European Journal of Radiology 174 (2024) 111400

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Research article

Association of epicardial adipose tissue with early structural and functional cardiac changes in Type 2 diabetes

Sarah L. Ayton [a,1], Jian L. Yeo [a,1], Gaurav S. Gulsin [a], Abhishek Dattani [a], Joanna Bilak [a], Aparna Deshpande [b], J. Ranjit Arnold [a], Anvesha Singh [a], Matthew P.M. Graham-Brown [a], Leong Ng [a,c], Donald Jones [a,c], Piotr Slomka [d], Damini Dey [d], Alastair J. Moss [a,c], Emer M. Brady [a], Gerry P. McCann [a,*]

[a] Department of Cardiovascular Sciences, University of Leicester and the NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, UK
[b] Department of Imaging Services, Glenfield Hospital, University Hospitals of Leicester, Leicester UK
[c] Leicester van Geest Multi-Omics Facility, University of Leicester, Leicester, UK
[d] Biomedical Imaging Research Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

ARTICLE INFO

Keywords:
Epicardial adipose tissue
Adiposity
Type 2 diabetes
Cardiac dysfunction

ABSTRACT

Background: Dysregulated epicardial adipose tissue (EAT) may contribute to the development of heart failure in Type 2 diabetes (T2D). This study aimed to evaluate the associations between EAT volume and composition with imaging markers of subclinical cardiac dysfunction in people with T2D and no prevalent cardiovascular disease.
Methods: Prospective case-control study enrolling participants with and without T2D and no known cardiovascular disease. Two hundred and fifteen people with T2D (median age 63 years, 60 % male) and thirty-nine non-diabetics (median age 59 years, 62 % male) were included. Using computed tomography (CT), total EAT volume and mean CT attenuation, as well as, low attenuation (Hounsfield unit range −190 to −90) EAT volume were quantified by a deep learning method and volumes indexed to body surface area. Associations with cardiac magnetic resonance-derived left ventricular (LV) volumes and strain indices were assessed using linear regression.
Results: T2D participants had higher LV mass/volume ratio (median 0.89 g/mL [0.82–0.99] vs 0.79 g/mL [0.75–0.89]) and lower global longitudinal strain (GLS; 16.1 ± 2.3 % vs 17.2 ± 2.2 %). Total indexed EAT volume correlated inversely with mean CT attenuation. Low attenuation indexed EAT volume was 2-fold higher (18.8 cm^3/m^2 vs. 9.4 cm^3/m^2, $p < 0.001$) in T2D and independently associated with LV mass/volume ratio (ß = 0.002, p = 0.01) and GLS (ß = −0.03, p = 0.03).
Conclusions: Higher EAT volumes seen in T2D are associated with a lower mean CT attenuation. Low attenuation indexed EAT volume is independently, but only weakly, associated with markers of subclinical cardiac dysfunction in T2D.

1. Introduction

Increased deposition of visceral adipose tissue has been implicated in the development of cardiovascular disease [1]. Dysregulated adipocyte metabolism associated with its volumetric increase may alter pathophysiological processes contributing to cardiac dysfunction in metabolic diseases, including Type 2 diabetes (T2D). Epicardial adipose tissue (EAT) is a unique deposit of particular interest, as it lies in direct communication with the myocardium with a shared blood supply and may exert local effects through direct and indirect pathways [2]. In T2D, alterations in lipid handling by epicardial adipocytes and imbalances in adipokine homeostasis [3,4] have been associated with cardiomyocyte dysfunction [5]. Early deleterious effects on cardiac structure and function, including concentric left ventricular (LV) remodelling and

Abbreviations: CMR, Cardiac magnetic resonance; CT, Computed tomography; EAT, Epicardial adipose tissue; GLS, Global longitudinal strain; HU, Hounsfield units; LV, Left ventricular; NT-proBNP, N-terminal pro B-type natriuretic peptide; PEDSR, Peak early diastolic strain rate; T2D, Type 2 diabetes.

* Corresponding author.
E-mail address: gpm12@leicester.ac.uk (G.P. McCann).

[1] Equal contribution to manuscript.

https://doi.org/10.1016/j.ejrad.2024.111400
Received 16 November 2023; Received in revised form 29 January 2024; Accepted 27 February 2024
Available online 29 February 2024

reductions in systolic strain and diastolic strain rates, commonly precede the onset of heart failure symptoms in people with T2D (termed stage B heart failure) [6]. However, the relative contribution of excess EAT accumulation to the development of stage B heart failure in these patients is poorly understood [7,8].

Fully automated deep learning methods are now available allowing for rapid quantification of EAT volume from non-contrast computed tomography (CT) images [9,10]. Additionally, CT measurement of EAT allows for measurement of adipose tissue density using x-ray attenuation. The attenuation of adipose tissue may reflect differences in the adipose tissue present, including adipocyte size, [11] and as EAT volume and x-ray attenuation are negatively correlated, [12] this suggests as increased EAT is deposited the size and, therefore, likely the function of the adipocytes change. Accumulation of EAT of a lower CT attenuation may represent deposition of larger lipid-laden adipocytes, which may be of interest in T2D, as these adipocyte populations have been associated with the adverse changes seen in metabolic disease [11]. We hypothesized that increased 'low attenuation' EAT volume is independently associated with markers of stage B heart failure in people with T2D.

2. Methods

2.1. Study design and population

Participants were prospectively recruited between November 2017 and 2021 as part of the ongoing Prevalence and Determinants of Subclinical Cardiovascular Dysfunction in Adults with Type 2 Diabetes (PREDICT) study, which is a single centre, case-control study conducted at the National Institute for Health Research xxx Biomedical Research Centre (NCT03132129). Participants were identified from both primary and secondary care using electronic databases. Inclusion and exclusion criteria have been previously reported [13]. Briefly, included were individuals aged 18–75 years with a diagnosis of T2D and no prior history, signs, or symptoms of cardiovascular disease. Non-diabetic controls, aged 18–75 years with no prior history of cardiovascular disease and no diagnosis of diabetes mellitus or impaired glucose tolerance, were recruited for comparison. Additional exclusion criteria within this comparator cohort included: uncontrolled hypertension (blood pressure $>$ 160/100 mmHg) and conditions that may limit exercise capacity or be associated with subclinical cardiac dysfunction. Ethical approval was granted by the National Research Ethics Service (17/WM/0192) and the study was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to any study procedures.

2.2. Study procedures

Information was collected on demographic variables, medical history and medications taken. Anthropometric measurements including height, weight, waist and hip circumference were recorded and 24-hour blood pressure monitoring performed. Body surface area was calculated using the Mosteller formula [14]. Fasting blood samples were analysed in a National Health Service approved pathology laboratory for: glycaemic control, lipids, kidney function and cardiac biomarkers. The assay lower limit of detection for N-terminal pro B-type natriuretic peptide (NT-proBNP) was 35 ng/L and for high sensitivity troponin I (hs-troponin I) was 2.5 ng/L. Insulin and leptin were analysed in a research laboratory and quantified by multiplex assay on a Luminex platform, and plasma adiponectin was analysed using a Quantikine ELISA assay (R&D Systems, Minneapolis, USA). All samples analysed in the research laboratory were assayed in duplicate (the mean reported), with all samples having a co-efficient of variance $\leq$20 %. Homeostatic Model Assessment for Insulin Resistance was calculated according to the formula: fasting insulin * fasting glucose/22.5 [15].

