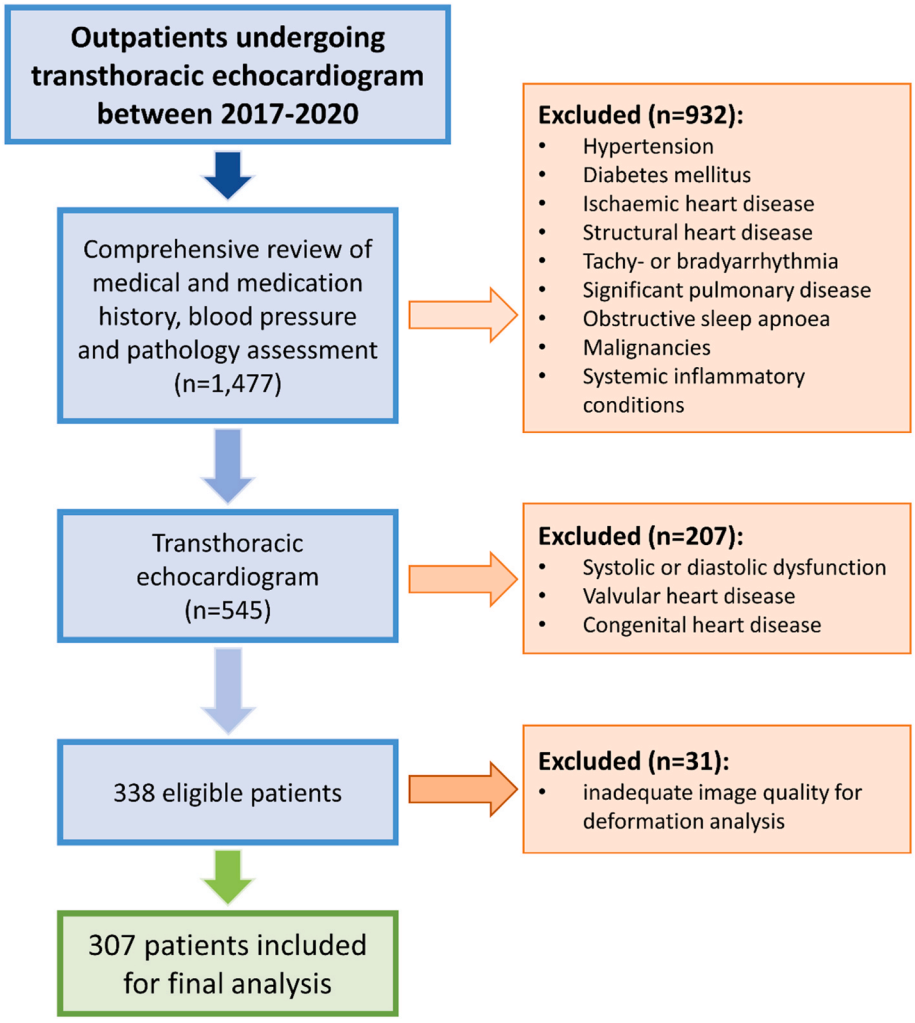


Fig. 1. CONSORT diagram
1,477 outpatient transthoracic echocardiogram were performed during the study period. 912 patients were excluded due to cardiovascular disease or risk factors. A further 207 patients were excluded due to structural heart disease including diastolic dysfunction. Finally, 51 patients did not have adequate imaging quality for deformation analysis of all three chambers. 307 patients were included for the final analysis.

percentages and compared using Chi-square testing. All tests were 2-tailed with a p value less than 0.05 considered statistically significant. One-way ANOVA was used to assess the associations of all clinical and echocardiographic parameters with BMI class. Post hoc analysis with Tukey-HSD was performed for the advanced echocardiographic parameters found to be significant on one-way ANOVA if assumption of equal variance can be confirmed on Welch test. Jonckheere-Terpstra test for ordered alternatives was performed to confirm the trend of advanced echocardiographic parameters across the rising BMI groups.

To evaluate whether the degree of BMI elevation can discriminate cardiac chamber dysfunction and dilatation, we computed receiver operating characteristic (ROC) curves of BMI values against the strain parameters found to be significant on one-way ANOVA for the differences from the group mean. The optimal cut-off values were selected using Youden index analysis. Impairment of LV-GLS, LASr, and RV-FWS was defined as <17.5%, <26%, and <23% respectively based on previously published normal values [12–14].

