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Association of epicardial adipose tissue thickness and cardiac structure and function in early midlife: the cardiovascular risk in Young Finns Study

Behnoush Gustafsson [1,2], Suvi P. Rovio [1,2,3], Saku Ruohonen [1,4], Juha Mykkänen [1,2], Terho Lehtimäki [5,6], Eero Jokinen [7], Päivi Tossavainen [8,9], Tomi P. Laitinen [10], Mika Kähönen [11], Jorma S. Viikari [12,13], Katja Pahkala [1,2,14], and Olli T. Raitakari [1,2,15]

[1]Research Center of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland; [2]Center for Population Health Research, University of Turku and Turku University Hospital, Turku, Finland; [3]Department of Public Health, University of Turku and Turku University Hospital, Turku, Finland; [4]Orion Pharma, Turku, Finland; [5]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; [6]Department of Clinical Chemistry, Fimlab Laboratories, Tampere, Finland; [7]Department of Pediatric Cardiology, Hospital for Children and Adolescents, Helsinki University Hospital and University of Helsinki, Helsinki, Finland; [8]Department of Pediatrics, Research Unit of Clinical Medicine, MRC Oulu, University of Oulu, Oulu, Finland; [9]Department of Children and Adolescents, Oulu University Hospital, Oulu, Finland; [10]Department of Clinical Physiology, University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland; [11]Department of Clinical Physiology, Tampere University Hospital and Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; [12]Department of Medicine, University of Turku, Turku, Finland; [13]Division of Medicine, Turku University Hospital, Turku, Finland; [14]Paavo Nurmi Centre, Unit for Health and Physical Activity, University of Turku, Turku, Finland; and [15]Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland

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Aims Previous studies who have reported associations between higher epicardial adipose tissue (EAT) and alterations in cardiac geometry and function are mainly derived from older adults. In this cross-sectional study, we examined whether these relations are also seen in the young and middle-aged study population of the Cardiovascular Risk in Young Finns Study.

Methods and results Echocardiography was performed ($N = 1667$), and echocardiographic metrics were derived according to European Association of Echocardiography guidelines. EAT thickness was measured from parasternal long-axis echocardiograms at end-systole. Multivariable linear regression analysis was used to study the associations between EAT thickness and echocardiographic metrics. Possible effect modification by sex was analysed. Direct associations were observed between higher EAT and left ventricular (LV) wall thickness parameters [(LV mean (back-transformed $\beta = 0.72\%$, $P = 0.002$), relative (back-transformed $\beta = 0.64\%$, $P = 0.002$) and posterior wall thickness ($\beta = 0.0005$, $P = 0.0002$)] and left atrium (LA) size ($\beta = 0.02$, $P = 0.001$), while an inverse association of higher EAT and decreased mitral annular velocity (e′) (back-transformed $\beta = -1.0\%$, $P = 0.02$) was found after adjustments for age, sex, waist circumference and systolic blood pressure.

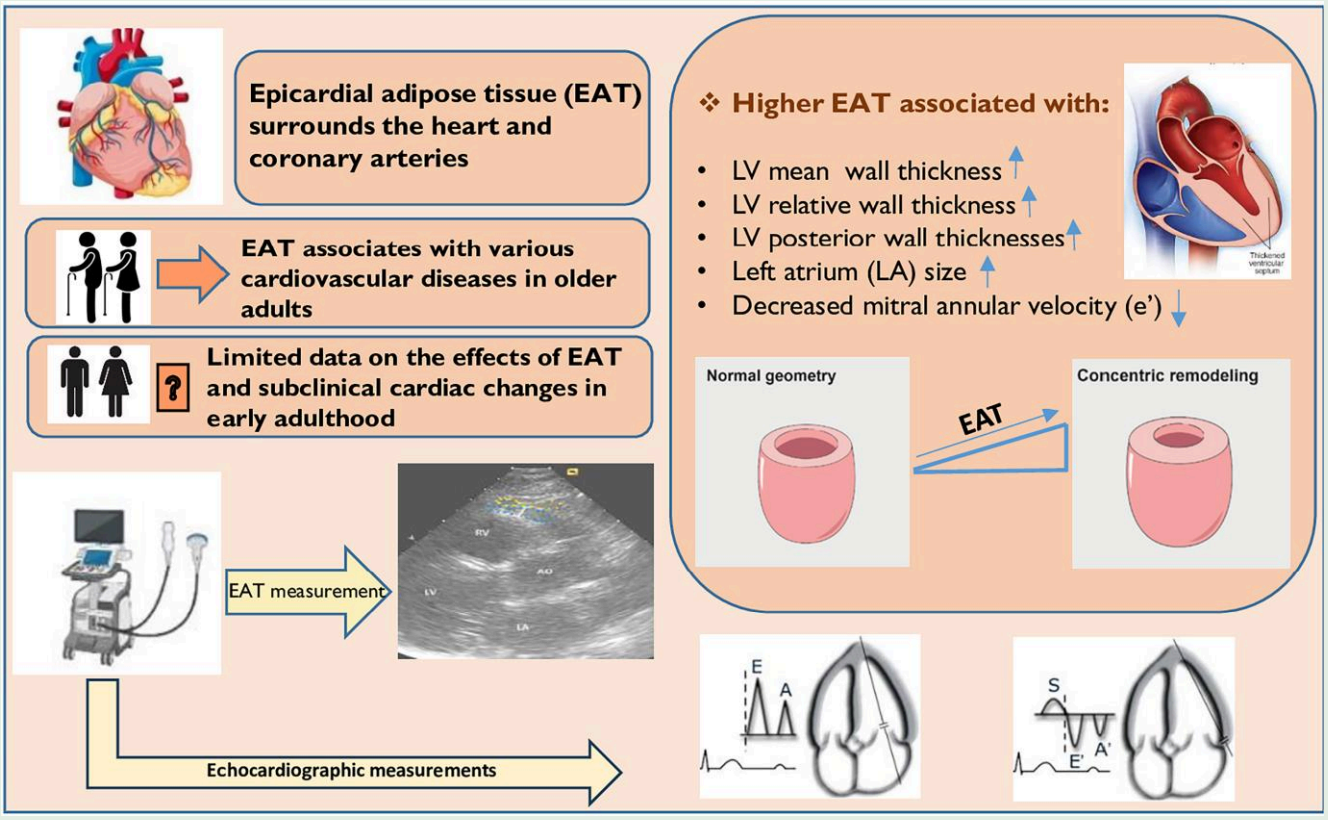
Conclusion Our results suggest associations between EAT thickness, increased LV wall thickness, LA size, and decreased mitral annular velocity in early adulthood. The observed alterations in these specific cardiac metrics are particularly known as early structural alterations linked with obesity-related LV concentric remodelling and relaxation abnormalities. Thus, EAT may contribute in cardiac subclinical remodelling initiating in early adulthood, which may lead to various cardiovascular outcomes later in life. However, due to the modest effect sizes observed, further studies are required to assess the magnitude of these associations over long-term follow-up.