2.3. Image acquisition

2.3.1. Cardiac magnetic resonance imaging

CMR scans were performed on a 3-tesla scanner (Siemens Skyra or Vida, Erlangen, Germany), with retrospective electrocardiogram gating and using a standardised protocol, as previously described [16]. Short and long axis balanced steady-state free precession cine images were obtained for determination of LV mass, volumes, function and global strain and strain rates.

2.3.2. Computed tomography imaging

Non-contrast electrocardiogram-gated CT scans were acquired on a 128-detector CT scanner (Siemens Somatom Flash, Erlangen, Germany) with prospective electrocardiographic triggering at 70 % R-R interval and a tube voltage of 120kVp. Raw data were reconstructed at a slice thickness of 3.0 mm for the assessment of EAT and other adipose tissues within the chest.

2.4. Image analysis

2.4.1. Cardiac magnetic resonance imaging measurements

Left ventricular (LV) volumes, function, mass and strain measurements were measured using cvi42 (version 5.10, Circle Cardiovascular Imaging, Calgary, Canada). LV volumes, function and mass were derived by automated contouring of the short axis cine stack, excluding papillary muscles and trabeculations from the mass, with manual adjustment as required. LV volumes and mass were indexed to body surface area. Myocardial strain and strain rates were derived by the dedicated cvi42 Tissue Tracking module. Automated contour detection of short axis end-diastolic epicardial and endocardial borders were also used to obtain LV global circumferential strain measurements and manually defined contours were used for LV global longitudinal strain (GLS). Circumferential and longitudinal peak early diastolic strain rates (PEDSR) were also obtained. Our group has previously demonstrated excellent reproducibility for strain and strain rate measures [16]. All strain values are presented as positive percentages for ease of interpretation, with a lower number indicating worse strain [17,18].

2.4.2. Computed tomography adipose tissue quantification

EAT volume and mean CT attenuation were measured from non-contrast CT scans using a fully automated deep learning software (QFat, version 2.0; Cedars-Sinai Medical Center, Los Angeles, California) [9]. The software automatically detects superior and inferior borders, defined as the bifurcation of the pulmonary artery and the posterior descending artery, respectively. The EAT margin at the visceral pericardium is then defined [9]. Minimal correction of superior and inferior borders and pericardial contours was applied by a single researcher trained in the software (xx). A Hounsfield unit (HU) range of -30 to -190 HU was used for total EAT volume and 'low attenuation' EAT volume was defined using the cut off of -90 to -190 HU, based on prior studies investigating brown and white adipose tissue, to estimate areas containing lipid-laden adipocytes [11,19]. Total and low attenuation EAT volume (cm^3) were indexed to body surface area. The mean attenuation (HU) of the total EAT volume was also calculated.

Thoracic adipose tissue was defined as adipose tissue identified within the chest cavity outside the visceral pericardium; volume (cm^3) and mean attenuation (HU) of this adipose tissue were calculated [9]. A 5 mm circular area of subcutaneous adipose tissue was selected at the level at which the right coronary artery was first viewed after arising from the aorta for measurement of the mean attenuation of subcutaneous adipose tissue (HU). Where there was not sufficiently imaged subcutaneous adipose tissue at this level, a 5 mm area was taken from the first CT slice.

2.5. Statistical analysis

Variables were assessed for normality using the Shapiro–Wilk test, and visually with histograms and QQ plots. Continuous, normally distributed data are presented as mean (standard deviation), non-normally distributed data as median (interquartile range) and categorical data as frequency (percentage). Missing data are indicated within the results tables. The independent *t*-test, Mann Whitney *U* test and Chi-square test, as appropriate, were used to compare participants with T2D and non-diabetic controls, as well as differences between adipose tissue deposits. Differences in CMR measures between T2D and non-diabetic controls were also compared using analysis of covariance (ANCOVA) with age, BMI and mean 24-hour systolic blood pressure as co-variates.

Associations between total and low attenuation indexed EAT volumes and cardiac biomarkers were assessed in participants with T2D using boxplots and ordinal logistic regression due to a large proportion of values being below the lower limit of detection for NT-proBNP (35 ng/L) and hs-troponin I (2.5 ng/L). Associations were also assessed with log transformed serum adipokines using scatterplots, Pearson's correlation and univariable regression analysis. In participants with T2D, multiple linear regression models, as described below, were used to assess associations of total and low attenuation indexed EAT volume with markers of early cardiac dysfunction identified by differences seen between participants with T2D and non-diabetic participants, as well as previous work [20]. Variables known to be associated with markers of subclinical cardiac dysfunction, as well as serum adipokines of interest, were used to form a 'baseline' multiple regression model: age, gender, ethnicity, waist to hip ratio, systolic blood pressure, adiponectin and leptin (Model 1). Total and low attenuation indexed EAT volumes were then added to this model separately (Models 2 and 3, respectively) to assess their independent association with markers of subclinical cardiac dysfunction. Additionally, linear regression models with total and low attenuation indexed thoracic adipose tissue volumes were performed. Statistical analyses were performed using the R environment for statistical computing [21]. A p value < 0.05 was considered statistically significant.

3. Results

A total 238 participants with T2D and 42 non-diabetic controls were enrolled. Twenty-three participants with T2D and three non-diabetic controls were ineligible after consent (Fig. 1), resulting in a study population of 254 participants (n = 215 T2D, n = 39 non-diabetic controls). Participants with T2D were older, with more centripetal adiposity and a higher prevalence of hypertension and dyslipidaemia (Table 1). Gender and ethnicity were well matched between the cohorts. As anticipated, participants with T2D had higher biomarkers of insulin resistance (Table 1). There was a two-fold higher level of leptin and lower circulating adiponectin levels in the T2D cohort (Table 2). Statin use was higher in the T2Ds cohort (Supplementary Table 1), 74 % of whom were taking a biguanide, 17 % were using insulin, 10 % were taking a glucagon-like peptide-1 agonist and 20 % a sodium-glucose cotransporter-2 inhibitor.

3.1. Cardiac magnetic resonance imaging

Participants with T2D had smaller indexed LV end-diastolic and end-systolic volumes (Table 2). LV mass to volume ratio was significantly higher, indicative of concentric LV remodelling. There was no difference in LV ejection fraction between the two groups. However, LV GLS and diastolic performance (circumferential PEDSR) were lower in those with T2D. These results remained when age, BMI and mean 24-hour systolic blood pressure were added as co-variates (Table 2).

