Factors Associated With Left Atrial Remodeling in the General Population

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Background—Although 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 among 748 participants in the Dallas Heart Study at 2 visits a mean of 8 years apart. Associations of changes in LA volume (ΔLAV) with traditional risk factors, biomarkers, LV geometry, and remodeling by cardiac magnetic resonance imaging and detailed measurements of global and regional adiposity (by magnetic resonance imaging and dual-energy x ray absorptiometry) were assessed using multivariable linear regression. Greater ΔLAV was independently associated with black and Hispanic race/ethnicity, change in systolic blood pressure, LV mass and ΔLV mass, N-terminal probrain natriuretic peptide and change in N-terminal probrain natriuretic peptide, and body mass index (P<0.05 for each). In subanalyses, the associations of ΔLAV with LV mass parameters were driven by associations with baseline and ΔLV end diastolic volume (P<0.0001 for each) and not wall thickness (P=0.21). Associations of ΔLAV with body mass index were explained exclusively by associations with visceral fat mass (P=0.002), with no association seen between ΔLAV 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 in white individuals and is associated with parallel changes in the LV. LA dilatation may be mediated by blood pressure control and the development of visceral adiposity. **(*Circ Cardiovasc Imaging*. 2017;10:e005047. DOI: 10.1161/CIRCIMAGING.116.005047.)**

Key Words: ethnic groups ■ left atrial volume index ■ left atrium ■ magnetic resonance imaging ■ obesity ■ race ■ remodeling

Although the contributions of left ventricular (LV) size and function to cardiovascular disease (CVD) in the general population are firmly established,[1–4] much less is known about the role of the 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] Several cross-sectional studies have identified factors associated with variation in LA size, finding that older age, hypertension, LV dilation, and measures of obesity associate with larger LA volume.[7,10–12]

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Beyond static measurements of LA size at a single time point, changes in LA size over time (LA remodeling) may be important contributors to CVD. Previous studies of LA remodeling have been limited by the use of selective cohorts of diseased subjects, where imaging was performed for clinical indications.[13,14] In the general population, there are few data evaluating changes in LA size and function, and the limited data available have been generated from studies with poor ethnic minority representation.[15] Therefore, in a large, multiethnic, general population study, we sought to determine factors that may influence change in LA 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 residents[16] that was conducted in 2 phases. DHS phase 1, performed in years 2000 to 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 University of Texas 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%

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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 University of Texas Southwestern in years 2007 to 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 LA dimensions (n=796). Participants with prevalent CVD (history of heart failure, myocardial infarction, or stroke; n=36), and those who developed incident CVD between DHS phase 1 and DHS phase 2 (heart failure, myocardial infarction, 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 (SBP) of ≥140 mm Hg or an average diastolic blood pressure (DBP) 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, nonfasting glucose ≥200 mg/dL, or use of hypoglycemic medications.[16] Current smoking was defined as cigarette use within the previous 30 days.

Laboratory Measurements

N-terminal probrain natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein, and highly sensitive cardiac troponin T 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 (m^2). Waist circumference was measured on a horizontal plane 1 cm above the iliac crest and reported in centimeter. Total body fat, lean mass, and lower body fat were measured at the DHS-1 visit by dual-energy x ray absorptiometry (DEXA; 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 masses were measured at the DHS-1 visit by 1.5-T MRI (Intera; Philips Medical Systems, Best, The Netherlands). 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-T system (Philips Medical System) in DHS phase 1[21] and on a 3-T system (Achieva; Philips Medical Systems) in DHS phase 2. At both time points, LV images were acquired using prospective ECG gating and turbo field echo sequencing. 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 (EDV), 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 was calculated from these measurements.