Lay summary In this study, we investigated the associations between epicardial adipose tissue thickness and cardiac structural and functional abnormalities on echocardiography in asymptomatic young and middle-aged adults.

Corresponding author. Tel: +358 29 450 4375, Email: behfor@utu.fi.

- This study results suggest multivariable-adjusted associations of increased epicardial adipose tissue and subclinical echocardiographic abnormalities in early adulthood representative of obesity-related LV remodelling and diminished relaxation properties in clinically asymptomatic young and middle-aged adults.
- Epicardial adipose tissue may contribute in cardiac subclinical abnormalities initiating already in early adulthood, which may further link with various cardiovascular outcomes later in life. Further studies are required to assess the magnitude of these associations over long-term follow-up.

Graphical Abstract



Keywords Epicardial adipose tissue • Echocardiography • Cardiovascular disease • Left ventricular remodelling • Left ventricular hypertrophy • Myocardial relaxation

Background

Epicardial adipose tissue (EAT) is the cardiac visceral fat depot surrounding the heart and coronary vasculature. The role of EAT as an emerging cardiovascular risk factor has been a topic of growing research interest.[1] Due to its proximity to the myocardium without any separating fascia, EAT is proposed to contain paracrine properties locally at the heart and to play a role in the aetiology of various cardiovascular outcomes. In normal condition, EAT contains cardioprotective properties to protect and maintain cardiac homeostasis. However, in obesity and various cardiometabolic disorders, EAT becomes enlarged, which initiates with a deranged adipogenesis process in EAT adipocytes further leading to their hypertrophic, hypoxic and inflammatory state. While obesity *per se* is thought to affect cardiac structure and function in systemic ways, EAT is proposed to act as a metabolic transducer of obesity locally at the heart by exertion of mechanical stress and secretion of proinflammmatory adipocytokines affecting atrial and ventricular structure and function.[2,3] In fact associations of EAT and increased left ventricular (LV) wall thickness, increased left atrium (LA) size and LV hypertrophy as well as increased LV filling pressures and diastolic dysfunction have been previously addressed. Furthermore, significant associations of higher EAT and various cardiovascular outcomes, such as coronary artery disease, diastolic dysfunction and heart failure with preserved ejection fraction have been also addressed.[1,4–6] However, the majority of the currently available data on these relations are mainly derived from older study populations and in presence of various cardiovascular diseases as confounding comorbidities, thus, making it difficult to leverage the independent contribution of this fat depot on the observed cardiac outcomes.[7,8] There is currently limited data available on the associations between increased EAT and potential subclinical alterations in cardiac structure and function in youth and early adulthood. Therefore, in order to minimize the confounding effect

of aging and presence of cardiovascular diseases, it is crucial to study the associations between EAT and potential subclinical alterations in cardiac structure and function earlier in life. This particularly contains high clinical importance in terms of primordial and primary prevention of cardiovascular diseases by introducing EAT as an important clinically accessible imaging biomarker. Furthermore, addressing the links between EAT and adverse alterations in cardiac structure and function at subclinical level in clinically asymptomatic middle-aged adults will provide new avenues to identify individuals at higher risk of obesity-related cardiovascular events earlier in life and to apply preventive dietary, lifestyle and pharmaceutical approaches.[9] To this end, in this observational cross-sectional study we sought to investigate the associations of echocardiographically measured EAT and cardiac structure and function in a population of young and middle-aged clinically asymptomatic adults. We hypothesized that higher EAT thickness is associated with subclinical echocardiographic abnormalities in young and middle-aged adults even when accounting for a wide array of demographic and cardiometabolic risk factors such as age, obesity, systolic blood pressure and other well-established cardiometabolic risk markers.

Materials and methods

Study participants

This study is a part of the ongoing multi-centre longitudinal Cardiovascular Risk in Young Finns Study (YFS), focusing on cardiovascular risk factors from childhood through adulthood.[10] In 1980, a representative sample ($N = 3596$) of Finnish 3–18-year-old children and adolescents participated in the baseline study. Follow-up studies have been conducted in 1983, 1986, 2001, 2007 and 2011. Extensive data on cardiovascular risk factors have been collected and archived from all follow-up studies.[10] In this cross-sectional study, the data from the follow-up year 2011 has been used. (*Figure 1*) From the original cohort, 1937 individuals underwent transthoracic echocardiographic examination in the 2011 follow-up study. Pregnant women ($N = 9$) and individuals with no/low quality echocardiographic images for EAT measurement ($N = 261$) were excluded from this study. In total, 1667 participants (770 men vs. 897 women) provided acceptable echo images and were included. Data on cardiovascular outcomes ($N = 14$) have been obtained from registry data on the year 2011 [myocardial infarction ($N = 5$), angina pectoris ($N = 8$), congestive heart failure ($N = 2$), peripheral vascular disease ($N = 1$), stroke ($N = 1$), A transient ischaemic attack or temporary stroke symptoms (e.g. blurred vision, dizziness, fainting, numbness) ($N = 2$), A blocked carotid artery ($N = 1$)]. YFS study has been approved by ethics committee of Turku University Hospital in accordance with the guidelines and regulations issued by Finnish National Board on Research Integrity and written informed consent has been obtained from all participants.