3.2. Computed tomography quantification and phenotyping of adipose tissue

Fig. 2 shows a representative CT slice from participants with T2D and

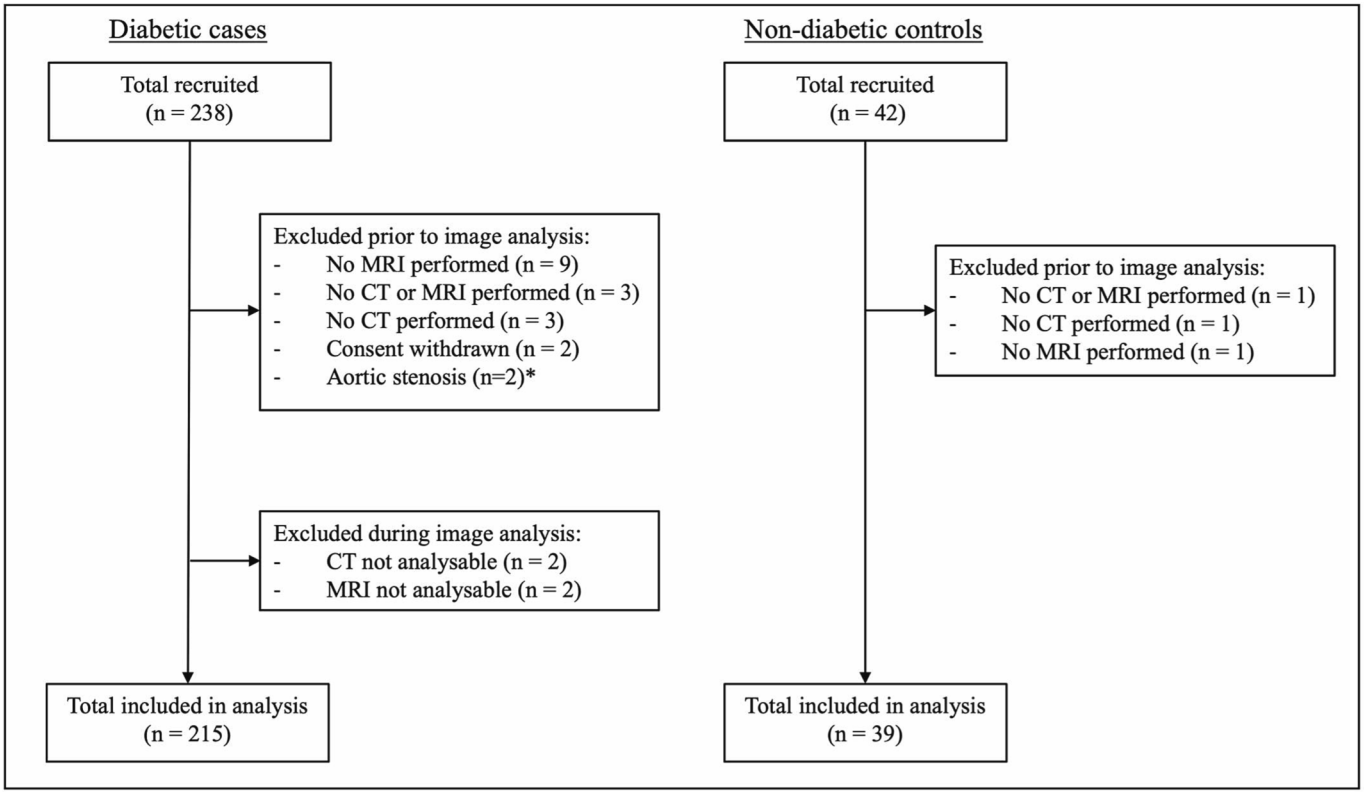

Fig. 1. Participant flow through study. *Aortic stenosis was diagnosed on research echocardiography.

Table 1
Demographics, anthropometric measurements and serum biochemistry.

	Type 2 diabetes (n = 215)	Non-diabetic controls (n = 39)	p-value
Age (years)	63.0 (58.0, 69.0)	59.0 (54.0, 66.5)	**0.022**
Gender (male)	130 (60 %)	24 (62 %)	
Ethnicity*			0.7
- White	155 (72 %)	27 (69 %)	
- Minority ethnic group	59 (27 %)	12 (31 %)	
Duration of diabetes, (years)	9.0 (5.0, 15.0)	–	
Hypertension	128 (60 %)	6 (15 %)	**<0.001**
Dyslipidaemia	159 (74 %)	7 (18 %)	**<0.001**
Mean 24-hour systolic BP (mmHg)	128.0 (122.0, 135.0)	122.0 (112.0, 133.0)	**0.007**
Mean 24-hour diastolic BP (mmHg)	74.2 ± 7.2	74.9 ± 7.9	0.6
Mean 24-hour HR (bpm)	76.5 ± 9.2	67.6 ± 6.5	**<0.001**
BMI (kg/m^2)	30.3 (26.6, 33.5)	25.7 (23.2, 29.8)	**<0.001**
BSA (m^2)	2.07 ± 0.50	1.88 ± 0.48	**0.03**
Height (cm)	170 (162, 176)	172 (164.5, 182.5)	0.12
Waist circumference (cm)	108.0 (100.0, 116.0)	95.0 (85.0, 103.0)	**<0.001**
Hip circumference (cm)	110.0 (104.0, 117.0)	104.0 (99.5, 110.0)	**<0.001**
Waist to hip ratio	1.0 ± 0.1	0.9 ± 0.1	**<0.001**
Haemoglobin (g/l)	141.1 ± 14.2	147.2 ± 11.8	**0.017**
Creatinine (umol/l)	75.0 (66.0, 87.0)	78.0 (67.0, 88.0)	0.5
Total cholesterol (mmol/l)	4.2 (3.5, 4.8)	5.7 (4.8, 6.0)	**<0.001**
HDL (mmol/l)	1.3 (1.1, 1.5)	1.6 (1.3, 2.1)	**<0.001**
LDL (mmol/l)	2.0 (1.6, 2.6)	3.2 (2.7, 3.8)	**<0.001**
Triglycerides (mmol/l)	1.5 (1.1, 2.1)	1.2 (0.9, 1.4)	**<0.001**
Fasting glucose (mmol/l)	7.7 (6.6, 8.9)	5.0 (4.8, 5.6)	**<0.001**
HbA1c (%)	7.1 (6.6, 8.0)	5.5 (5.3, 5.7)	**<0.001**
HbA1c (mmol/mol)	55.0 (48.0, 64.0)	36.0 (34.2, 38.0)	**<0.001**
Insulin (pg/ml)[a]	724.6 (485.4, 1,151.1)	283.1 (228.5, 472.5)	**<0.001**
HOMA-IR[b]	5.6 (3.5, 10.1)	1.6 (1.1, 2.7)	**<0.001**

BMI, body mass index; BP, blood pressure; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HR, heart rate; LDL, low density lipoprotein
Mean ± SD, Median (IQR) or n (%).
[a] n = 209.
[b] n = 207.
* 1 participant did not disclose ethnicity. Minority ethnic group included participants who identified as South Asian, Black and mixed ethnicity.

without T2D, where EAT is distinguished from the overlying thoracic adipose tissue using automated contouring of the pericardium. Compared with EAT, mean CT attenuation values of thoracic and subcutaneous adipose tissue were significantly lower (Table 2, Fig. 3A). Participants with T2D had lower EAT mean CT attenuation values compared with non-diabetic controls. Mean CT attenuation of EAT had a linear negative correlation with the total indexed EAT volume (Fig. 3B), such that a volume expansion of 20 mL/m^2 resulted in a decrease in CT attenuation by 4HU. The total indexed EAT volume was 1.6-fold higher in participants with T2D, whilst there was a 2-fold increase in low attenuation indexed EAT volume in participants with T2D (Table 2).