In DHS-1, LA images were acquired using prospective ECG gating and turbo field echo sequencing. In DHS-2, LA images were acquired using retrospective ECG gating and balanced fast field echo sequencing. Contours of the LA 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 LV outflow tract was present in the 4-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 (S.G.), with interobserver and intraobserver 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 intraobserver and interobserver variability, contours were redrawn by the investigators for a random selection of subjects (n=20). The intraclass correlation was 0.96 (95% confidence interval 0.90–0.98), and interclass correlation was 0.98 (95% confidence interval 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 time points (ΔLAV). 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 ΔLAV over follow-up. ΔLAV 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 ΔLAV. Model 1 was adjusted for age, race/ethnicity, sex, BMI at DHS-1, ΔBMI from DHS-1 to DHS-2, SBP at DHS-1, ΔSBP from DHS-1 to DHS-2, blood pressure medications at both DHS-1 and DHS-2, NT-proBNP levels at DHS-1 and ΔNT-proBNP from DHS-1 to DHS-2, and prevalent diabetes mellitus at DHS-1. Model 2 additionally included estimated glomerular filtration rate, LV mass at DHS-1, and ΔLV mass between DHS-1 and DHS-2. Model 3 replaced LV mass variables with DHS-1 LVEDV and ΔLVEDV between DHS-1 and -2 and DHS-1 wall thickness. Analyses were repeated replacing SBP and ΔSBP with DBP and ΔDBP. Finally, 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 SD change in DHS-2 LA maximal size and a 1 SD 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 maximum 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 SBP (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 highly sensitive cardiac troponin T or high-sensitivity C-reactive protein.

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/m2	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, y	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	<0.0001
White	46.3	48.9	33.2	26.8	<0.0001
Hispanic	12.6	9.5	15.3	18.9	0.028
Other	4.7	2.6	1.6	0.5	0.006
Diabetes mellitus, %	14.7	11.6	13.2	10.5	0.30
Hypertension, %	37.9	37.9	42.1	48.9	0.019
Systolic blood pressure, mm Hg	125 [114–136]	124 [115–137]	127 [117–140]	131 [120–144]	<0.0001
Diastolic blood pressure, mm Hg	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]	<0.001
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]	<0.0001
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]	<0.0001
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]	<0.0001
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-proBNP, 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]	<0.0001
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
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

Left atrial size was indexed to body surface area. BMI indicates body mass index; BSA, body surface area; DHS, Dallas Heart Study; EDV, end diastolic volume; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, highly sensitive cardiac troponin T; LA, left atrial; LV, left ventricular; and NT-proBNP, N-terminal probrain natriuretic peptide.

Univariable analyses evaluating variables associated with ΔLAV between DHS-1 and DHS-2 are shown in Table 2. Although no association was seen for prevalent or incident hypertension or baseline SBP, participants in higher ΔLAV quartiles had higher baseline DBP and greater increases in SBP between visits (P<0.05 for each). Body composition measurements, including baseline BMI, waist circumference, and visceral and subcutaneous fat mass, were associated with ΔLAV (P<0.05 for each). Additionally, parallel changes in the LV, including ΔLV mass/BSA and ΔLVEDV/BSA, were strongly associated with change in LA size (P<0.0001 for each). Finally, significant positive associations were found between ΔNT-proBNP and ΔLAV, with a weak inverse association seen between change in high-sensitivity C-reactive protein and ΔLAV.

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

Table 4 shows more detailed assessment of body composition associations with ΔLAV. When BMI (Table 4, model 1) was replaced with lean and fat mass measurements from DEXA at DHS-1, fat mass (estimated β=0.13; P=0.0005), but not lean mass, was robustly associated with ΔLAV (Table 4, model 2). When fat mass was replaced with its different compartments, an association was seen between visceral fat mass and ΔLAV (estimated β=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 ΔLAV in the adjusted models; forcing these adipokines into the models did not attenuate the associations of other variables with ΔLAV (data not shown).