Echocardiographic measurements of EAT thickness

Trained sonographers performed echocardiographic examination at five research centres using identical Siemens Acuson Sequoia 512 (Acuson Mountain view, CA) ultrasonography mainframes, equipped with 3.5 MHz scanning frequency phased-array transducers. Echocardiograms have been analysed by one observer blinded to clinical details using ComPACS 10.8.7 (Medimatic Solutions, Italy) analysis software. EAT thickness was measured on the year 2014 based on previously introduced and validated protocol by Iacobellis et al.[11] and by manual delineation from parasternal long-axis echocardiograms perpendicularly to the right ventricle at end-systole. Due to the young

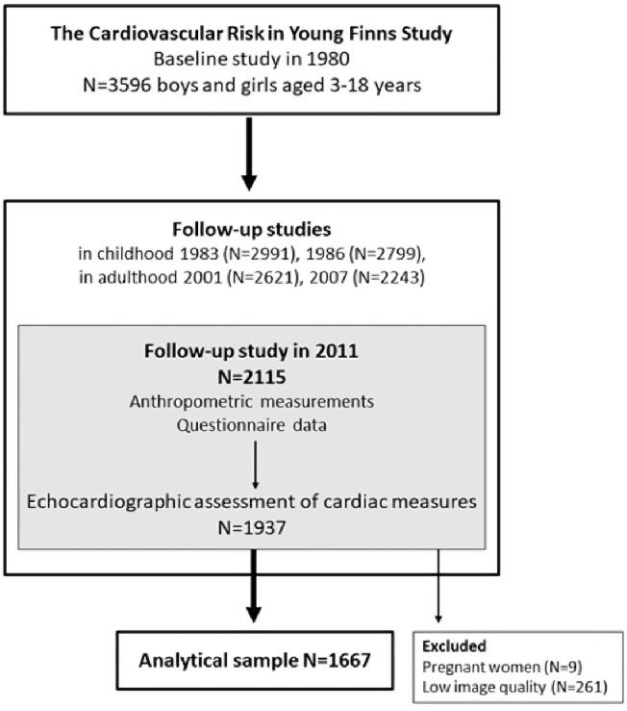


Figure 1 Flow-chart of the study participants.

age of the study population, the EAT layer was relatively narrow and mostly ranged within normal cut-off values. Thus, we prioritized to minimize the plausible measurement error by conducting all image analyses by a single rater. A subsample of 50 randomly selected images were re-measured to assess intra-observer variability of EAT measurements. Intraclass correlation coefficient showed good reproducibility of EAT measurements (0.91, 95% CI: 0.84–0.94). Detailed description of EAT measurement had been published earlier.[12]

Echocardiographic measurements of cardiac structure and function

Echocardiographic measurements of cardiac structural and haemodynamic parameters were derived according to EAS and ESC guidelines.[13] Atrial and ventricular dimensions and chamber quantifications were performed.[14] LA volume was measured from the apical four chamber view by Simpson single plane method. Left atrium volume index was calculated as 'LA volume/body surface area (BSA),' and BSA was calculated according to Du Bois formula (BSA = 0.007184 × weight $(kg)^{0.425}$ × height $(cm)^{0.725}$).[15] Right atrial volume was measured by area-length method. Left ventricle volume was calculated from apical for chamber view using biplane disc summation method.[15] LV mass was calculated as {[(0.8*[1.04 (LV end-diastolic diameter + end-diastolic posterior wall thickness + end-diastolic inter-ventricular septum thickness)**3—LV end-diastolic diameter]**3) + 0.6 g}. Relative wall thickness was calculated as (2 × end-diastolic posterior wall thickness)/LV end- diastolic diameter.[14] LV mean and posterior wall thickness as well as intraventricular septal wall thickness were measured from parasternal long axis images at end-diastole.[13,14] Tissue Doppler (TD) pulsed-wave mitral inflow and pulsed wave lateral/medial mitral annular velocities were derived. From pulsed-wave Doppler mitral inflow measurements, early *trans*-mitral inflow velocity (E) [indicative of the mitral blood flow velocity during LV early (passive) filling phase], late *trans*-mitral inflow velocity (A) [indicative of the mitral blood flow velocity during LV late (active) filling phase at the time of LA contraction] and deceleration time were extracted. From TD mitral annulus velocity measurements, medial and lateral annular peak early (e') (indicative of mitral annular early diastolic velocity) and late (a') (indicative of mitral annular late diastolic velocity) were measured. Previously established ratios of E/A, E/e' were calculated and utilized as the measures of LV filling pressure.[14] E/é-ratio as the echocardiographic representative parameter of LV filling pressure in early diastole was calculated using the mean value of lateral and septal values é velocity. LV ejection fraction as the representative parameter of LV systolic function was calculated as 100 × (LV end-diastolic volume—LV end-systolic volume)/LV end-diastolic volume. LV concentric remodelling (CR) phenotype was assessed by using the population 85th cut-offs values for BSA-indexed LV mass and relative wall thickness.[11] CR is defined as increased relative wall thickness without LV hypertrophy.[14] Heart rate was reported directly from the electrocardiography reading. Detailed methodology of echocardiographic protocol has been described earlier.[14]

Anthropometric measurements, clinical and lifestyle characteristics

BMI was calculated as weight (kg)/height $(m)^2$. Waist circumference was measured at the mid-point between lowest rib and crest ilium. Blood pressure was measured three times in sitting position by random zero sphygmomanometer with a 2-min interval between the measurements. Average of the three measurements was calculated and used in the analysis. Participants were classified as having type 2 diabetes if the fasting serum glucose was ≥ 7.0 mmol/L or if they received oral hypoglycaemic drugs and/or insulin, if they were diagnosed by a physician for type 2 diabetes or diagnosis was confirmed from patient data registry of Social Insurance Institution of Finland.[16] Participants were considered having hypertension if they had systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or they were under antihypertensive medications. Data on cardiovascular outcomes was obtained from national data registries and the Care Register for Health Care and the National Death Index.[17] Data on lipid-lowering ($N = 62$), antihypertensive ($N = 163$) and diabetes medication was self-reported ($N = 22$).