Total and low attenuation indexed EAT volumes were not associated with NT-proBNP, hs-troponin or adiponectin levels (Fig. 4; $p > 0.05$ for all regression models), however, both were associated with log-transformed leptin levels.

3.3. Associations of EAT with baseline characteristics and cardiac structure and function in T2D

With univariable regression analysis, total and low attenuation indexed EAT volumes were associated with increasing age, waist:hip ratio and ethnicity in participants with T2D (Supplementary Table 2). There were significant univariable associations of total and low attenuation indexed EAT volumes with LV mass/volume ratio and

Table 2
Cardiac function, adipokines, cardiac biomarkers and adipose tissue measurements.

	Type 2 diabetes (n = 215)	Non-diabetic controls (n = 39)	p-value	ANCOVA p-value*
Cardiac Magnetic Resonance measurements				
LV EDVi (mL/m^2)	63.7 ± 12.4	79.9 ± 12.8	**<0.001**	**<0.001**
LV ESVi (mL/m^2)	20.3 (16.4, 24.4)	26.6 (22.2, 30.8)	**<0.001**	**<0.001**
LV EF (%)	67.2 ± 7.3	65.8 ± 6.5	0.3	0.3
LVMi (g/m^2)	56.5 (49.6, 62.6)	61.4 (56.0, 70.9)	**<0.001**	**<0.001**
LV M/V ratio	0.89 (0.82, 0.99)	0.79 (0.75, 0.89)	**<0.001**	**<0.001**
LV GCS (%)	19.3 ± 2.5	19.1 ± 2.3	0.6	0.5
LV GLS (%)	16.1 ± 2.3	17.2 ± 2.2	**0.009**	**0.007**
Circ. PEDSR (1/s)	0.87 ± 0.24	0.97 ± 0.24	**0.032**	**0.04**
Long. PEDSR (1/s)	0.65 (0.51, 0.77)	0.69 (0.59, 0.75)	0.3	0.4
Serum Biomarkers				
Leptin (ng/ml)[a]	14 ± 2.5	7.9 ± 2.3	**<0.001**	
Adiponectin (g/ml)[a]	8.7 ± 1.3	10.4 ± 1.4	**<0.001**	
Leptin:Adiponectin Ratio[a]	2.0 (0.9, 3.5)	0.7 (0.4, 1.8)	**<0.001**	
hs-Troponin I (ng/L)				
<2.5	115 (55 %)	22 (56 %)		
2.5–6.4	50 (24 %)	8 (21 %)		
>6.4	44 (21 %)	9 (23 %)		
NT-proBNP (ng/L)				
<35	70 (34 %)	11 (29 %)		
35–64	69 (34 %)	12 (32 %)		
>64	66 (32 %)	15 (39 %)		
Non-contrast Computed Tomography				
Total EAT volume (cm^3)	121.4 (91.4, 165.3)	76.2 (48.7, 102.8)	**<0.001**	
Total EAT volume indexed to BSA (cm^3/m^2)	61.3 (46.8, 77.0)	38.8 (29.6, 51.9)	**<0.001**	
Mean EAT CT attenuation (HU)	−77.0 ± 5.2	−69.9 ± 5.4	**<0.001**	
Low attenuation EAT volume (cm^3)	37.7 (25.6, 58.6)	17.6 (8.5, 27.3)	**<0.001**	
Low attenuation EAT volume indexed to BSA (cm^3/m^2)	18.8 (13.2, 27.0)	9.4 (5.7, 13.5)	**<0.001**	
Total TAT volume (cm^3)	252.28 (182.53, 350.60)	150.09 (94.23, 214.73)	**<0.001**	
Total TAT volume indexed to BSA (cm^3/m^2)	125.48 (99.99, 155.34)	83.02 (59.90, 109.98)	**<0.001**	
Mean TAT CT attenuation (HU)	−89.83 ± 5.26	−83.99 ± 4.81	**<0.001**	
Low attenuation TAT volume (cm^3)	112.61 (76.00, 172.75)	52.14 (29.64, 98.57)	**<0.001**	
Low attenuation TAT volume indexed to BSA (cm^3/m^2)	58.28 (41.68, 80.42)	29.06 (17.02, 47.77)	**<0.001**	
Coronary artery calcium score			0.06	
	55 (26 %)	18 (46 %)		
0–100	67 (31 %)	9 (23 %)		
100–400	50 (23 %)	5 (13 %)		
>400	43 (20 %)	7 (18 %)		

ANCOVA, analysis of covariance; BSA, body surface area; EAT, epicardial adipose tissue, EDVi, end diastolic volume indexed to body surface area; EF, ejection fraction; ESVi, end systolic volume indexed to body surface area; GCS, global circumferential strain; GLS, global longitudinal strain; HU, Hounsfield units; LV, left ventricular; LVMi, left ventricular mass indexed to body surface area; M/V, mass/volume; SAT, subcutaneous adipose tissue; TAT, thoracic adipose tissue.
Mean ± SD or Median (IQR).
[a] n = 212; geometric mean and SD.

* ANCOVA test, covariates used: age, body mass index and mean 24-hour systolic blood pressure.

circumferential PEDSR (Fig. 5). Using multiple linear regression to evaluate associations with cardiac structure and function (LV M/V ratio, LV GLS and Circ PEDSR), the baseline models (Model 1) demonstrated independent associations with age (LV M/V ratio and Circ PEDSR), waist/hip ratio (LV GLS) and ethnicity (Circ PEDSR) (Supplementary Table 3). Total and low attenuation indexed EAT volumes (Models 2 and 3, respectively) were both independently associated with LV M/V ratio and LV GLS. On average, a 10 cm^3/m^2 increase in total indexed EAT volume was associated with an absolute reduction of 0.2 % in LV GLS, when adjusted for confounders. Neither total nor low attenuation indexed EAT volumes were independently associated with circumferential PEDSR. Similar results were seen with total and low attenuation indexed thoracic adipose tissue volumes (Supplementary Table 4).