3. Theory

We theorize that increasing grades of obesity in isolation is associated with reduction in subclinical cardiac chamber function, even in the absence of cardiovascular risk factors that are usually associated with obesity.

4. Results

4.1. Participant characteristics

We screened 7481 echocardiographic studies during the study period, of which 1477 were individual "healthy" outpatient studies. These studies consisted mainly of hospital staff undergoing health checks, incidental murmurs for investigation and low risk troponin negative chest pains referred for outpatient assessment. From this cohort, we identified 338 healthy individuals who were eligible for inclusion into our study. Of this number, 31 patients were excluded due to inadequate image quality for strain analysis, with 3 patients (3.2%) in the normal, 5 (8.2%) in the overweight, 6 (12%) in the class I obesity, 6 (12%) in the class II obesity, and 11 (21.6%) in the class III obesity groups (Fig. 1).

The final 307 included patients were separated into 5 groups based on their BMI: normal (BMI 18.5–24.9 kg/m^2, n = 95) overweight (BMI 25–29.9 kg/m^2, n = 61), class 1 obesity (BMI 30–34.9 kg/m^2, n = 50), class 2 obesity (BMI 35–39.9 kg/m^2, n = 50) and class 3 obesity (BMI ≥40 kg/m^2, n = 51).

The mean age of the entire cohort was 41.5 ± 13.3 years, of which 36.5% were males. Age was not significant on one-way ANOVA analysis across the BMI groups (p = 0.124), but gender was (p = 0.002). Class 3 obesity group was predominantly female with only 11.8% male. BMI was significant on ANOVA analysis for differences from the group mean by design (p < 0.01). (Table 1).

There was a significant increase in HbA1c level, systolic and diastolic

Table 1
Baseline characteristics across the BMI groups.

Table 1.1 Patient baseline characteristics						
	Normal Weight (n=95)	**Over-Weight** (n=61)	**Class 1 Obesity** (n=50)	**Class 2 Obesity** (n=50)	**Class 3 Obesity** (n=51)	One-way ANOVA (p-value)
Age (yrs)	42.2±14.8	41.8±12.4	44.6±13.1	41.2±12.6	37.7±11.5	0.124
Male n (%)	39 (41.1)	27 (44.3)	19 (38)	21 (42)	6 (11.8)	0.002
Height (cm)	167±0.9	167±1.2	166±1.0	167±1.1	166±0.9	0.944
Weight (kg)	62.4±8.0	76.8±9.7	89.8±11.7	104.4±14.6	127.4±23.4	<0.001
BMI (kg/m^2)	22.4±1.9	27.5±1.4	32.6±1.3	37.3±1.48	46.2±5.8	<0.01
HR (bpm)	74.4±13.4	75.6±14.8	72.4±14.4	72.3±10.9	75.6±11.3	0.530
SBP (mmHg)	114.5±12.0	117.2±8.9	118.2±9.7	123.5±12.0	122.9±13.0	<0.001
DBP (mmHg)	72.6±8.9	74.1±9.0	74.9±8.8	76.9±8.8	76.7±10.2	0.030
HbA1c (%)	5.5±0.4	5.4±0.3	5.6±0.4	5.6±0.5	5.7±0.5	0.031

BMI: body mass index, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, bpm: beats per minute, HbA1c: glycated hemoglobin A1c

blood pressures across the five groups (p = 0.03; <0.01; 0.03 respective), although all blood pressure and HbA1c values remained within the normotensive and non-diabetic range (Table 1).

4.2. Echocardiographic parameters across BMI groups

One-way ANOVA analysis was performed on echocardiographic parameters across the five BMI groups. Unsurprisingly, all non-indexed measures of chamber dimension were significant on one-way ANOVA for differences from the group mean. Similarly, LV mass, LV end diastolic volume, LV end systolic volume and LA volume were also significant on allometric indexation using height, height to the power of 1.7 and of 2.7. All echocardiographic measures indexed to BSA, on the other hand, were not significant. LV hypertrophy based on BSA indexed LV mass (≥115 g/m^2 for males, ≥95 g/m^2 for females) was not significant across the BMI groups on one-way ANOVA analysis for the measure present in 3 (3%) patients in the normal, 1 (2%) patient in the overweight, 4 (8%) patients in the class 1 obesity, 5 (10%) patients in the class 2 obesity, and 4 (8%) patients in the class 3 obesity groups (Table 2).

