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Factors Associated with Left Atrial Remodeling in the General Population

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Abstract

Background—While contributors to remodeling of the left ventricle (LV) have been well studied in general population cohorts, few data are available describing factors influencing changes in left atrial (LA) structure.

Methods and Results—Maximum LA volume was determined by cardiac magnetic resonance imaging (cMRI) among 748 participants in the Dallas Heart Study at two visits a mean of 8 years apart. Associations of changes in LA volume (LAV) with traditional risk factors, biomarkers, LV geometry and remodeling by cMRI, and detailed measurements of global and regional adiposity (by MRI and Dual-energy x-ray absorptiometry [DEXA]) were assessed using multivariable linear regression. Greater LAV was independently associated with Black and Hispanic Race/Ethnicity, systolic blood pressure, LV mass and LV mass, NT-proBNP and NT-proBNP and BMI ($p < 0.05$ for each). In subanalyses, the associations of LAV with LV mass parameters were driven by associations with baseline and LV end diastolic volume ($p < 0.0001$ for each) and not wall thickness ($p = 0.21$). Associations of LAV with BMI were explained exclusively by associations with visceral fat mass ($p = 0.002$), with no association seen between LAV and subcutaneous abdominal fat ($p = 0.47$) or lower body fat ($p = 0.30$).

Conclusions—Left atrial dilatation in the population is more common in Black and Hispanic than white individuals, and is associated with parallel changes in the left ventricle. LA dilatation may be mediated by blood pressure control and the development of visceral adiposity.

Keywords

left atrium; left atrial volume index; remodeling; magnetic resonance imaging; obesity

While the contributions of left ventricular (LV) size and function to cardiovascular disease in the general population are firmly established,^{1–4} much less is known about the role of the

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left atrium (LA). Recent studies suggest that variability in LA size and function may be associated with adverse cardiovascular outcomes in the general population including atrial fibrillation, stroke, and cardiovascular and all-cause mortality^{5–9}. A number of cross sectional studies have identified factors associated with variation in left atrial size, finding that older age, hypertension, LV dilation and measures of obesity associate with larger LA volume.^{7, 10–12}

Beyond static measurements of LA size at a single time-point, changes in LA size over time (LA remodeling) may be important contributors to cardiovascular disease. Previous studies of left atrial remodeling have been limited by the use of selective cohorts of diseased subjects, where imaging was performed for clinical indications.¹³ In patients with heart failure, differential change in left atrial size and function has been explained by traditional cardiovascular risk factors such as diabetes, chronic kidney disease, smoking, and alcohol consumption.¹⁴ In the general population, there are few data evaluating changes in left atrial size and function, and the limited data available have been generated from studies with small sample size and poor ethnic minority representation.¹⁵ Therefore, in a large, multiethnic, general population study, we sought to determine factors that may influence change in left atrial size over a specified follow-up period.

Methods

Study Population

The Dallas Heart Study (DHS) is a multiethnic, population-based cohort study of Dallas County residents¹⁶ that was conducted in two phases. DHS Phase 1, performed in years 2000–2002, included 3 visits, a home visit where demographics and blood pressure measurements were collected and a health survey was administered, a second home visit to collect blood and urine specimens, and a third visit to UT Southwestern Medical where extensive imaging studies were performed. To better reflect populations that were underrepresented in previous epidemiological studies, black participants were oversampled in DHS Phase 1, such that they represent ~50% of the cohort. DHS Phase 2 was designed as a longitudinal follow-up visit of DHS Phase 1 participants, completed in a single day visit to UT Southwestern in years 2007–2009.

The analysis cohort for the present study included participants from DHS Phase 1 who returned for the DHS Phase 2 visit and had cardiovascular magnetic resonance imaging (cMRI) performed at both visits, with cMRI images adequate for assessment of left atrial (LA) dimensions (n=796). Participants with prevalent cardiovascular disease (history of heart failure, myocardial infarction [MI], or stroke; n=36), and those who developed incident CVD between DHS phase 1 and DHS phase 2 (heart failure, MI, unstable angina, stroke, transient ischemic attack, atrial fibrillation, or coronary or peripheral revascularization; n=12), were excluded, yielding a final study cohort of 748 participants with paired cMRI measurements evaluable for the study. The study was approved by the University of Texas Southwestern Medical Center Institutional Review Board and all participants provided written informed consent.