Discussion

The present study reports a comprehensive epidemiological evaluation of LA 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

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
ΔLA volume/BSA, mL/m^2	−13.9 [−17.9 to −11.0]	−5.1 [−6.8 to −3.4]	1.3 [−0.5 to 2.6]	8.3 [6.0 to 12.5]	
DHS-1 age, y	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
DHS-1 systolic blood pressure, mm Hg	120 [111–132]	121[112–133]	120 [112–129]	124 [114–133]	0.18
Change in systolic blood pressure, mm Hg	4.7 [−4.7 to 13]	4.2 [−4.7 to 13.7]	6.7 [−2.7 to 18.0]	6.3 [−2.3 to 18.3]	0.015
DHS-1 diastolic blood pressure, mm Hg	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
Change in diastolic blood pressure, mm Hg	2.8 [−2.7 to 8.7]	4.3 [−2.3 to 9.3]	3.5 [−1.7 to 11.0]	1.7 [−4.3 to 8.3]	0.27
DHS-1 diabetes mellitus, %	6.3	7.9	5.8	7.4	0.90
Incident diabetes mellitus, %	8.9	6.3	5.1	8.0	0.61
DHS-1 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
Change in BMI, kg/m^2	0.7 [−0.7 to 2.1]	1.0 [−0.6 to 2.5]	0.6 [−0.9 to 2.4]	0.7 [−1.3 to 2.4]	0.62
DHS-1 waist circumference, cm	92.5 [82.5–103]	93.5 [84–101]	93.3 [85–102]	98 [88–108]	0.002
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]	<0.0001
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
Change in LV mass/BSA, g/m^2	−3.3 [−7.6 to 1.3]	−2.4 [−6.7 to 1.4]	−1.3 [−5.7 to 2.7]	−1.0 [−4.9 to 4.0]	<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
ΔLVEDV/BSA, mL/m^2	−5.0 [−11.8 to −0.6]	−3.8 [−7.5 to 0.4]	−1.2 [−5.3 to 3.3]	2.5 [−2.6 to 6.8]	<0.0001
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
ΔLV ejection fraction, %	−0.1 [−2.9 to 4.1]	0.9 [−3.4 to 4.5]	1.3 [−2.1 to 4.9]	0.9 [−1.9 to 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
Δhs-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-proBNP, 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
ΔNT-proBNP, pg/mL	8.4 [−11.8 to 25.5]	10.4 [−4.3 to 27.3]	14.7 [1.2–34.9]	18.4 [2.4–50.7]	<0.0001
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
Δhs-CRP, mg/L	0.1 [−1.1 to 1.5]	0.2 [−0.9 to 1.2]	−0.1 [−1.4 to 1]	−0.2 [−2.9 to 1]	0.021
Glomerular filtration rat,e mL/min per 1.73 m^2	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
Change in glomerular filtration rate, mL/ min per 1.73 m^2	−4.4 [−13.5 to 6.5]	−4.2 [−14.0 to 7.8]	−6.0 [−14.8 to 5.4]	−5.7 [−16.6 to 1.9]	0.29

Left atrial size was indexed to body surface area in both DHS-1 and DHS-2. BMI indicates body mass index; BSA, body surface area; DHS, Dallas Heart Study; EDV, end diastolic volume; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, highly sensitive cardiac troponin T; LA, left atrial; LV, left ventricular; and NT-proBNP, N-terminal probrain natriuretic peptide.

Table 3. Multivariable Linear Regression Models for Change in LA Volume, With DHS-2 LA Maximal Volume as the Dependent Variable