In terms of functional parameters, the conventional measure of left ventricular systolic function – left ventricular ejection fraction, was not significant across the BMI groups (p = 0.659). Of the diastolic functional parameters, average peak mitral e' velocity (e') and E/e' ratio were the only parameters significant on one-way ANOVA for differences from the group mean. As the BMI rose across the groups, average e' value reduced while the E/e' ratio increased.

The two-dimensional measure of RV systolic function – RV fractional area change (RV-FAC) was also significant on one-way ANOVA for differences from the group mean (p = 0.001), with the higher BMI groups having lower RV-FAC. Both measures of right ventricular longitudinal function– tricuspid annulus S′ velocity (RV S') and tricuspid annular plane systolic excursion, were not significant.

Deformation imaging parameters of LV-GLS, LASr and RV-FWS were all significant on one-way ANOVA for differences from the group mean (all p < 0.001). All three of the advanced measures were significantly lower in the higher BMI groups (Table 2).

4.3. Subclinical myocardial function across the BMI classes

On post hoc analysis the advanced echocardiographic parameters using Tukey HSD, LV-GLS was not significantly different between any adjacent BMI groups, but significantly lower in the class 3 obesity group compared to the class 1 obesity group (p = 0.01). There was a significant reduction of LASr in the class 1 obesity group compared to the preceding overweight group (p = 0.04). RV-FWS demonstrated a significant reduction going from class 1 obesity to the adjacent class 2 obesity group (p < 0.01).

A Jonckheere-Terpstra test for ordered alternatives confirmed that there was a statistically significant trend of lower absolute LV-GLS, LASr and RV-FWS values with higher BMI class (from normal, overweight, class 1, class 2 to class 3 obesity groups; all P > 0.001). (Fig. 2).

4.4. Prevalence of subclinical myocardial dysfunction by BMI class

We tabulated the prevalence of subclinical myocardial dysfunction in each of the BMI groups.

An incremental increase in the prevalence of subclinical myocardial dysfunction was seen in all three cardiac chambers as the BMI increased. The overall prevalence of LV-GLS impairment was lowest at 7.3%, ranging from 2.1% to 21.6%. LASr impairment followed with an average prevalence of 16.7%, ranging from 3.2% to 35.3%. RVFWS impairment was the most common at 39.5% across the cohort, ranging from 7.4% to 56.9%.