Variable definitions

Sex and race/ethnicity were determined by participant self-report. Blood pressure measurements were obtained after 5 minutes of rest in the seated position using an automated oscillometric device, and the last 3 of 5 total measurements were averaged. Hypertension was defined as an average systolic blood pressure of ≥ 140 mm Hg or an average diastolic blood pressure of ≥ 90 mm Hg or if the participant self-reported antihypertensive therapy [17]. Diabetes mellitus was defined by a fasting glucose level ≥ 126 mg/dL, non-fasting glucose ≥ 200 mg/dL, or use of hypoglycemic medications [15]. Current smoking was defined as cigarette use within the previous 30 days.

Laboratory measurements

N-terminal pro-BNP (NT-pro-BNP), high sensitivity C-reactive protein (hs-CRP) and highly sensitive cardiac troponin T (hs-cTnT) levels were measured at both DHS-1 and DHS-2, as previously described.^{17, 18} Adiponectin and leptin were measured at the DHS-1 visit only, as previously described.¹⁹

Assessment of Body Composition

Weight and height were measured at both DHS 1 (baseline) and DHS 2 (follow up), and body mass index (BMI) was defined as weight (kg)/ height² (m²). Waist circumference was measured on a horizontal plane 1 cm above the iliac crest and reported in cm. Total body fat, lean mass, and lower body fat were measured at the DHS-1 visit by Dual-energy x-ray absorptiometry (Delphi W scanner, Hologic, and Discovery software version 12.2). Using a method of fat mass prediction from a single MRI slice at the L2–L3 intervertebral level, visceral and subcutaneous abdominal fat mass were measured at the DHS-1 visit by 1.5-T MRI (Intera, Philips Medical Systems). Single-slice measurement of visceral and subcutaneous fat mass at this intervertebral level has been shown to be highly concordant with total abdominal fat mass measured at all intervertebral levels ($R^2 = 85\%–96\%$)^{16, 20}.

Magnetic Resonance Imaging

cMRI was performed on a 1.5 Tesla system (Phillips Medical System, Best, The Netherlands) in DHS Phase 1²¹ and on a 3-T system (Achieva, Philips Medical Systems, Best, The Netherlands) in DHS Phase 2. At both time points, LV images were acquired using prospective ECG gating and turbo field echo (TFE) sequencing. In order to calibrate the images, measurements from both time points were normalized to a phantom, which was imaged on both MRI systems. LV mass, LV end-diastolic volume, LV end systolic volume, and LV wall thickness were calculated from short-axis sequences, where papillary muscles were included in LV mass and excluded from LV volume. LV ejection fraction (LVEF) was calculated from these measurements.

In DHS1 LA images were acquired using prospective ECG gating and TFE sequencing. In DHS 2, LA images were acquired using retrospective ECG gating and balanced fast field echo (BFFE) sequencing. Contours of the left atrium were drawn using QMass software (Dallas, TX). Maximum LA volume was measured using the biplane area-length method following the American Society of Echocardiography's guidelines as previously described.²² Studies were excluded from analysis if the left ventricular outflow tract was present in the

four chamber view, images were of poor resolution, or there was unclear demarcation of the pulmonary veins. For quality control, all DHS-1 measurements were made by a single analyst (SG), with inter-observer and intra-observer reliability previously described.⁷ All measurements of LA parameters in DHS-2 were performed by 2 analysts (W.O. or G.W.) only after satisfactory completion of a training set of images (with measurements within 10% of established training set values). The training set used for DHS-2 was identical to that used for DHS-1 to ensure consistency between the reviewers and training. To assess for intra-observer and inter-observer variability, contours were redrawn by the investigators for a random selection of subjects (n=20). The intra-class correlation was 0.96 (95% CI 0.90, 0.98) and inter-class correlation was 0.98 (0.96, 0.99). Finally, 10% of studies analyzed by the primary readers were over-read by senior investigators.