4. Discussion

In this case-control multi-modality imaging assessment of a multi-ethnic cohort with T2D and no prevalent cardiovascular disease, total and low attenuation indexed EAT volumes, measured using machine learning methods, were higher compared to non-diabetic controls and independently associated with markers of stage B heart failure, even after adjusting for measures of systemic adiposity and serum adipokines. Individuals with higher volumes of indexed EAT volume showed a lower mean CT attenuation, which may pertain to differences in composition

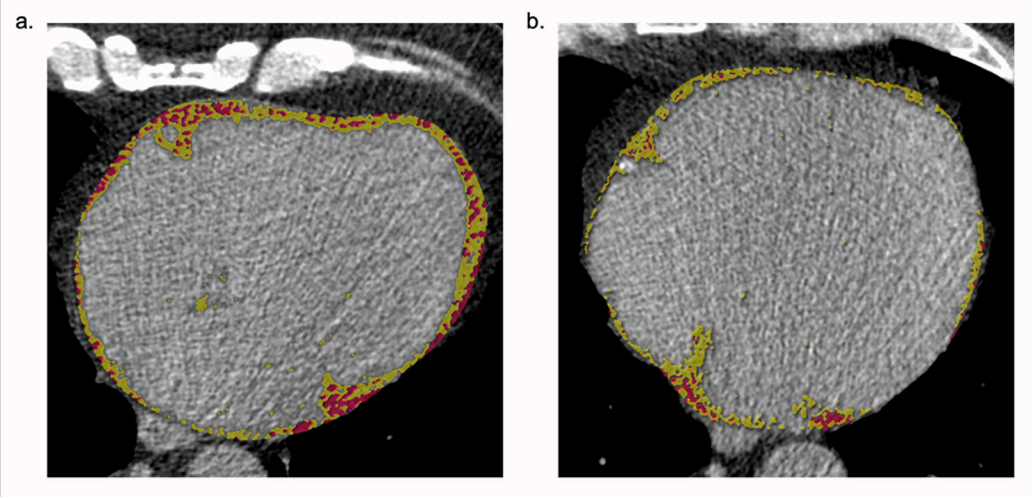

Fig. 2. Example CT slices from participants a) with Type 2 diabetes (T2D) and b) without diabetes. Red = low attenuation epicardial adipose tissue (EAT) (−90 to −190 Hounsfield units (HU)) and yellow = high attenuation EAT (−30 to −90 HU). The participant with T2D was a 73-year-old male with a body mass index (BMI) of 31 kg/m^2. Total EAT volume was 234 cm^3 with a mean CT attenuation of −79HU. The participant without T2D was a 72-year-old male with a BMI 27 kg/m^2. Total EAT volume was 100 cm^3 with a mean CT attenuation of −69HU.

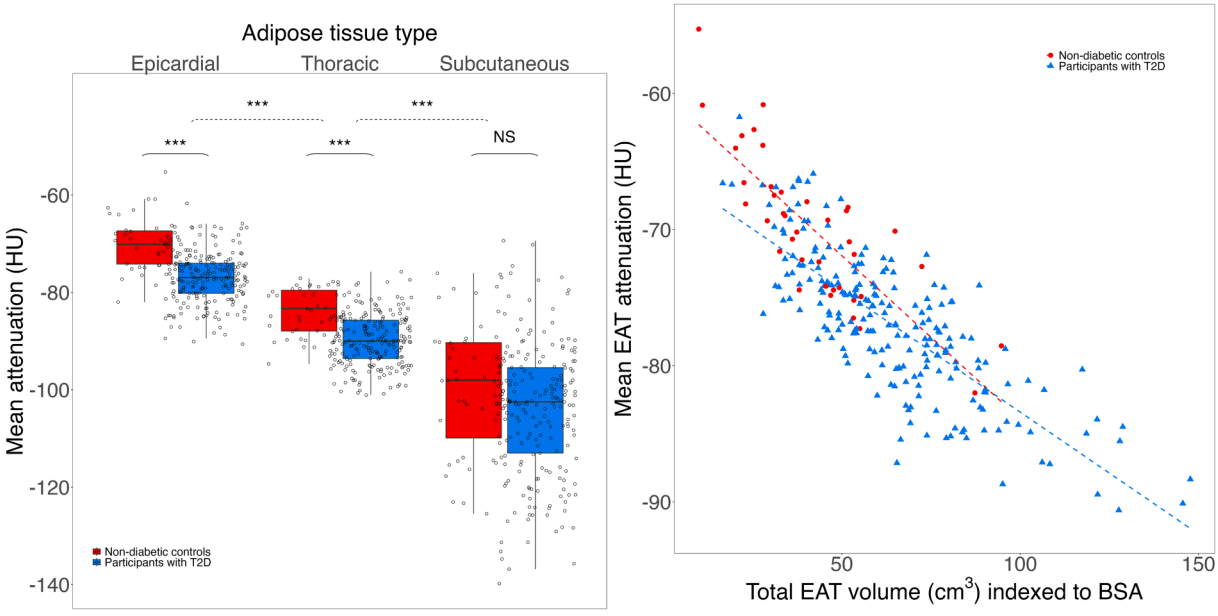

Fig. 3. (A) Computed tomography (CT) attenuation of different visceral adiposity deposits. Boxplots showing the mean x-ray attenuation of different adipose tissues in non-diabetics (red) and type 2 diabetics (blue). (B) Total indexed EAT and mean CT attenuation for all participants. Total epicardial adipose tissue (EAT) volume indexed to body surface area (cm^3/m^2) and mean CT attenuation (Hounsfield units) in non-diabetic (red circle) and type 2 diabetic (blue triangle) participants. The dotted line shows the regression line