4.5. Predictor of cardiac chamber subclinical dysfunction

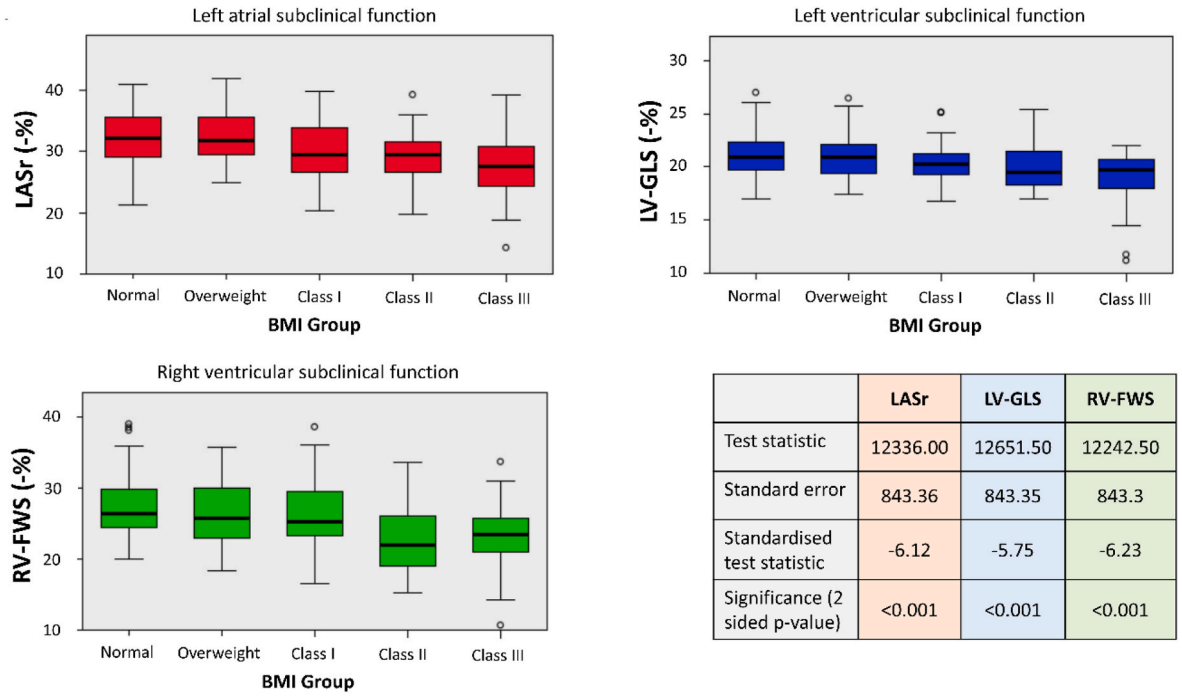
We utilised receiver operator characteristic (ROC) curves to find the optimal BMI cut-off values associated with cardiac chamber subclinical dysfunction.

The optimal BMI cut-off value associated with LASr impairment was the lowest at 29.9 kg/m^2 (sensitivity 86%, specificity 57%). This was followed by RV-FWS which had a BMI cut-off of 35.1 kg/m^2 (sensitivity 58%, specificity 79%). The highest BMI cut-off value was for LV-GLS impairment, at 37.3 kg/m^2 (sensitivity 67%, specificity 79%) (Fig. 3 Top).

Table 2
Echocardiographic parameters across the BMI groups.