Biochemical analysis

Venous blood samples were drawn after overnight fast and serum was separated, aliquoted, and stored at −70°C. Fasting serum glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides were measured by standard enzymatic methods.[10] Low-density lipoprotein cholesterol (LDL-C) was assessed using the Friedewald's formula.[18] Serum apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), and C-reactive protein (CRP) were analysed using a turbidimetric immunoassay kit.[19] Lp(a) was measured using an immunoturbidimetric method [Lp(a)-HA reagent, Wako Chemicals GmbH, Germany] on an AU400 instrument (Olympus, Japan).[17] Serum insulin concentrations were determined with microparticle immunoassay and glycated haemoglobin A1c (HbA1c) with immunoturbidimetric method.[10] HOMA-IR index was calculated by homeostasis model assessment of insulin resistance; (insulin × fasting glucose)/22.5. Detailed description of the methods has been reported earlier.[10]

Statistical analysis

Study population was divided into EAT quartiles defined based on EAT thickness percentile points (25th percentile 3.0 mm, 50th percentile 3.8 mm, 75th percentile 4.9 mm). Clinical characteristics and anthropometric parameters as well as cardiac structural and haemodynamic echocardiographic metrics are described across EAT quartiles (*Tables 1* and *S2*). Continuous variables are reported as mean and standard deviation, and dichotomous/categorical variables as frequencies and percentages. Age and sex adjusted analysis of variance was performed to compare means of cardiometabolic variables (*Table 1*) and echocardiographic metrics across EAT quartiles, as well as to assess mean EAT differences between normal geometry (NG) and CR phenotype.

To examine the associations of EAT thickness and echocardiographic metrics, multivariable linear regression models were defined with each echocardiographic metric as a dependent variable and EAT as an independent continuous variable. After unadjusted analyses (Model 1), two separate linear multivariable regression analysis models were defined; Model 2 was adjusted for age and sex, while Model 3 was additionally adjusted for waist circumference and systolic blood pressure. For the echocardiographic metrics showing significant associations with EAT in Model 3, further adjustments were done for a plethora of conventional cardiometabolic risk factors with potential confounding role and biologic plausibility including serum lipids and apolipoproteins (total cholesterol, LDL-cholesterol, HDL–cholesterol, triglycerides, apolipoprotein B and apolipoprotein A1), glucose, insulin, HOMA-IR, hypertension, type 2 diabetes, smoking and physical activity by adding each of these confounders one at a time to Model 3.

Normal distribution of the dependent variables was evaluated visually and analyzed using Kolmogorov-Smirnov test. If non-normal distribution was observed, the dependent variables were logarithmically transformed

Table 1 Clinical and anthropometric characteristics of the study population across epicardial adipose tissue quartiles

Variables	Total N = 1667 770 males/ 897 females	1st quartile N = 409 197 males/ 212 females	2nd quartile N = 394 177 males/ 217 females	3rd quartile N = 442 215 males/ 227 females	4th quartile N = 422 181 males/ 241 females	P-value
EAT	4.0 (1.5)	2.4 (0.4)	3.3 (0.2)	4.2 (0.3)	6.1 (1.2)	
Men	3.9 (1.4)	2.4 (0.4)	3.3 (0.2)	4.2 (0.3)	6.0 (1.1)	
Women	4.1 (1.6)	2.4 (0.3)	3.3 (0.2)	4.2 (0.3)	6.3 (1.3)	
Age (yrs)	41.9 (4.98)	41.4 (4.86)	41.6 (5.00)	42.0 (4.97)	42.4 (5.05)	**0.02**
BMI (kg/m^2)	26.4 (5.00)	25.4 (4.57)	25.7 (4.40)	26.7 (4.96)	27.7 (5.62)	**<0.0001**
Waist circumference (cm)	92.3 (14.08)	89.6 (13.79)	90.4 (13.26)	93.3 (13.40)	95.5 (15.03)	**<0.0001**
Total cholesterol (mmol/L)	5.1 (0.94)	5.1 (0.93)	5.1 (0.88)	5.2 (0.97)	5.2 (0.96)	0.48
HDL-cholesterol (mmol/L)	1.3 (0.33)	1.3 (0.37)	1.3 (0.30)	1.3 (0.31)	1.3 (0.34)	0.60
LDL-cholesterol (mmol/L)	3.2 (0.82)	3.2 (0.77)	3.2 (0.78)	3.3 (0.87)	3.2 (0.86)	0.49
Triglycerides (mmol/L)	1.3 (0.89)	1.3 (0.90)	1.2 (0.70)	1.3 (1.04)	1.3 (0.87)	**0.004**
ApoA1 (g/L)	1.5 (0.23)	1.5 (0.25)	1.5 (0.22)	1.5 (0.22)	1.6 (0.24)	0.63
ApoB (g/L)	1.0 (0.28)	1.0 (0.27)	1.0 (0.27)	1.0 (0.29)	1.0 (0.28)	0.14
Lp(a) (mg/L)	149.0 (166.5)	146.0 (155.1)	151.5 (173.8)	140.9 (159.7)	158.3 (177.2)	0.57
Glucose (mmol/L)	5.3 (0.81)	5.2 (0.56)	5.3 (1.07)	5.3 (0.69)	5.4 (0.84)	**0.02**
Insulin (mU/L)	9.7 (12.7)	8.7 (9.06)	9.9 (18.24)	10.0 (12.93)	10.2 (8.73)	**0.004**
HOMA-IR	2.4 (4.12)	2.1 (3.35)	2.4 (5.49)	2.6 (4.42)	2.6 (2.78)	**0.001**
HbA1c (mmol/mol)	36.6 (5.16)	36.2 (3.66)	36.7 (6.11)	36.6 (5.03)	37.0 (5.57)	0.32
CRP (mg/L)	1.6 (2.62)	1.2 (1.84)	1.4 (2.24)	1.5 (2.64)	2.2 (3.36)	**<0.0001**
Systolic BP (mmHg)	118.4 (13.87)	116.8 (13.96)	117.1 (13.20)	119.0 (13.91)	120.5 (14.07)	**<0.0001**
Diastolic BP (mmHg)	74.6 (10.41)	73.7 (11.08)	74.1 (9.81)	75.0 (10.13)	75.6 (10.49)	**0.02**
Type 2 diabetes (%, N)	3.9 (65)	0.4 (7)	0.6 (11)	1.0 (18)	1.7 (29)	**0.0009**
Hypertension (%, N)	18.7 (311)	4.1 (69)	3.6 (61)	5.3 (89)	5.5 (92)	0.16
Medications (%, N)						
Lipid lowering	3.9 (62)	1.0 (17)	0.5 (9)	0.8 (14)	1.4 (22)	0.11
Hypertension	10.3 (163)	2.1 (33)	1.7 (27)	2.9 (46)	3.6 (57)	**0.02**
Diabetes	1.4 (22)	0.1 (2)	0.2 (4)	0.2 (4)	0.7 (12)	**0.03**
Smoking (%, N)	15.1 (238)	3.3 (52)	3.3 (53)	4.0 (64)	4.3 (69)	0.32
PAI (range: 5–15)	9.0 (1.87)	9.1 (1.75)	9.0 (1.92)	9.0 (1.92)	8.8 (1.8)	0.06
Alcohol intake (drinks/day)	0.8 (1.22)	0.7 (1.05)	0.8 (1.15)	0.8 (1.21)	0.9 (1.42)	0.40