Statistical methods

Participants were divided into quartiles based on LA maximal volume at the DHS-2 study visit, and into separate quartiles based on change in LA maximal volume between DHS-1 and DHS-2 timepoints (Δ LAV). Participant characteristics were compared across quartiles using the Jonckheere-Terpstra test for trend for continuous variables and the Cochran-Armitage trend test for binary variables.

Multivariable linear regression models were constructed to delineate variables independently associated with Δ LAV over follow-up. Δ LAV was modeled by considering DHS-2 LA maximal volume as the dependent variable and including DHS-1 LA maximal volume as an independent variable. With this modeling strategy, any variable that emerges after accounting for baseline LA maximal volume as statistically significant is independently associated with Δ LAV. Model 1 adjusted for age, race/ethnicity, sex, BMI at DHS-1, Δ BMI from DHS-1 to DHS-2, SBP at DHS-1, Δ SBP from DHS-1 to DHS-2, blood pressure medications at both DHS-1 and DHS-2, NT-proBNP levels at DHS-1 and Δ NT-proBNP from DHS-1 to DHS-2, and prevalent diabetes at DHS-1. Model 2 additionally included estimated GFR, LV mass at DHS-1 and Δ LV mass between DHS-1 and DHS-2. Model 3 replaced LV mass variables with DHS-1 LV end diastolic volume (EDV) and Δ LV EDV between DHS-1 and 2, and DHS-1 wall thickness. Analyses were repeated replacing SBP and Δ SBP with DBP and Δ DBP. Finally, in order to better characterize associations between different body fat distribution patterns and LA volume change, BMI variables were replaced by lean and fat mass by DEXA, and then with abdominal subcutaneous fat mass, visceral fat mass, and lower body adipose mass from MRI and DEXA. All models report standardized Beta coefficients as the measure of effect size, in which the parameter estimate reflects a 1 standard deviation change in DHS-2 LA maximal size and a 1 standard deviation change in each of the continuous independent variables. All statistical analyses were performed with SAS version 9.4.

Results

Table 1 displays participant characteristics across quartiles of LA maximum volume (LAV) at DHS-2. In these cross sectional analyses, higher LAV quartiles were significantly associated with Black and Hispanic race/ethnic group, and with prevalent hypertension and

with systolic blood pressure ($P < 0.05$ for each), but not age or sex. Furthermore, LAV was also associated with larger BMI and waist circumference ($P < 0.01$ for each). LV mass and volume, and levels of NT-proBNP were all higher among individuals with larger LAV ($p < 0.0001$ for each). No differences were seen across LAV quartiles for hs-cTnT or hs-CRP.

Univariable analyses evaluating variables associated with change in LA volume (LAV) between DHS 1 and DHS 2 are shown in Table 2. Although no association was seen for prevalent or incident hypertension or baseline systolic BP, participants in higher LAV quartiles had higher baseline diastolic BP and greater increases in systolic BP between visits ($P < .05$ for each). Body composition measurements including baseline BMI, waist circumference, and visceral and subcutaneous fat mass were associated with LAV ($p < 0.05$ for each). Additionally, parallel changes in the left ventricle, including LV Mass/BSA and LVEDV/BSA, were strongly associated with change in left atrial size ($p < 0.0001$ for each). Finally, significant positive associations were found between NT-Pro-BNP and LAV, with a weak inverse association seen between hs-CRP and LAV.

In multiple linear regression analyses, LAV was independently associated with Black and Hispanic race/ethnicity, baseline BMI and BMI, SBP, baseline NT-proBNP and NT-proBNP. An inverse association was seen with prevalent diabetes status (Table 3, model 1). Further adjustment for eGFR, DHS-1 LV mass, and LV mass demonstrated independent associations between LV mass and LV mass with LAV (Table 3, model 2). When LV mass was replaced with LVEDV and wall thickness, LVEDV and LVEDV, but not LV wall thickness, emerged as strongly associated with LAV (Table 3 3, model 3). No association was seen with DBP or DBP when these variables replaced SBP and SBP in the models (data not shown).