Table 1.2 Echocardiographic parameters						
	Normal Weight (n=95)	**Over-Weight** (n=61)	**Class 1 Obesity** (n=50)	**Class 2 Obesity** (n=50)	**Class 3 Obesity** (n=51)	One-way ANOVA (p-value)
Left ventricular parameters						
LVIDd (mm)	43.7±4.9	44.8±5.6	46.0±5.9	47.1±5.1	49.0±5.6	<0.001
LVIDs (mm)	28.5±4.2	28.9±4.3	29.5±4.5	30.2±4.6	31.7±4.5	0.001
IVSd (mm)	8.5±1.4	8.9±1.8	9.4±2.2	9.5±2.0	9.7±1.9	0.001
PWd (mm)	8.5±2.7	8.6±1.7	9.2±3.3	9.4±2.1	10.0±1.9	0.005
RWT	0.39±0.1	0.40±0.1	0.43±0.2	0.41±0.1	0.41±0.1	0.171
LV mass (g)	118.7±28.5	135.7±42.1	155.9±42.0	166.2±49.8	183.0±59.4	<0.001
LV mass / $Ht^{2.7}$ (g/m^2)	29.8±6.5	33.5±7.4	40.0±11.5	41.6±12.0	46.3±11.3	<0.001
LV mass / BSA (g/m^2)	69.7±15.0	71.8±18.9	76.9±20.7	75.4±20.3	75.5±20.2	0.129
LV hypertrophy (n, %)	3 (3%)	1 (2%)	4 (8%)	5 (10%)	4 (8%)	0.254
MV inflow E velocity (m/s)	0.77±0.16	0.76±0.16	0.77±0.15	0.79±0.19	0.81±0.21	0.499
MV inflow A velocity (m/s)	0.59±0.16	0.60±0.16	0.62±0.14	0.61±0.16	0.64±0.16	0.365
E/A	1.4±0.5	1.4±0.5	1.3±0.4	1.4±0.5	1.3±0.5	0.644
Average e' (cm/s)	11.4±2.8	11.2±3.3	10.2±2.4	10.2±2.6	10.1±2.9	0.021
E/e'	7.1±1.9	7.2±2.3	7.8±1.9	8.2±2.4	8.9±5.9	0.013
Biplane LVEF (%)	61.8±5.1	61.0±5.0	61.6±3.5	60.7±4.4	61.0±5.4	0.659
LVED volume (ml)	83.2±24.7	86.1±25.4	94.9±30.0	100.3±29.9	114.1±33.6	<0.001
LVED vol / $Ht^{2.7}$ (ml/m^2)	20.9±5.4	22.0±5.0	24.1±6.5	25.3±7.5	29.1±7.6	<0.001
LVED vol / BSA (ml/m^2)	48.5±13.2	45.3±11.6	46.5±13.1	45.6±13.0	47.2±12.7	0.551
LVES volume (ml)	32.2±11.8	34.8±11.9	36.7±12.7	39.4±13.1	45.2±16.7	<0.001
LVES vol / $Ht^{2.7}$ (ml/m^2)	8.1±2.6	8.6±2.4	9.3±2.8	9.9±3.2	11.5±3.7	<0.001
LVES vol / BSA (ml/m^2)	18.9±6.4	18.3±5.4	18.0±5.6	18.0±5.7	19.2±8.0	0.757
LV-GLS (-%)	21.2±2.0	21.0±2.0	20.4±1.9	20.0±2.0	19.0±2.3	<0.001
Left atrial parameters						
LA volume (ml)	42.1±12.2	45.0±11.0	46.6±13.4	52.8±16.0	54.31±15.6	<0.001
LA volume / $Ht^{2.7}$ (ml/m^2)	11.4±3.4	11.7±3.0	13.1±4.2	15.1±6.5	15.9±4.8	<0.001
LA volume / BSA (ml/m^2)	24.9±7.2	23.9±5.5	22.9±6.4	24.0±6.7	22.8±7.4	0.377
LASr (-%)	32.1±4.5	32.6±3.8	30.2±4.8	29.0±3.9	27.7±5.0	<0.001
Right ventricular parameters						
RV basal dimension (cm)	3.2±0.5	3.2±0.6	3.2±0.5	3.4±0.5	3.5±0.5	0.004
TAPSE (cm)	2.4±0.5	2.4±0.4	2.4±0.5	2.4±0.5	2.4±0.4	0.828
RV S' velocity (m/s)	12.3±2.5	12.1±1.8	12.7±2.6	12.2±2.1	12.6±2.7	0.729
RVSP (mmHg)	18.7±8.3	17.4±7.5	18.3±11.8	20.2±7.8	19.1±10.0	0.711
RV end diastolic area (cm^2)	14.1±3.8	15.0±4.6	14.1±4.3	14.2±3.4	15.5±5.2	0.261
RV end systolic area (cm^2)	7.3±2.1	7.9±2.9	7.6±2.7	7.8±2.2	8.8±3.4	0.023
RV-FAC (%)	48.4±6.9	47.8±6.6	46.3±6.6	45.1±6.4	43.9±7.5	0.001
RV-FWS (-%)	27.3±4.1	26.3±4.2	26.4±4.6	22.5±4.4	22.9±4.6	<0.001

LVIDd: left ventricular internal diameter end diastole, LVIDs: left ventricular internal diameter end systole, IVSd: interventricular septum thickness end diastole, PWd: posterior wall thickness end diastole, RWT: relative wall thickness, LV: left ventricular, LA: left atrial, MV: mitral valve, LVEF: left ventricular ejection fraction, LVED: left ventricular end diastolic, LVES: left ventricular end systolic, RV: right ventricular, RVSP: right ventricular systolic pressure, RV-FAC: right ventricular fractional area change, LV-GLS: left ventricular global longitudinal strain, LASr: left atrial reservoir strain, RV-FWS: right ventricular free wall strain.



	LASr	LV-GLS	RV-FWS
Test statistic	12336.00	12651.50	12242.50
Standard error	843.36	843.35	843.3
Standardised test statistic	-6.12	-5.75	-6.23
Significance (2 sided p-value)	<0.001	<0.001	<0.001

Fig. 2. Trends of advanced echocardiographic parameters across the BMI groups on Jonckheere-Terpstra test
Jonckheere-Terpstra test confirms a significant drop in the absolute strain values of the three measured cardiac chambers across the rising BMI groups.