For continuous variables values depict mean and standard deviation of the mean (SD) and for categorical variables number (*N*) and percentage (%). *P*-values are derived from age and sex adjusted analysis of variance of the means across EAT quartiles separately for each variable and marked as bold where significant.
ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; BMI, Body mass index; BP, blood pressure; CRP, C-reactive protein; HbA1c, glycated haemoglobin A1c; HDL, High-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, Low-density lipoprotein; Lp(a), lipoprotein (a); PAI, physical activity index.

for the multivariable regression analysis. For the logarithmically transformed variables, back-transformation of β estimates to the original scale was conducted to ease interpretation. After the back-transformation, the estimates were interpreted as the percentage change in echocardiographic variables per one unit of increase in EAT. To study for possible effect modification caused by sex, we entered a multiplicative interaction term (sex × EAT) in the multivariable models and significance level was set as 0.05. Furthermore, the parameters showing significant associations with EAT in Model 3, were divided into EAT deciles to seek for possible EAT cut-offs as well as to observe possible non-linear associations between EAT and echocardiographic metrics. To account for multiple comparisons, multiple testing correction was further conducted using Benjamin-Hochberg approach and the formal control of false discovery rate was set to the acceptable level of 0.05.

Sensitivity analyses excluding the participants ($N = 45$) with cardiovascular outcomes (coronary artery disease, peripheral artery disease and atherosclerotic cerebrovascular disease) showed virtually similar results. Therefore, the main analyses were conducted including these participants. SAS 9.4 software version was used for all statistical analysis and all available data were used. The level of statistical significance was set as $P < 0.05$.

Results

Clinical characteristics and anthropometric measurements

Clinical characteristics of the study population across the EAT quartiles are shown in *Table 1*. Of the total population ($N = 1667$), 53.8% were female. Mean age was 41.9 years in total population and did not differ significantly between men and women (41.9 ± 5.0 vs. 42.0 ± 5.0, $P = 0.69$). Mean EAT thickness was 4.07 ± 1.5 mm in total population

Table 2 Multivariable-adjusted associations between epicardial adipose tissue thickness and echocardiographic metric

N = 1667	1st quartile *N* = 409	2nd quartile *N* = 394	3rd quartile *N* = 442	4th quartile *N* = 422	Beta	*P*
Right Heart						
EAT (mm)	2.4 (0.4)	3.3 (0.2)	4.2 (0.3)	6.1 (1.2)		
Heart rate (b.p.m.)	61.5 (9.4)	61.7 (9.5)	61.9 (10.1)	63.4 (10.2)	0.05	0.74
RA area (d) (cm^2)[b]	10.5 (2.7)	10.9 (2.9)	11.0 (2.7)	11.0 (2.8)	0.65%	0.08
RA volume (d) (ml)[b]	26.7 (10.4)	28.4 (12.2)	28.2 (11.1)	28.0 (11.4)	0.71%	0.22
RV area (d) (cm^2)[b]	18.8 (4.1)	18.9 (4.4)	19.2 (4.3)	18.8 (4.0)	0.03%	0.90
RV area (s) (cm^2)[b]	10.5 (2.5)	10.6 (2.7)	10.8 (2.6)	10.8 (2.4)	**0.68%**	**0.03**
Left heart						
LA diameter (cm)	3.7 (0.5)	3.7 (0.4)	3.8 (0.4)	3.9 (0.4)	**0.02**	**0.001**
LA area (d) (cm^2)	8.9 (2.5)	9.4 (2.8)	9.9 (2.7)	9.6 (2.9)	**0.08**	**0.04**[a]
LA volume index (mL/m^2)	21.9 (6.1)	22.4 (6.3)	23.1 (6.4)	22.6 (6.4)	0.10	0.31
LV area (d) (cm^2)	36.9 (5.8)	37.0 (6.0)	37.8 (5.8)	37.2 (5.5)	0.02	0.78
LV area (s) (cm^2)	21.1 (3.8)	21.3 (3.9)	21.7 (3.7)	21.3 (3.4)	0.00	0.90
LV end-diastolic volume (mL/m^2)	67.7 (12.1)	68.6 (13.7)	69.3 (12.9)	67.4 (12.3)	0.19	0.32
LV end-systolic volume (mL/m^2)	28.3 (5.9)	28.7 (6.4)	29.1 (6.1)	28.0 (5.7)	0.05	0.58[a]
LV mass (g)[b]	133.1 (36.4)	132.1 (35.0)	138.0 (36.3)	136.1 (34.2)	0.14%	0.63
LV mass index (g/m^2)[b]	69.7 (14.3)	69.6 (14.4)	71.0 (14.2)	69.8 (13.2)	0.11%	0.69
LV mean wall thickness (cm)[b]	0.72 (0.10)	0.73 (0.0)	0.75 (0.1)	0.75 (0.1)	**0.72%**	**0.0002**
Relative wall thickness (cm)[b]	0.27 (0.0)	0.28 (0.0)	0.28 (0.0)	0.28 (0.0)	**0.64%**	**0.002**
IVS thickness (d) (cm)	0.69 (0.1)	0.70 (0.0)	0.71 (0.1)	0.71 (0.0)	**0.45**	**0.03**
LV posterior wall thickness (d) (cm)	0.69 (0.1)	0.70 (0.0)	0.71 (0.0)	0.72 (0.0)	**0.005**	**0.0002**