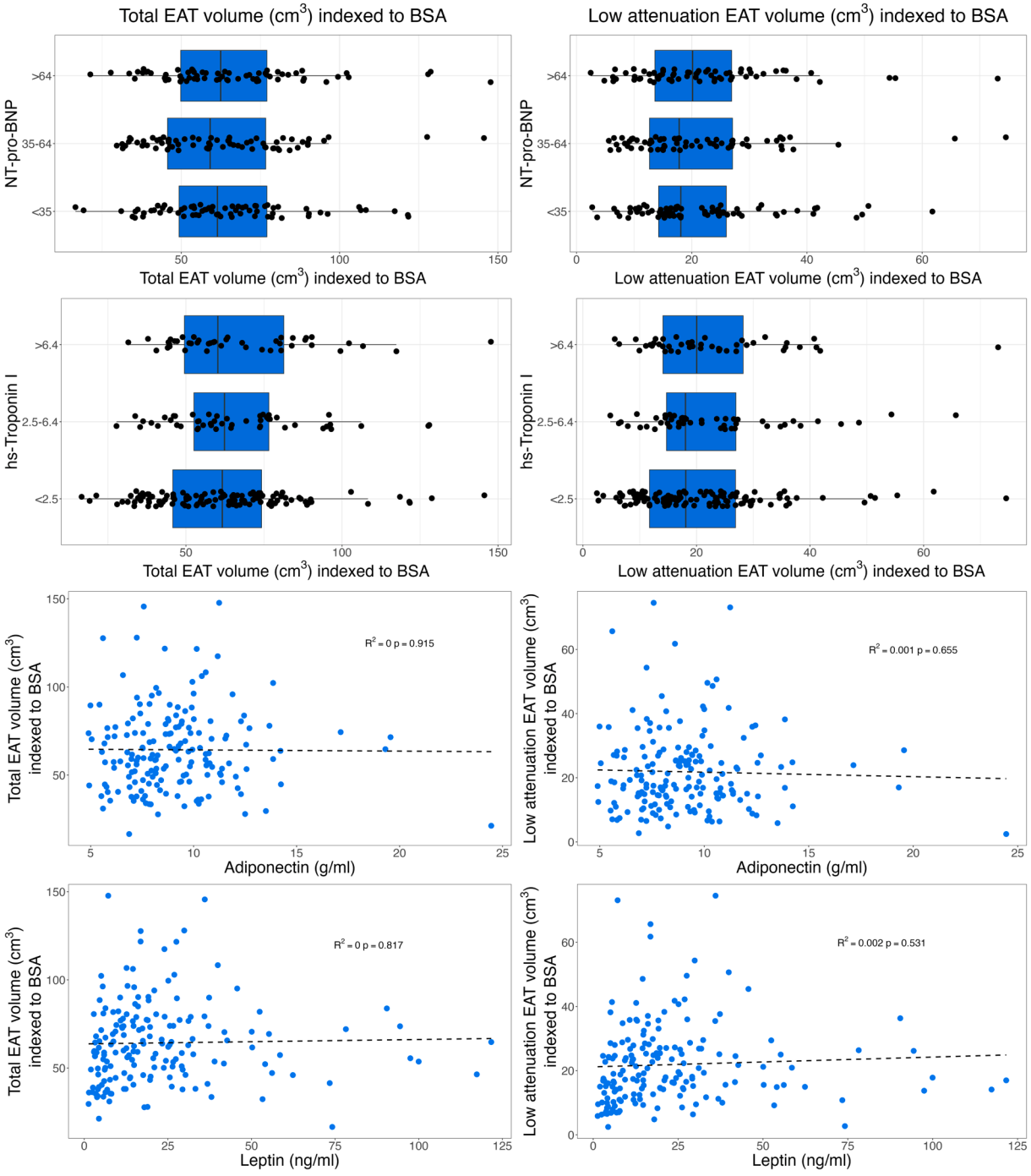

Fig. 4. Indexed epicardial adipose tissue volumes and cardiac biomarkers and adipokines.

of adipocytes.

EAT is a unique visceral adipose tissue deposit bounded by the visceral pericardium. Histological studies have found epicardial adipocytes are 40 % smaller than subcutaneous adipocytes with intrinsically high rates of lipogenesis and lipolysis [22–24]. Under conditions of calorie excess, epicardial adipocytes undergo hyperplasia resulting in an increased number of lipid-laden adipocytes within this tissue [25]. This increase in lipid content can be tracked using CT as a more lipid-laden adipocyte population yields a more negative CT attenuation value [11]. Epicardial adipocytes exposed to chronic metabolic stress produce inflammatory cytokines with downstream upregulation of interleukin-1ß and interleukin-6, [26] which may induce myocardial changes through paracrine and microcirculatory release [5]. Monitoring the composition of epicardial adiposity may be critically important in the measurement of these local inflammatory effects given that plasma concentrations of these interleukins significantly underestimate tissue concentration [26]. Cardiometabolic diseases are risk factors for heart failure with preserved ejection fraction (HFpEF) with a long latent chronic inflammatory phase prior to symptom development, therefore this offers an opportunity for intervention prior to the onset of impaired myocardial mechanics and symptoms.

To date, most studies have measured EAT using echocardiography which is limited to 2-dimensional quantification in a single plane [2,8]. The high isotropic spatial resolution of CT provides a more precise volumetric measurement of EAT around the entire heart and enables quantification of specific densities of adipose tissue. In this study, total

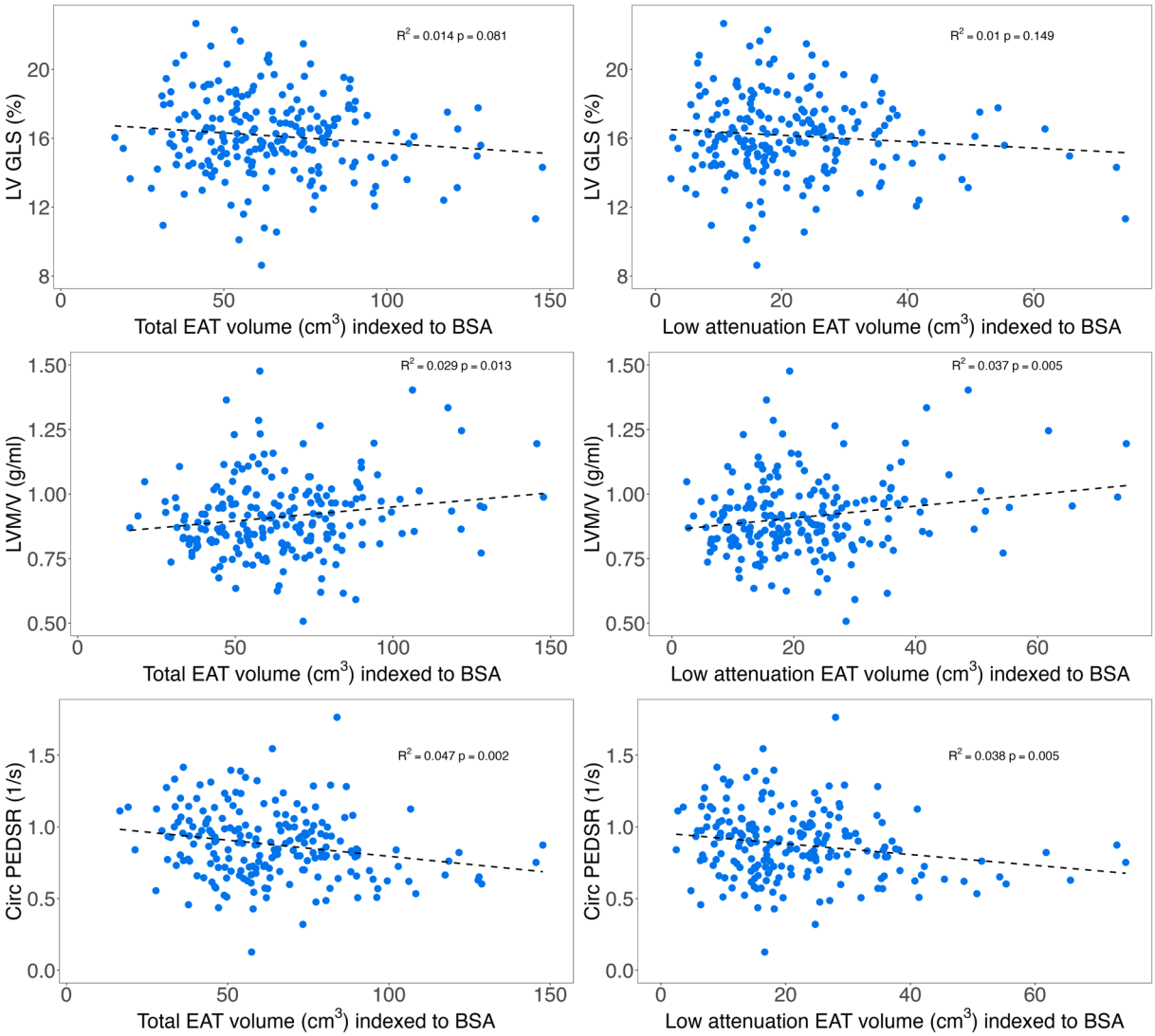

Fig. 5. Univariable association of indexed epicardial adipose tissue (EAT) with left ventricular function.