Table 4 shows more detailed assessment of body composition associations with LAV. When BMI (Table 4, model 1) was replaced with lean and fat mass measurements from DEXA at DHS-1, fat mass (estimated $\beta = 0.13$, $p = 0.0005$), but not lean mass, was robustly associated with LAV (Table 4, model 2). When fat mass was replaced with its different compartments, an association was seen between visceral fat mass and LAV (estimated $\beta = 0.13$, $p = 0.002$), but no association was seen with subcutaneous or lower body fat mass (Table 4, model 3). Neither leptin nor adiponectin was associated with LAV in the adjusted models; forcing these adipokines into the models did not attenuate the associations of other variables with LAV (data not shown).

DISCUSSION

The present study reports a comprehensive epidemiological evaluation of left atrial remodeling in a multiethnic population of individuals free from CVD. We identified several independent determinants of LA enlargement over follow-up, including black or Hispanic race/ethnicity, higher BMI, increase in SBP between visits, higher baseline left ventricular mass (and change in LV mass over follow-up), and larger increases in NT-proBNP. These findings extend our prior observations from DHS-phase 1, in which we reported an association between LA enlargement and well-established risk factors including hypertension, natriuretic peptides, and LV structural and functional abnormalities, as well as

an association between LA enlargement and mortality independent of traditional risk factors.⁷ The cross sectional analyses from DHS-phase 2 reported here (Table 1) confirm these prior observations from DHS phase-1, using measurements from this same cohort obtained 8 years later. Moreover, the analyses of LAV represent a novel evaluation of LA remodeling among individuals without existing CVD.

The finding that LAV was larger in Black and Hispanic race/ethnic groups than in whites is notable. A recent analysis using echo measures of LA size in younger individuals from the Coronary Artery Risk Development in Young Adults (CARDIA) study also demonstrated larger LA size among Black than white individuals, but these differences attenuated after multivariable adjustment.²³ In our study, despite adjustment for known race/ethnic differences in blood pressure, diabetes, body composition, LV mass and geometry, natriuretic peptides, and adipokines, race/ethnic differences in LA remodeling persisted. This suggests that left atrial remodeling may be influenced by genetic variants that are reflected by race/ethnicity. Prior studies of White²⁴ and Caribbean Hispanic²⁵ populations estimated moderate heritability of LA size after adjusting for covariates, and identified several possible susceptibility genes. LV hypertrophy and remodeling also differ substantially by race/ethnicity²¹ with gene variants identified in causal pathways limited to specific race/ethnic groups.²⁶ To what extent race/ethnic differences in LA and LV remodeling reflect genetic differences vs. differences in the cumulative burden of risk factor exposure remains to be determined.

Increasing SBP but not DBP over the study period associated independently with LAV, suggesting that systolic pressure load may be more important determinant of left atrial remodeling. Several different parameters of LV enlargement were also associated with LAV. Of interest, the associations between LV mass and LA volume changes appeared to be mediated by LV dilatation rather than wall thickening, as LVEDV and increases in LVEDV were associated with greater LAV, whereas no association was seen with LV wall thickness. These findings suggest a coupling between LV and LA remodeling, perhaps pointing to similar underlying pathophysiological pathways.

Utilizing advanced DEXA and MRI imaging methods to assess body composition and regional fat distribution, we found that the association of baseline BMI with LA enlargement appeared to be explained by increased fat mass, as no association seen with lean mass. More importantly, assessment of regional fat distribution demonstrated that visceral adiposity was robustly associated with LA enlargement, with no association seen for subcutaneous or lower body fat mass. This finding extends prior studies linking visceral adiposity with adverse left ventricular remodeling^{27, 28}, and adverse cardiovascular events²⁹. It is possible that associations between visceral adiposity and atrial fibrillation may be reflective of systemic lipotoxicity, mediated via ectopic fat deposition in the peri-atrial epicardium or pericardium, resulting in local lipotoxic effects and subsequent atrial remodeling and enlargement^{6, 30, 31}. Prior studies have shown associations between thickness of epicardial fat and cardiac physiologic and morphologic changes, including LA enlargement, which may result from compensatory remodeling caused by the mechanical load on the heart due to the epicardial fat pad.^{6, 32, 33} We have previously demonstrated associations between

increased visceral adipose tissue mass and LV hypertrophy as well as incident hypertension,³⁴ both of which are mechanisms that could also contribute to LA enlargement.