4.6. Single versus multi-chamber subclinical dysfunction

We further sought to identify the best BMI cut-offs for discriminating single versus multi-chamber longitudinal strain impairment utilising ROC curve analysis. Single-chamber strain impairment was defined as longitudinal strain impairment in one or more of the cardiac chambers assessed, while multi-chamber strain impairment refers to strain impairment in at least two cardiac chambers.

A BMI cut-off of 29.2 kg/m^2 was found to be associated with single-chamber impairment with a sensitivity of 78% and specificity of 65%. For multi-chamber impairment, a BMI cut-off of 35.1 kg/m^2 was ideal with a sensitivity of 84% and specificity of 74% (Fig. 3 Bottom).

4.7. Reproducibility analysis

There was good reproducibility of the strain parameters based on the inter- and intra-observer variability. For inter-observer variability, the intra-class correlation coefficient and the coefficient of variation were 0.90 (95% CI 0.72–0.97) and 3.5% (95% CI 2.9–4.0) for LV-GLS, 0.86 (95% CI 0.75 to 0.92) and 4.8% (95% CI 4.0–5.6) for LASr, 0.95 (95% CI 0.74–0.99) and 4.3% (95% CI 3.6–5.0) for RV-FWS. For intra-observer variability, the intra-class correlation coefficient and the coefficient of variation were 0.93 (95% CI 0.74–0.98) and 2.8% (95% CI 2.4–3.3) for LV-GLS, 0.95 (95% CI 0.81 to 0.99 and 2.9% (95% CI 2.4–3.4) for LASr, 0.97 (95% CI 0.81–0.99) and 2.9% (95% CI 2.5–3.4) for RV-FWS.

5. Discussion

In this retrospective study of otherwise 'healthy' patients undergoing transthoracic echocardiography, we found an association between increasing BMI and subclinical cardiac dysfunction independent of loading conditions, cardiovascular disease and risk factors. Furthermore, our findings suggest the degree of BMI elevation is associated with incremental risk of subclinical myocardial dysfunction.

To our knowledge this is the first echocardiographic study that examined subclinical cardiac dysfunction of the LV, LA and RV in the absence of cardiovascular diseases and risk factors. Additionally, the use of stratified BMI groups allowed us to demonstrate the incremental changes with the step wise increase in BMI.

5.1. Indexation of cardiac volumes in obesity

Current echocardiographic guidelines recommend indexation of values based on body surface area (BSA) [11]. However, accurate adjustment of echocardiographic measurements has been an ongoing challenge in obesity [15]. It is believed that BSA indexation of LV mass and LA volume in obese patients lead to an under recognition of LV hypertrophy and LA dilatation [16].

Our study showed that non-indexed LV mass, LV and LA volumes are significantly higher with rising BMI groups as expected. After indexing to BSA, these values did not change despite the degree of BMI elevation. These results support the idea that isometric indexation of echocardiographic parameters using BSA may not be as sensitive in detecting structural and functional changes in higher grades of obesity since it has the potential to overcorrect for body size [17]. Allometric indexation using height, height to the power of 1.7 (height$^{1.7}$) and 2.7 (height$^{2.7}$) in contrast, may be more suitable to correct for body size in patients with higher BMI. However, allometric indexation can then over- and under-estimate LV mass in shorter and taller patients respectively [16,17].

5.2. Isolated effect of obesity on subclinical myocardial function

Other similar studies have included cardiac conditions and cardiovascular risk factors which may potentially impact on the echocardiographic measurements obtained [7,8], which is why we have implemented this stringent selection criteria. Our results have confirmed the effect of BMI on cardiac structure and function in the normotensive "healthy" obese population.

Due to the strict inclusion criterion, the class 3 obesity cohort in our study was predominantly female with a trend towards younger age. We hypothesise this inequality in the highest BMI group is due to age and male gender both being associated with cardiovascular disease or risk factors in extreme obesity, which were subsequently excluded based on our study protocol.