indexed EAT volume was 1.6-fold higher in T2D compared to non-diabetic controls and the difference was amplified to 2-fold when restricting to low attenuation indexed EAT volume. EAT volume was correlated with CT attenuation, suggesting that when larger EAT deposits are observed the density and composition of the deposit also changes. Previous histological findings have demonstrated that a lower CT attenuation in perivascular EAT correlates with size of adipocytes and secretory profile [11]. Furthermore, the differentiation of brown and white adipose tissue using CT attenuation has been ratified using positron emission tomography [19,27]. We used a cut off of −90HU to distinguish higher and lower attenuation adipose tissue based on the distinction between brown and white adipose tissue [19], but it is important to consider other factors which may influence CT tissue attenuation such as imaging artefacts, namely local structures of higher density, partial volume effects and image interpolation [28]. Kilovoltage of the CT acquisition will also affect CT attenuation, but all CT images were acquired using the same kilovoltage setting (120kVp) in this study. Lower mean CT attenuation is associated with an increased prevalence of metabolic disease, beyond increased adipose tissue volume, meaning that differences in CT attenuation is likely not to be solely due to differences caused by imaging EAT deposits of different volumes [29]. Additionally, it has been shown that adipocyte size differs throughout the epicardial deposit, with smaller adipocytes found closer to coronary arterial walls which correlates with CT attenuation measurements [11]. By combining CT attenuation and volume, we used low attenuation EAT volume to measure this more pathological deposit which was 2-fold higher in T2Ds.

Studies utilising echocardiography to measure EAT thickness in T2D have yielded conflicting results when assessing associations with LV measures [30,31], however these studies are limited by the imaging modality used. Prior work by Levelt et al. found a relationship between insulin resistance, EAT volume measured by CT and myocardial mechanics. In this study of twenty-seven obese and fifteen lean patients with T2D, hyperinsulinemia in obese T2D correlated with ectopic fat accumulation and reductions in LV global peak circumferential strain rate [32]. However, the small sample size did not permit regression analysis with adjustment for important confounders, including body composition and adipokines. In this much larger study, EAT volumes were associated with markers of structural and functional perturbations in myocardial mechanics and these associations persisted after adjusting for these measures. Despite indexing EAT volumes to body surface area and using validated markers of systemic adiposity, such as waist to hip ratio, the association of low attenuation EAT volumes with LV mass to volume ratio and LV GLS remained. These results support a possible local effect of EAT on the myocardium.

The novel finding that low attenuation indexed EAT volume, measured using a validated deep learning method [9,10], is associated with CMR measures of cardiac structure and function is timely and may

provide a mechanism to explain how higher volumes of EAT confer an increased risk of developing symptomatic HFpEF [33] and increased mortality and heart failure hospitalisations in those with established disease [34]. Although, the differences in CMR measures of cardiac structure and function seen in participants with differing amounts of EAT are not clinically significant they may highlight early phenotypic changes which may develop into overt cardiac dysfunction. Identification of people with T2D who have dysregulated EAT may allow for early detection of individuals at risk of developing heart failure providing the opportunity for early intervention. Although it is prudent to highlight the linear regression models had low adjusted R^2 values, suggesting unmeasured variables may have a stronger effect on the measures assessed and therefore the potential to improve cardiac remodelling in T2D by targeting EAT is likely to be extremely limited.

4.1. Strengths and Limitations

This was a moderately large prospectively designed study using gender and ethnicity matched controls, which included detailed phenotyping using multi-modality imaging and CMR measures with excellent test–retest reproducibility [16]. Our cohort includes a high proportion of South Asian individuals who have a lower body mass index and a lower frequency of diastolic dysfunction compared with Caucasian males. Without abdominal subcutaneous or visceral adipose quantification available it is difficult to assess whether EAT volume is acting as a surrogate for overall adipose tissue volume or whether it imposes direct effects on the myocardium. Similar results were, however, seen with thoracic adipose tissue which may reflect systemic adiposity. Although we have demonstrated independent associations, causality cannot be inferred. Long-term follow-up is in progress but, at present, we cannot report outcome measures such as the development of heart failure or cardiovascular death. However, the measures of subclinical cardiac dysfunction used have been shown to be predictive of cardiovascular outcomes [35,36]. Additionally, by design, this study involved individuals without cardiovascular disease and the measures of cardiac function were therefore largely within normal range. Results cannot, therefore, be extrapolated to individuals with symptomatic heart failure.

5. Conclusions

Total and low attenuation indexed EAT volumes are higher in individuals with T2D, and excess EAT accumulation is independently, but weakly, associated with early markers of stage B heart failure.

CRediT authorship contribution statement

Sarah L. Ayton: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Jian L. Yeo:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Gaurav S. Gulsin:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Abhishek Dattani:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Joanna Bilak:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Aparna Deshpande:** Writing – review & editing, Methodology, Investigation. **J. Ranjit Arnold:** Writing – review & editing, Methodology, Investigation. **Anvesha Singh:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Matthew P.M. Graham-Brown:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Leong Ng:** Writing – review & editing, Resources, Methodology, Investigation. **Donald Jones:** Writing – review & editing, Resources, Methodology, Investigation. **Piotr Slomka:** Writing – review & editing, Software, Methodology, Investigation. **Damini Dey:** Writing – review & editing, Software, Methodology, Investigation. **Alastair J. Moss:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Emer M. Brady:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Gerry P. McCann:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Alastair J Moss reports a relationship with AstraZeneca UK Limited that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We acknowledge support from the National Institute for Health Research, Leicester Biomedical Research Centre, Clinical Research Facility and Clinical Research Network.

Acknowledgement of grant support

SLA was supported by a National Institute for Health Research (NIHR), United Kingdom, Academic Clinical Fellowship. JLY, EMB, and GPM received funding from NIHR Research Professorship award (RP-2017-08-ST2-007). AS is supported by an NIHR Advanced Fellowship (NIHR300867) and JRA by an NIHR Clinician Scientist Award (CS-2018-18-ST2-007). The British Heart Foundation, United Kingdom, provides funding support for GSG (FS/16/47/32190) and AJM (AA/18/3/34220). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejrad.2024.111400.