Numbers depict variables' mean values and standard deviation (SD) across EAT quartiles. P: Depicts *P*-value for multivariable regression analysis final model (Model 3) (age, sex, waist circumference, and systolic blood pressure adjusted multivariable linear regression model with each echocardiographic metric as dependent variable and EAT as independent variable). Significant *P*-values are marked as bold. Beta: indicates the change in echocardiographic metrics (dependent variables) per one unit of increase in EAT thickness (mm) for normally distributed variables. For non-normally distributed dependent variables (marked with star) logarithmic transformation was performed and the beta estimate were back-transformed. After back transformation, beta estimates depict percentage change in echocardiographic metric (dependent variables) per one unit increase in EAT thickness (mm).
d, diastole; IVS, interventricular septum; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; s, systole.
[a]significant sex interaction.
[b]Logarithmically transformed variables.

and 3.9 ± 1.4 mm in men vs. 4.1 ± 1.6 mm in women respectively. (*Table 1*) Significant increase across EAT quartiles was observed for age, BMI, waist circumference, triglycerides, glucose, insulin, HOMA-IR, CRP, systolic and diastolic blood pressure levels as well as type 2 diabetes prevalence (*Table 1*).

Cardiac structural and functional echocardiographic parameters

Descriptive mean values of each echocardiographic metric across EAT quartiles are shown in *Table 2*. Covariate-adjusted ANOVA (adjusted for age, sex and waist circumference) showed significant increase across EAT quartiles for LA area, LV mean, relative and posterior wall thickness measures while TD mitral annular early velocity lateral e′ was significantly lower with increasing amount of EAT thickness (see Supplementary material online, *Tables S4* and *S5*). Baseline characteristics were compared between LV CR and NG groups. Statistically significant differences of the variables' means between these two groups were observed for triglyceride levels and indicative parameters of glycemic profile (glucose, insulin, HOMA-IR, HbA1c). (see Supplementary material online, *Table S6*). Higher EAT thickness was observed in participants with CR compared with those with normal cardiac geometry ($P < 0.05$). However, when the analysis was performed sex-specifically the statistical significance diluted. (*Figure 2*).

Multivariable linear regression analysis

Initially, unadjusted (Model 1) and age and sex-adjusted (Model 2) linear regression analyses were conducted and significant associations of EAT with structural/volume metrics (RA, RV areas, LA size and area, LV mass and all indicative parameters of wall thickness) and with TD metrics (late mitral inflow velocity A, E/A and E/e′ ratios, mitral annular early velocities lateral e′ and mean e′, late velocity a′ medial as well as cardiac output) were observed ($P < 0.05$). (See Supplementary material online, *Table S1*, Models 1 and 2). After additional adjustments for waist circumference and systolic blood pressure in the final multivariable model (Model 3), the direct significant associations between EAT and RV area (back-transformed $\beta = 0.68\%$, $P = 0.02$), LA size ($\beta = 0.02$, $P = 0.001$), LV mean (back-transformed $\beta = 0.72\%$, $P = 0.002$), posterior ($\beta = 0.0005$, $P = 0.0002$) and relative wall thicknesses (back-transformed $\beta = 0.64\%$, $P = 0.002$) persisted (*Table 2*). Among TD parameters after additional adjustments for waist circumference and systolic blood pressure in final multivariable model (Model 3), the direct associations of late medial mitral annular velocity a′ ($\beta = 0.07$, $P = 0.02$) and inverse associations of EAT with mitral annular early lateral velocity index e′ (back-transformed $\beta = -1.0\%$, $P = 0.02$) persisted (*Table 3*), while all the other initially observed associations in Models 1 and 2 were diluted.

Multiplicative interaction analysis was conducted to seek for potential effect modifications by sex in final multivariable regression model (Model 3). Statistically significant sex interaction ($P < 0.05$) was

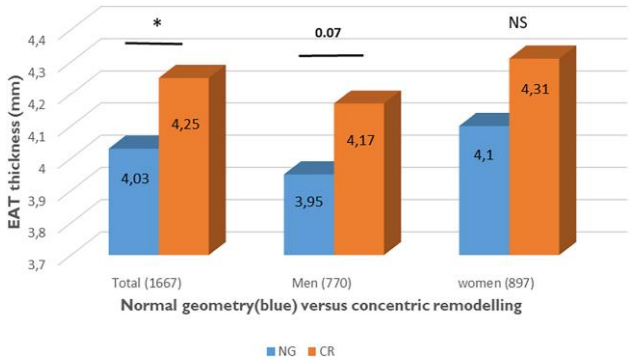


Figure 2 Comparison of mean epicardial adipose tissue between left ventricular normal geometry and concentric remodelling group.