Strengths and Limitations

Strengths of this study include its large size, representation of multiple race/ethnic groups, and the careful phenotyping of participants with methods including cMRI, DEXA and abdominal MRI. Limitations include the measurement of blood pressure only at the two study visits, and the absence of follow-up measurements of body fat distribution. Due to the change in cMRI technique and readers between the two study visits, it is possible that the measurements of cardiac dimensions are not perfectly calibrated between visits. However, we performed careful quality control procedures to ensure accurate image analyses, and calibration corrections that are standard for population-based studies. Similar variables associated with LA volume at DHS-1 and DHS-2, supporting internal validity of the measurements. Most importantly, our modeling strategy that considers DHS-2 LA volume as the dependent variable and DHS-1 volume as an independent variable, is insensitive to calibration issues. We did not perform echocardiography, so are unable to evaluate the role of diastolic dysfunction on LA remodeling. In addition, we acknowledge the potential for selection bias among those who returned for DHS phase 2 imaging.

Clinical Implications

It is well established that left ventricular hypertrophy (LVH) is associated with morbidity and mortality in the population, including the development of heart failure and death from cardiovascular disease.² In comparison, much less is known about the clinical implications of LA enlargement. In our previous study of DHS phase 1, larger LA volume was associated with mortality independent of traditional risk factors and LV parameters.⁷ Here, we are not able to assess directly the implications of changes in LA size on CV outcomes, given the small number of events that have occurred since the DHS phase 2 visit. However, given the associations of LAV with other pathological phenotypes, including increased systolic blood pressure, visceral adiposity, LV dilatation, and increasing NT-proBNP, it is likely that LA dilatation represents an unfavorable intermediate phenotype. Longer term follow-up will be needed to evaluate this hypothesis.

Better understanding of the risk factors for increased left atrial size over time may help to identify strategies to prevent or modify LA remodeling, which could help to prevent atrial fibrillation as well as the development and consequences of other cardiovascular diseases including heart failure with preserved and reduced ejection fraction and valvular heart disease.³⁵ It is plausible that preventive measures, including weight loss and more rigorous control of hypertension, may decrease the risk of left atrial enlargement and prevent downstream clinical consequences.

Clinical Perspective

While contributors to remodeling of the left ventricle (LV) have been well studied in general population cohorts, few data are available describing factors influencing changes in left atrial (LA) structure. Previous studies have shown that larger LA volume is associated with worse clinical outcomes, including atrial fibrillation, heart failure and mortality. In this

study, serial measurement of LA volume were performed using cardiac magnetic resonance imaging approximately 8 years apart. Factors associated with LA enlargement over time included black and hispanic race/ethnicity, increases in systolic blood pressure, and parallel changes in the left ventricle, in particular LV dilation. Obesity was also associated with LA remodeling with the strongest link seen with visceral adiposity. These findings suggest that improved blood pressure control and prevention or reduction of visceral obesity may prevent pathological LA remodeling, which may prevent downstream consequences including atrial fibrillation and heart failure.

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Table 1
Cross Sectional Associations of Demographic and Clinical Variables with Left Atrial Volume at DHS-2