	Model 1		Model 2		Model 3	
Variable	Parameter Estimate*	*P* Value	Parameter Estimate*	*P* Value	Parameter Estimate*	*P* Value
DHS-1 LA maximal volume, mL	0.50	<0.0001	0.46	<0.0001	0.43	<0.0001
Age, y	–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	004	0.94
DHS-1 BMI	0.22	<0.0.0001	0.20	<0.0001	0.18	<0.0001
ΔBMI	0.08	0.01	0.06	0.06	0.05	0.07
DHS-1 SBP	0.07	0.07	0.04	0.34	0.06	0.07
ΔSBP	0.12	0.0003	0.11	0.001	0.11	0.0002
DHS-1 hypertension medications	–0.01	0.66	–0.006	0.86	0.02	0.59
DHS-2 hypertension medications	–0.004	0.91	–0.009	0.81	0.006	0.87
DHS-1 NT-proBNP	0.41	0.001	0.34	0.007	0.24	0.04
ΔNT-proBNP	0.10	0.001	0.07	0.02	0.04	0.17
Diabetes mellitus	–0.07	0.02	–0.08	0.008	–0.08	0.004
Estimated GFR			0.02	0.51	0.02	0.39
DHS-1 LV mass			0.15	0.002		
ΔLV mass			0.07	0.04		
DHS-1 LV EDV					0.25	<0.0001
ΔLVEDV					0.34	<0.0001
DHS-1 LV wall thickness					0.05	0.21

BMI indicates body mass index; DHS, Dallas Heart Study; EDV, end diastolic volume; GFR, glomerular filtration rate; LA, left atrial; LV, left ventricular; NT-proBNP, N-terminal probrain natriuretic peptide; and SBP, systolic blood pressure.

*The parameter estimate is a standardized beta coefficient, which reflects a 1 SD change in the dependent variable (DHS-2 maximal size) and a 1 SD change in each of the continuous independent variables.

SBP between visits, higher baseline LV 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

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

	Model 1		Model 2		Model 3	
Variable	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

BMI indicates body mass index; DHS, Dallas Heart Study; and LA, left atrium.

*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 SD change in DHS-2 LA maximal size and a 1 SD change in each of the continuous independent variables.

phase 1, using measurements from this same cohort obtained 8 years later. Moreover, the analyses of ΔLAV represent a novel evaluation of LA remodeling among individuals without existing CVD.

The finding that ΔLAV 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 CARDIA study (Coronary Artery Risk Development in Young Adults) 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 mellitus, body composition, LV mass and geometry, natriuretic peptides, and adipokines, race/ethnic differences in LA remodeling persisted. This suggests that LA remodeling may be influenced by genetic variants that are reflected by race/ethnicity. Prior studies of white[24] and Caribbean Hispanic[25] 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/ethnicity,[21] 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 versus 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 ΔLAV, suggesting that systolic pressure load may be more important determinant of LA remodeling. Several different parameters of LV enlargement were also associated with ΔLAV. Of interest, the associations between LV mass and LA volume changes appeared to be mediated by LV dilatation rather than wall thickening because LVEDV and increases in LVEDV were associated with greater ΔLAV, 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.

Using 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 rather than 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 LV remodeling[27,28] and adverse cardiovascular events.[29] It is possible that associations between visceral adiposity and atrial fibrillation may be reflective of systemic lipotoxicity, mediated via ectopic fat deposition in the periatrial 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 physiological and morphological changes, including LA enlargement, which may result from compensatory remodeling caused by the mechanical load on the heart because of the epicardial fat pad.[6,32,33] We have previously demonstrated associations between increased visceral adipose tissue mass and LV hypertrophy,[27] 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 advanced imaging methods, including cMRI, DEXA, and abdominal MRI. Limitations include the measurement of blood pressure only at the 2 study visits and the absence of follow-up measurements of body fat distribution. Because of the change in cMRI technique and readers between the 2 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 LV hypertrophy is associated with morbidity and mortality in the population, including the development of heart failure and death from CVD.[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 ΔLAV with other pathological phenotypes, including increased SBP, 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 LA 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 CVD, 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 LA enlargement and prevent downstream clinical consequences.

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Disclosures

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CLINICAL PERSPECTIVE

Although contributors to remodeling of the left ventricle 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 was performed using cardiac magnetic resonance imaging ≈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 left ventricular 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.

Factors Associated With Left Atrial Remodeling in the General Population

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