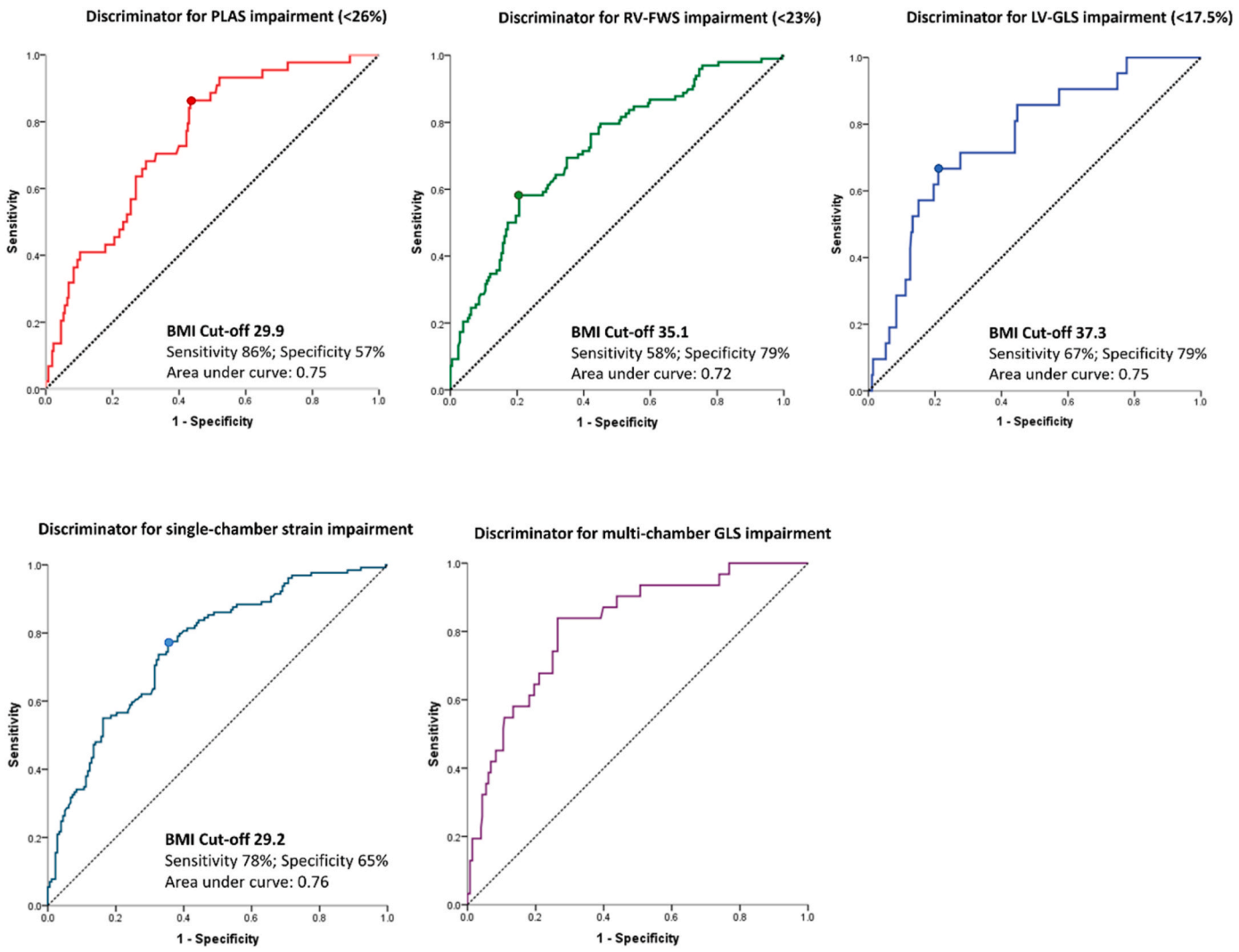


Fig. 3. BMI cut off values which discriminate subclinical cardiac dysfunction
(Top). Receiver operating characteristic curves found that a BMI of ≥29.9 predicts left atrial reservoir strain impairment (LASr<26%), a BMI of ≥35.1 predicted right ventricular free wall strain impairment (RV-FWS<23%), and a BMI of ≥37.3 predicted left ventricular global longitudinal strain impairment (LV-GLS<17.5%) (Bottom). Receiver operating characteristic curves demonstrated that single chamber subclinical dysfunction is best discriminated as the BMI approaches obesity (BMI≥29.2), while subclinical dysfunction in two or more cardiac chambers was best discriminated as the BMI crossed into class 2 obesity (BMI≥35.1).