Variable	Q1	Q2	Q3	Q4	P trend
LA volume/BSA (mL/m ²)	22.4 [19.5, 24.6]	30.0 [28.0, 31.2]	36.1 [34.7, 37.9]	46.0 [42.6, 51.4]	
Age (years)	50 [44, 58]	49 [41, 58]	49 [42, 56]	50 [44, 58]	0.93
Male Sex (%)	41.1	36.3	42.1	43.2	0.44
Race/Ethnicity (%)					
Black	36.3	38.9	50.0	53.7	<.0001
White	46.3	48.9	33.2	26.8	<.0001
Hispanic	12.6	9.5	15.3	18.9	0.028
Other	4.7	2.6	1.6	0.5	0.006
Diabetes (%)	14.7	11.6	13.2	10.5	0.30
Hypertension (%)	37.9	37.9	42.1	48.9	0.019
Systolic Blood Pressure (mmHg)	125 [114, 136]	124 [115, 137]	127 [117, 140]	131 [120, 144]	<.0001
Diastolic Blood Pressure (mmHg)	79 [72, 85]	79 [74, 85]	79 [74, 85]	79 [73, 85]	0.86
Smoking (%)	21.9	19.5	20.3	18.8	0.52
BMI (kg/m ²)	28.4 [25.2, 31.6]	28.0 [24.6, 32.4]	29.5 [25.3, 33.2]	30.1 [26.4, 35.1]	<.0001
Waist Circumference (cm)	91.4 [81.3, 99.1]	92.7 [83.8, 101.3]	92.4 [83.8, 102.9]	96.2 [86.4, 105.4]	0.008
LV Mass/BSA (g/m ²)	58.6 [51.1, 68.9]	58.2 [51.2, 67.6]	63.3 [53.4, 73.0]	68.7 [56.6, 79.2]	<.0001
LVEDV/BSA (mL/m ²)	55.0 [47.9, 61.6]	56.5 [50.4, 65.5]	61.7 [54.6, 68.6]	65.2 [59.0, 72.5]	<.0001
LV Wall Thickness (mm)	10.7 [9.8, 11.9]	10.6 [9.9, 12.0]	11.0 [10.0, 12.1]	11.3 [10.4, 12.6]	<.0001
LV Ejection Fraction (%)	69.8 [65.5, 74.1]	69.4 [64.9, 73.8]	69.5 [64.4, 73.0]	69.6 [66.2, 74.4]	0.98
NT-Pro-BNP (pg/mL)	34.3 [18.9, 63.7]	37.9 [23.4, 67.8]	42.2 [24.0, 73.6]	51.4 [29.6, 90.4]	<.0001
hsCRP (mg/L)	2.6 [1.1, 5.6]	2.0 [1, 4.3]	2.3 [1, 5.1]	2.4 [1.1, 4.6]	0.76

Variable	Q1	Q2	Q3	Q4	P trend
hs-cTnT (ng/L)	4.7 [1.5, 6.9]	4.4 [1.5, 8.0]	4.7 [1.5, 7.4]	4.5 [1.5, 8.0]	0.95

DHS: Dallas Heart Study; LA: left atrial; LV=left ventricular; EDV=end diastolic volume; BMI=body mass index; BSA = body surface area; NT-Pro-BNP – N-terminal pro-brain natriuretic peptide; hs-CRP=high sensitivity C-Reactive Protein; GFR=glomerular filtration rate.

Left atrial size was indexed to body surface area

Table 2
Associations of Demographic and Clinical Variables with Change in Left Atrial Volume from DHS-1 to DHS-2

Variable	Q1	Q2	Q3	Q4	P trend
LA volume/BSA (mL/m ²)	-13.9 [-17.9, -11.0]	-5.1 [-6.8, -3.4]	1.3 [-0.5, 2.6]	8.3 [6.0, 12.5]	
DHS1 age (years)	44 [37, 51]	44 [36, 49]	42 [35, 49]	42 [36, 50]	0.27
Male Sex (%)	44.7	40.5	38.9	38.4	0.20
Race/Ethnicity (%)					
Black	35.3	42.1	45.8	55.8	<0.0001
White	48.4	40.0	36.3	30.5	<0.0001
Hispanic	12.6	14.2	16.8	12.6	0.82
Other	3.7	3.7	1.1	1.1	0.033
DHS1 Systolic Blood Pressure (mmHg)	120 [111, 132]	121 [112, 133]	120 [112, 129]	124 [114, 133]	0.18
Systolic Blood Pressure (mmHg)	4.7 [-4.7, 13]	4.2 [-4.7, 13.7]	6.7 [-2.7, 18.0]	6.3 [-2.3, 18.3]	0.015
DHS1 Diastolic Blood Pressure (mmHg)	74.8 [70.0, 80.7]	75.8 [70.0, 82.7]	75 [70.0, 80.7]	77.3 [71.2, 84.0]	0.043
Diastolic Blood Pressure (mmHg)	2.8 [-2.7, 8.7]	4.3 [-2.3, 9.3]	3.5 [-1.7, 11.0]	1.7 [-4.3, 8.3]	0.27
DHS1 Diabetes (%)	6.3	7.9	5.8	7.4	0.90
Incident Diabetes (%)	8.9	6.3	5.1	8.0	0.61
DHS1 Smoking (%)	22.2	24.2	20.5	22.6	0.86
Incident Smoking (%)	4.1	4.2	6.0	4.1	0.81
BMI (kg/ m ²)	27.4 [24.1, 32.1]	27.5 [24.3, 31.5]	28.1 [24.8, 31.6]	29.3 [25.2, 35.2]	0.001
BMI (kg/ m ²)	0.7 [-0.7, 2.1]	1.0 [-0.6, 2.5]	0.6 [-0.9, 2.4]	0.7 [-1.3, 2.4]	0.62
DHS1 waist circumference (cm)	92.5 [82.5, 103]	93.5 [84, 101]	93.3 [85, 102]	98 [88, 108]	0.002