Table 3 Associations between epicardial adipose tissue thickness and tissue Doppler metrics

Tissue Doppler parameters						
***N* = 1667**	**1st quartile *N* = 409**	**2nd quartile *N* = 394**	**3rd quartile *N* = 442**	**4th quartile *N* = 422**	**Beta**	***P***
Mitral inflow E (cm/s)	77.1 (13.3)	76.5 (12.5)	75.6 (12.9)	77.0 (12.0)	0.02	0.91
Mitral inflow A (cm/s)[a]	50.2 (11.5)	51.6 (11.3)	50.9 (11.9)	53.0 (11.3)	0.08%	0.79
E/A[a]	1.59 (0.4)	1.53 (0.3)	1.55 (0.4)	1.50 (0.3)	0.00%	0.96
E/e[a]	4.68 (0.9)	4.76 (1.0)	4.74 (0.9)	4.88 (1.0)	0.37%	0.25
e′ Medial (cm/s)	14.5 (2.6)	14.5 (2.5)	14.3 (2.4)	14.4 (2.4)	0.05	0.13
e′ Lateral (cm/s)[a]	19.0 (3.7)	18.4 (3.5)	18.1 (3.6)	17.8 (3.5)	**−1.0%**	**0.02**
e′ mean (cm/s)	26.3 (4.7)	25.6 (4.4)	25.3 (4.4)	25.0 (4.3)	−0.10	0.11
a′ Medial (cm/s)	12.9 (2.1)	13.0 (2.1)	13.1 (2.2)	13.4 (2.2)	**0.07**	**0.02**
a′ Lateral (cm/s)[a]	14.5 (2.9)	14.4 (3.1)	14.4 (3.1)	14.8 (3.4)	−1.0%	0.46
Cardiac output (l/min)[a]	4.6 (1.2)	4.6 (1.2)	4.7 (1.2)	4.8 (1.3)	0.45%	0.21
Ejection fraction (%)	58.2 (3.5)	58.1 (3.2)	58.0 (3.5)	58.4 (3.4)	0.03	0.57
Deceleration time (m/s)	214.9 (39.2)	221.3 (39.2)	215.7 (35.9)	216.2 (37.7)	1.13	0.07
Stroke volume (mL)	75.1 (17.9)	75.5 (18.8)	78.1 (19.0)	76.5 (17.9)	0.29	0.22

Numbers depict variables' mean values and standard deviation (SD) across EAT quartiles. E, mitral inflow early filling velocity; A, Mitral inflow late filling velocity; e′, longitudinal velocity of the mitral annulus during early diastole; a′, longitudinal velocity of the mitral annulus during late diastole (atrial contraction). P: Depicts *P*-value for multivariable regression analysis Model 3 (age, sex, waist circumference, and systolic blood pressure adjusted multivariable linear regression model with each echocardiographic metric as dependent variable and EAT as independent variable). Significant *P*-values are marked as bold. Beta: indicates the change in echocardiographic metrics (dependent variables) per one unit of increase in EAT thickness (mm) for normally distributed variables. For non-normally distributed dependent variables (marked with star) logarithmic transformation was performed and the beta estimate were back-transformed. After back transformation, beta estimates depict percentage change in echocardiographic metric (dependent variables) per one unit increase in EAT thickness (mm).
[a]Logarithmically transformed variables.

observed only for LA area and LV end-systolic volume. For these two echocardiographic parameters multivariable regression analysis was performed sex-specifically and significant association was observed between LA area and EAT thickness only in men ($\beta = 0.20$, $P = 0.005$) (see Supplementary material online, *Table S3*). For other echocardiographic metrics, we performed linear regression analysis sexes combined.

For the cardiac metrics, which remained significantly associated with EAT in the fully adjusted multivariable model (Model 3), additional adjustments were conducted for a wide array of cardiometabolic factors which could plausibly confound the observed associations. These factors included serum lipids and apolipoproteins (total cholesterol, LDL-cholesterol, HDL–cholesterol, triglycerides, apolipoprotein B and apolipoprotein A1), glucose, insulin, HOMA-IR, hypertension, type 2 diabetes, smoking. In the additionally adjusted models, each of these confounders was added one at a time to the final multivariable model (Model 4, data not shown). The previously observed significant associations of EAT and the echocardiographic metrics (Model 3) persisted even after the additional adjustment for these cardiometabolic confounding factors (data not shown). Multiple testing corrections was further conducted to adjust for multiple comparisons using Benjamini-Hochberg procedure and we set the acceptable false discovery rate at the level of 0.05. Importantly, we observed that all our results that were originally statistically significant survived this testing for multiple comparisons.

To check for possible differences in the observed outcomes, we performed sensitivity analysis for final multivariable model (Model 3) by replacing waist circumference with BMI and weight/height ratio as covariates in the final multivariable regression model. We observed that the results remained unchanged, therefore, waist circumference was used as main adiposity covariate in Model 3. (see Supplementary

material online, *Table S7*) Ultimately, we further conducted sensitivity analysis excluding participants with diagnosed cardiovascular events. Sensitivity analysis showed virtually similar results, and therefore, these participants remained included in the main analysis.

The parameters showing significant associations with EAT in the final multivariable model (Model 3), were further divided into EAT thickness deciles to seek for possible threshold values as well as to check for possible presence of non-linear associations existing between EAT thickness and each of the parameters. Non-linear associations were not observed for any of these variables (see Supplementary material online, *Figures S1–S6*).

Discussion

In this study, we addressed the associations of EAT thickness and cardiac echocardiographic metrics in a cohort of clinically asymptomatic young and middle-aged adults. To our knowledge, this study is amongst the very few studies focusing on these associations in early adulthood. Our findings showed that higher EAT thickness may associate independently with unfavourable alteration in cardiac geometry (increased LV wall thickness and left atrial size) as well as decrease in mitral annular lateral wall velocity in early midlife. Of note, these associations persisted after adjustments for a wide array of potential confounders. However, due to the modest effect sizes observed at this age group, further studies are required to assess the magnitude of these associations over long-term follow-up.

Obesity *per se* is a well-known risk factor for cardiovascular diseases and is associated with cardiac subclinical remodelling patterns such as increased LV mass, LV hypertrophy as well as subclinical systolic and diastolic dysfunction.[9,20–23] Notably, visceral rather than subcutaneous adiposity is known to play more deleterious role in regulating metabolic derangements attributable to cardiovascular outcomes in prolonged obesity.[24–28] EAT as the cardiac visceral fat depot and a strong correlate of abdominal obesity has also been proposed to influence cardiac function and metabolism locally via exertion of mechanical stress on myocardial wall as well as containing paracrine and proinflammatory properties.[1,9,29] Albeit, considering the small size of the EAT depot, its potential contribution to adverse alterations in systemic metabolism in obesity remains questionable. In contrary, the local effects of EAT on myocardial mechanotransduction and energy metabolism in obesity have been widely reported.[30–34] Increased EAT reportedly associates with LV mass and wall thickness as well as LV CR and hypertrophy independent of age and obesity measures.[35–37] These findings are in agreement with our findings showing higher EAT thickness in CR phenotype and addressing (multivariable-adjusted) associations of higher EAT thickness with increased LV wall thickness parameters in young adulthood and early midlife.[6,38]