References

[1] J.P. Després, S. Moorjani, P.J. Lupien, A. Tremblay, A. Nadeau, C. Bouchard, Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease, Arteriosclerosis 10 (1990) 497–511.
[2] S.L. Ayton, G.S. Gulsin, G.P. McCann, A.J. Moss, Epicardial adipose tissue in obesity-related cardiac dysfunction, Heart 108 (2022) 339–344.
[3] L. Nasarre, O. Juan-Babot, P. Gastelurrutia, et al., Low density lipoprotein receptor-related protein 1 is upregulated in epicardial fat from type 2 diabetes mellitus patients and correlates with glucose and triglyceride plasma levels, Acta Diabetol. 51 (2014) 23–30.
[4] C. Bambace, A. Sepe, E. Zoico, et al., Inflammatory profile in subcutaneous and epicardial adipose tissue in men with and without diabetes, Heart Vessels 29 (2014) 42–48.
[5] S. Greulich, B. Maxhera, G. Vandenplas, et al., Secretory products from epicardial adipose tissue of patients with type 2 diabetes mellitus induce cardiomyocyte dysfunction, Circulation 126 (2012) 2324–2334.
[6] S.A. Hunt, D.W. Baker, M.H. Chin, et al., ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration With the International Society for Heart and Lung Transplantation; Endorsed by the Heart Failure Society of America, Circulation 104 (2001) 2996–3007.
[7] D.K. Song, Y.S. Hong, H. Lee, J.-Y. Oh, Y.-A. Sung, Y. Kim, Increased epicardial adipose tissue thickness in type 2 diabetes mellitus and obesity, Diabetes Metab. J. 39 (2015) 405–413.
[8] Y. Li, B. Liu, Y. Li, et al., Epicardial fat tissue in patients with diabetes mellitus: a systematic review and meta-analysis, Cardiovasc. Diabetol. 18 (2019) 3.
[9] F. Commandeur, M. Goeller, J. Betancur, et al., Deep learning for quantification of epicardial and thoracic adipose tissue from non-contrast CT, IEEE Trans. Med. Imaging 37 (2018) 1835–1846.
[10] F. Commandeur, M. Goeller, A. Razipour, et al., Fully automated CT quantification of epicardial adipose tissue by deep learning: a multicenter study, Radiol. Artif. Intell. 1 (2019) e190045.
[11] A.S. Antonopoulos, F. Sanna, N. Sabharwal, et al., Detecting human coronary inflammation by imaging perivascular fat, Sci. Transl. Med. 9 (2017) eaal2658.

[12] G. Milanese, M. Silva, L. Bruno, et al., Quantification of epicardial fat with cardiac CT angiography and association with cardiovascular risk factors in symptomatic patients: from the ALTER-BIO (Alternative Cardiovascular Bio-Imaging markers) registry, Diagn. Interv. Radiol. 25 (2019) 35–41.
[13] J.L. Yeo, G.S. Gulsin, E.M. Brady, et al., Association of ambulatory blood pressure with coronary microvascular and cardiac dysfunction in asymptomatic type 2 diabetes, Cardiovasc. Diabetol. 21 (1) (2022) 85.
[14] R.D. Mosteller, Simplified calculation of body-surface area, N. Engl. J. Med. 317 (17) (1987) 1098.
[15] D.R. Matthews, J.P. Hosker, A.S. Rudenski, B.A. Naylor, D.F. Treacher, R.C. Turner, Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man, Diabetologia 28 (1985) 412–419.
[16] M. Graham-Brown, G.S. Gulsin, K. Parke, et al., A comparison of the reproducibility of two cine-derived strain software programmes in disease states, Eur. J. Radiol. 113 (2019) 51–58.
[17] S.L. Ayton, A. Alfuhied, G.S. Gulsin, et al., The interfield strength agreement of left ventricular strain measurements at 1.5 T and 3 T using cardiac MRI feature tracking, J. Magn. Reson. Imaging 57 (4) (2023) 1250–1261.
[18] F.A. Flachskampf, R. Blankstein, P.A. Grayburn, et al., Global longitudinal shortening: a positive step towards reducing confusion surrounding global longitudinal strain, J. Am. Coll. Cardiol. Img. 12 (2019) 1566–1567.
[19] N. Ahmadi, F. Hajsadeghi, M. Conneely, et al., Accurate detection of metabolically active "brown" and "white" adipose tissues with computed tomography, Acad. Radiol. 20 (2013) 1443–1447.
[20] G.S. Gulsin, D.J. Swarbrick, L. Athithan, et al., Effects of low-energy diet or exercise on cardiovascular function in working-age adults with type 2 diabetes: a prospective, randomized, open-label, blinded end point trial, Diabetes Care 43 (2020) 1300–1310.
[21] R Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2022, https://www.R-project.org/.
[22] C. Bambace, M. Telesca, E. Zoico, et al., Adiponectin gene expression and adipocyte diameter: a comparison between epicardial and subcutaneous adipose tissue in men, Cardiovasc. Pathol. 20 (2011) 153.
[23] J.M. Marchington, C.M. Pond, Site-specific properties of pericardial and epicardial adipose tissue: the effects of insulin and high-fat feeding on lipogenesis and the incorporation of fatty acids in vitro, Int. J. Obes. 14 (1990) 1013–1022.
[24] H.M. Aitken-Buck, A.A. Babakr, S. Coffey, P.P. Jones, R.D. Tse, R.R. Lamberts, Epicardial adipocyte size does not correlate with body mass index, Cardiovasc. Pathol. 43 (2019) 107144.
[25] H.M. Aitken-Buck, M. Moharram, A.A. Babakr, et al., Relationship between epicardial adipose tissue thickness and epicardial adipocyte size with increasing body mass index, Adipocyte 8 (2019) 412–420.
[26] T. Mazurek, L. Zhang, A. Zalewski, et al., Human epicardial adipose tissue is a source of inflammatory mediators, Circulation 108 (2003) 2460–2466.
[27] H.H. Hu, S.A. Chung, K.S. Nayak, H.A. Jackson, V. Gilsanz, Differential computed tomographic attenuation of metabolically active and inactive adipose tissues: preliminary findings, J. Comput. Assist. Tomogr. 35 (2011) 65–71.
[28] M.M. Hell, S. Achenbach, A. Schuhbaeck, L. Klinghammer, M.S. May, M. Marwan, CT-based analysis of pericoronary adipose tissue density: relation to cardiovascular risk factors and epicardial adipose tissue volume, J. Cardiovasc. Comput. Tomogr. 10 (2016) 52–60.
[29] K.J. Rosenquist, A. Pedley, J.M. Massaro, et al., Visceral and subcutaneous fat quality and cardiometabolic risk, J. Am. Coll. Cardiol. Img. 6 (2013) 762–771.
[30] X.T. Song, S.K. Wang, P.Y. Zhang, L. Fan, Y.F. Rui, Association between epicardial adipose tissue and left ventricular function in type 2 diabetes mellitus: assessment using two-dimensional speckle tracking echocardiography, J. Diabetes Complications 36 (2022) 108167.
[31] R.H. Christensen, C.S. Hansen, B.J. von Scholten, et al., Epicardial and pericardial adipose tissues are associated with reduced diastolic and systolic function in type 2 diabetes, Diabetes Obes. Metab. 21 (2019) 2006–2011.
[32] E. Levelt, M. Pavlides, R. Banerjee, et al., Ectopic and visceral fat deposition in lean and obese patients with type 2 diabetes, J. Am. Coll. Cardiol. 68 (2016) 53–63.
[33] S. Kenchaiah, J. Ding, J.J. Carr, et al., Pericardial fat and the risk of heart failure, J. Am. Coll. Cardiol. 77 (2021) 2638–2652.
[34] G. van Woerden, D.J. van Veldhuisen, O.C. Manintveld, et al., Epicardial adipose tissue and outcome in heart failure with mid-range and preserved ejection fraction, Circ. Heart Fail. 15 (2022) e009238.
[35] K. Kalam, P. Otahal, T.H. Marwick, Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction, Heart 100 (2014) 1673–1680.
[36] S. Cheng, V.R. Fernandes, D.A. Bluemke, R.L. McClelland, R.A. Kronmal, J.A. Lima, Age-related left ventricular remodeling and associated risk for cardiovascular outcomes, Circ. Cardiovasc. Imaging 2 (2009) 191–198.