Variable	Q1	Q2	Q3	Q4	P trend
DHS 1 Lean Mass (kg)	54.0 [51.9, 61.8]	50.9 [42.5, 61.7]	52.1 [43.6, 60.5]	54.4 [45.3, 63.0]	0.31
DHS 1 Total Fat Mass (kg)	22.0 [16.3, 29.3]	23.7 [18.7, 30.2]	24.4 [18.6, 31.2]	26.2 [19.0, 34.9]	<0001
DHS 1 Abdominal Subcutaneous Fat Mass (kg)	3.7 [2.5, 5.2]	3.7 [2.6, 5.5]	4.0 [2.7, 5.6]	4.2 [2.8, 6.7]	0.003
DHS 1 Visceral Fat Mass (kg)	1.8 [1.3, 2.5]	1.8 [1.3, 2.4]	1.8 [1.3, 2.4]	2.1 [1.4, 2.7]	0.029
DHS 1 Lower Body Fat Mass (kg)	7.8 [5.8, 10.5]	8.7 [6.4, 11.3]	8.9 [6.4, 11.9]	9.1 [6.8, 12.6]	0.001
DHS 1 LV Mass/BSA (g/m ²)	65.2 [55.9, 77.8]	62.6 [53.7, 73.6]	62.7 [54, 71.3]	66.3 [57.6, 76.1]	0.91
LV Mass/BSA (g/m ²)	-3.3 [-7.6, 1.3]	-2.4 [-6.7, 1.4]	-1.3 [-5.7, 2.7]	-1.0 [-4.9, 4.0]	<0001
DHS 1 LVEDV/BSA (mL/m ²)	64.5 [56.0, 73.2]	60.8 [55.3, 68.8]	62.5 [56.3, 69.3]	60.2 [53.2, 68.9]	0.003
LVEDV/BSA (mL/m ²)	-5.0 [-11.8, 0.6]	-3.8 [-7.5, 0.4]	-1.2 [-5.3, 3.3]	2.5 [-2.6, 6.8]	<0001
DHS 1 LV Ejection Fraction (%)	68.5 [63.9, 73.1]	69.4 [65.1, 72.2]	68.1 [63.9, 72.2]	68.8 [64.3, 73.2]	0.99
LV Ejection Fraction (%)	-0.1 [-2.9, 4.1]	0.9 [-3.4, 4.5]	1.3 [-2.1, 4.9]	0.9 [-1.9, 4.3]	0.053
DHS 1 hs-cTnT ng/L	1.5 [1.5, 1.5]	1.5 [1.5, 1.5]	1.5 [1.5, 1.5]	1.5 [1.5, 1.5]	0.059
hs-cTnT ng/L	2.9 [0, 6.0]	1.8 [0, 4.3]	2.0 [0, 4.3]	2.5 [0, 5.0]	0.38
DHS 1 NT-Pro-BNP (pg/mL)	32.6 [16, 60.3]	24.4 [11.2, 55.5]	25.1 [11.7, 50.0]	29.0 [11.2, 56.9]	0.26
NT-Pro-BNP (pg/mL)	8.4 [-11.8, 25.5]	10.4 [-4.3, 27.3]	14.7 [1.2, 34.9]	18.4 [2.4, 50.7]	<0001
DHS 1 hs-CRP (mg/L)	2.0 [0.9, 4.3]	2.0 [0.8, 5.1]	2.3 [1.1, 5]	3.4 [1, 7.6]	0.001
hs-CRP (mg/L)	0.1 [-1.1, 1.5]	0.2 [-0.9, 1.2]	-0.1 [-1.4, 1]	-0.2 [-2.9, 1]	0.021
Glomerular Filtration Rate (mL/min per 1.73)	97.6 [84.7, 112.3]	97.6 [85.7, 110.2]	96.7 [84.4, 111.1]	98.3 [86.6, 109.7]	0.82