The effects of elevated BMI on cardiac structure and function are hypothesised to arise from several mechanisms. Firstly, increased cardiac work and stroke volume can lead to chamber dilatation and eccentric left ventricular hypertrophy [18], with associated increases in left ventricular wall stress and myocardial oxygen consumption [19]. Further, insulin resistance, a common complication of elevated BMI, has been shown to be associated with alterations in myocardial substrate metabolism which may lead to contractile dysfunction [20]. Insulin's effects have been proposed to be from its effect on growth stimulation, sodium retention and neuroendocrine mediated pathways [21]. Further, elevated adipose tissue can result in increased adipokine production and subsequent systemic inflammation, a possible causative factor in development of myocardial fibrosis and subclinical dysfunction [22]. Undiagnosed obstructive sleep apnoea is a confounding factor in the obese population and may contribute to structural cardiac changes from the combined effect of nocturnal hypertension, cardiac afterload increase, wall stress during apnoeic periods and from upregulation of inflammatory cytokines leading to myocardial fibrosis [23].

5.3. *Degree of BMI elevation affects subclinical myocardial function*

Our results have further shown that the degree of BMI elevation confers incremental risk of subclinical myocardial dysfunction across the BMI classes.

Left atrial subclinical functional appears to be the most sensitive to BMI elevation. As evidenced by the earlier drop in left atrial strain at just class 1 obesity (BMI ≥30) on post hoc analysis. The optimal cut-off value associated with LASr impairment on ROC curve analysis was similarly early at a BMI of ≥29.9.

As for right ventricular subclinical function, prevalence of RV-FWS impairment rises dramatically from 24% in class 1 obesity group to 56% and 56.9% in class 2 and 3 obesity groups respectively. This aligns with the pronounced drop of RV-FWS at class 2 obesity (BMI ≥35) on post hoc analysis, and the optimal BMI cut-off of ≥35.1 found to associate with RV-FWS impairment on ROC curve analysis.

LV subclinical function, on the other hand, exhibited a gradual decline spread across the entire BMI range on post hoc analysis. The ideal BMI cut-off value associated with LV-GLS impairment on ROC curve analysis was the highest at ≥37.3.

Additionally, we also found that a BMI of ≥29.2 and ≥ 35.1 predicted

single chamber and multi chamber subclinical dysfunction respectively. These findings are consistent with the Framingham population-based study where the incidence of heart failure has shown to rise with BMI elevation across the entire BMI range [24].

5.4. Limitations

The main limitation of echocardiographic assessment of the obese population was image quality, particularly in the higher obesity classes. Despite this limitation, we only excluded 10.1% of our cohort due to inadequate image quality for strain analysis. Unsurprisingly, this challenge disproportionately affected the class III obesity group, which had BMI values up to 75 kg/m^2. The utility of other modalities such as computed tomography, magnetic resonance and radionuclide imaging would also encounter issues of gantry size restriction and examination table weight limits in extreme obesity.

Another limitation of our study is that this is a single centre study. Despite this, the impact of obesity on subclinical cardiac function within our modest cohort size was evident.

Finally, obesity is a heterogenous condition with a complex array of physiological pathways contributing to cardiac dysfunction [5]. Due to the retrospective nature of this study, we did not have fasting and post meal serum insulin levels, uric acid levels or fibroscan data assessing for non-alcoholic steatohepatitis, as these tests are not standard of care routine tests performed in a healthy patient even if obese. Hence, we were not able to fully account for all underlying metabolic conditions. However, we did attempt to minimise the effect of some of these confounders by imposing a strict inclusion and exclusion criteria to exclude patients with an abnormal HBA1C, history of hyperlipidaemia or dyslipidaemia (including those on lipid lowering therapy) and history of chronic liver disease during our extensive background history screening.

6. Conclusions

Elevated body mass index can cause subclinical myocardial dysfunction even in the absence of any cardiovascular disease or risk factors. Furthermore, the degree of body mass index elevation confers incremental risk and prognosticate the presence of subclinical myocardial dysfunction.

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CRediT author statement

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Declaration of competing interest

None.

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