While it is not currently well-understood if the changes in obesity-related CR lead to an increase in EAT or vice versa, it is well-established that higher EAT is associated with CR and impaired myocardial relaxation, even in the absence of overt LV hypertrophy.[3] Several mechanistic pathways have been suggested on how EAT may affect myocardium. Secretion of free fatty acids from hypertrophied EAT adipocytes into the myocardium due to proximity of this fat depot with myocardium, may lead to increased myocardial triglyceride content, myocardial lipotoxic, steatotic and fibrotic state. This can further lead to increased heart weight and increased mechanical pumping strain, leading to LV remodelling increased LV mass, wall thickness and hypertrophic alteration in LV structure.[3,6,39]

Our findings further demonstrated that increased EAT thickness was directly associated with a larger LA size. Conversely, greater EAT thickness was inversely associated with the mitral annular velocity, an echocardiographic indicative measure of myocardial relaxation. These associations remained significant even after adjusting for potential cardiometabolic confounders, including age, sex, systolic blood pressure, and waist circumference. These findings are in line with previous studies addressing similar associations and support the notion that EAT may contribute to unfavourable alteration in cardiac structure and function already initiating from early adulthood.[1,5,40] The observed unfavourable alterations in these specific echocardiographic metrics (i.e. increased LV wall thickness and LA size and decreased TD mitral wall velocity) are particularly known as early stage structural changes linked with obesity-related conditions of LV pressure overload, LV remodelling, concentric hypertrophy and relaxation abnormalities, which also reflect the cardiac morphologic changes observed in subclinical diastolic dysfunction.[41] Accordingly, associations between increased EAT and subclinical diastolic dysfunction have also been previously addressed.[6,40,42–44] In addition, some studies have also suggested more pronounced associations of EAT accumulation and adverse markers of diastolic dysfunction in women rather than men.[45] In this study, although women had higher EAT than men, effect modification by sex was not observed in relation to the associations between EAT thickness and representative echocardiographic parameters of diastolic function. This may be at least partly explained by the young age of our study population. Considering the principal role of female hormonal regulation and menopausal state on increased visceral adiposity in women, it may be postulated that the previously addressed observations on the associations of higher EAT thickness and adverse alteration in diastolic function in women may be predominantly more identifiable after menopausal state, thus, assumably after middle-age.

Nevertheless, we did not find any associations between higher EAT and LV filling pressure indices. Diastolic dysfunction is a progressive disorder with initial echocardiographic manifestations of impairment in LV relaxation and increased myocardial stiffness while reduced LV filling pressure represents its latter clinical manifestation.[40] Hence, our results addressing associations between EAT and reduced myocardial relaxation properties but not with LV filling pressures in early adulthood are in line with echocardiographic manifestations of very early stage subclinical diastolic dysfunction. This probably reflects high cardiac adaptation properties in these young and middle-aged adults.

Two main pathways have been proposed to explain the links between increased EAT and cardiac structural and functional changes. The first pathway suggests exertion of mechanical stress on myocardial wall in increased EAT, thus influencing its contractile function and haemodynamic properties.[30] The second pathway proposes pathophysiologic adverse effects of enlarged dysfunctional EAT via secretion of free fatty acids and proinflammatory adipocytokines locally to the neighbouring cardiomyocytes.[37,36] Increased secretion of free fatty acid and inflammatory cytokines by enlarged dysfunctional EAT adipocytes may proposedly lead to intracellular myocardial fat accumulation, its lipotoxic, steatotic and ultimately fibrotic state subsequently resulting in diminished contractile and relaxation properties of the myocardium.[9,30,46,47] Increased LV mass and wall thickness in such condition are proposed as subclinical myocardial compensatory mechanism in youth and early adulthood in order to facilitate and maintain contractile function.[22] Nevertheless, such condition when prolonged is commonly accompanied by decrease in LV compliance and increase in LV end-diastolic pressure, leading to subsequent increase in LA pressure, which is not well-tolerated by thin atrial wall, thus, resulting in LA dilatation.[5,43]

Taken together, our results are in agreement with previous findings obtained from older study populations. Our results, particularly as they are derived from a much younger study population in which the plausible confounding role of aging is minimized, may highlight the notion that higher EAT thickness might contribute to subclinical alterations in cardiac structure and function. However, since the observed associations are modest and weak they may not address any associations of EAT with cardiac pathophysiologic abnormality at this age-point but they rather highlight the associations of EAT with the onset of cardiac structural changes in early adulthood Of note, as all studies also our study has some limitations. The study population consists of white Finnish individuals predominantly of Caucasian ethnic background, which might limit the generalizability of our findings to other populations with more diverse ethnic background. Therefore, acquiring data on the observed associations from cohorts of young and middle-aged study populations with more diverse ethnical background is crucial. Secondly, due to the cross-sectional study design, we cannot address causality of the observed associations. Third, different study populations and varying EAT measurement methods make the comparisons between our and prior results challenging. Finally, the echocardiographic measurement of EAT, which is mainly based on one single parameter measured from parasternal long axis view may also contain some level of uncertainty due to the user-dependence property of this imaging method linked, e.g. to the user's proficiency and experience.[9] Furthermore, EAT measurement via echocardiography does not provide information on EAT volume, which is a major constraint of this technique. However, since echocardiographic measurements are easily accessible in large cohorts, they still offer valuable data.[9] The strength of our study is the large population-based cohort of young and middle-aged adults including both sexes, which minimizes the possible confounding due to aging related cardiometabolic complications. To conclude, our results suggest that high EAT thickness is associated with subclinical structural and functional cardiac changes even in young adulthood and early midlife.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contributions

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Conflict of interest: none declared.

Data availability

Due to local legal restrictions, data sharing outside the study group requires a data-sharing agreement. Investigators can submit an expression of interest to the YFS Steering Group/Data Sharing Committee (olli.raitakari@utu.fi).

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