Variable	Q1	Q2	Q3	Q4	P trend
m ²)					
Glomerular Filtration Rate (mL/min per 1.73 m ²)	-4.4 [-13.5, 6.5]	-4.2 [-14.0, 7.8]	-6.0 [-14.8, 5.4]	-5.7 [-16.6, 1.9]	0.29

Abbreviations as in table 1

Left atrial size was indexed to body surface area in both DHS 1 and DHS 2

Table 3

Multivariable Linear Regression Models for Change in LA Volume, with DHS-2 LA Maximal Volume as the Dependent variable

Variable	Model 1		Model 2		Model 3	
	Parameter Estimate*	P Value	Parameter Estimate*	P Value	Parameter Estimate*	P Value
DHS1 LA maximal volume	0.50	<0.0001	0.46	<0.0001	0.43	<0.0001
age	-0.06	0.06	-0.02	0.55	0.03	0.41
Black (vs. white)	0.12	0.0003	0.09	0.008	0.10	0.002
Hispanic (vs. white)	0.09	0.005	0.10	0.002	0.10	0.0001
male	0.12	0.0002	0.05	0.24	0.04	0.94
DHS1 BMI	0.22	<0.0001	0.20	<0.0001	0.18	<0.0001
BMI	0.08	0.01	0.06	0.06	0.05	0.07
DHS1 SBP	0.07	0.07	0.04	0.34	0.06	0.07
SBP	0.12	0.0003	0.11	0.001	0.11	0.0002
DHS1 Hypertension Medications	-0.01	0.66	-0.006	0.86	0.02	0.59
DHS2 Hypertension Medications	-0.004	0.91	-0.009	0.81	0.006	0.87
DHS1 NT-proBNP	0.41	0.001	0.34	0.007	0.24	0.04
NT-proBNP	0.10	0.001	0.07	0.02	0.04	0.17
Diabetes	-0.07	0.02	-0.08	0.008	-0.08	0.004
Estimated GFR			0.02	0.51	0.02	0.39
DHS1 LV mass			0.15	0.002		
LV mass			0.07	0.04		
DHS1 LV EDV					0.25	<0.0001
LV EDV					0.34	<0.0001
DHS1 LV wall thickness					0.05	0.21

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The parameter estimate is a standardized Beta coefficient, which reflects a 1 standard deviation change in the dependent variable (DHS 2 maximal size) and a 1 standard deviation change in each of the continuous independent variables.^{*}

Abbreviations as in table 1

Table 4

Multivariable Linear Regression Models Evaluating Association of Body Composition Variables with Change in LA Volume, with DHS-2 LA Volume as the Dependent Variable.

Variable	Model 1		Model 2		Model 3	
	Parameter Estimate*	P Value	Parameter Estimate*	P Value	Parameter Estimate*	P Value
BMI	0.18	<0.0001				
Lean mass			0.04	0.60		
Total Fat mass			0.13	0.0005		
Visceral Fat					0.13	0.002
Subcutaneous Fat					0.04	0.47
Lower Body Fat					0.05	0.30

All models use DHS-2 LA maximal volume as the dependent variable and include as independent variables DHS-1 LA maximal volume and all of the components of model 3 from table 3. All of the variables significantly associated with DHS-2 LAV in model 3 from table 3 were also significantly associated with DHS-2 LAV in the models reported here. The parameter estimate is a standardized Beta coefficient, which reflects a 1 standard deviation change in DHS-2 LA maximal size and a 1 standard deviation change in each of the continuous independent variables.

LA=left atrium; BMI=body mass index