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Sex Differences in the Association of Cumulative Body Mass Index from Early Adulthood to Middle Age and Left Atrial Remodeling Evaluated by Three-Dimensional Echocardiography: The Coronary Artery Risk Development in Young Adults Study

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SUPPLEMENTARY DATA

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Abstract

Background: The relationship between long-term obesity and left atrial (LA) structure and function is not entirely understood. We examined the association of cumulative body mass index (cBMI) with LA remodeling using three-dimensional (3D) speckle-tracking echocardiography (STE).

Methods: The Coronary Artery Risk Development in Young Adults (CARDIA) study is a community-based cohort of black and white, men and women, ages 18–30 years at baseline in 1985–86 from four U.S. centers. This study included 2,144 participants who had satisfactory image quality and body mass index measurements during the entire follow-up period. The 3D STE-derived LA parameters were maximum, minimum, and pretrial contraction volumes; total, passive, and active emptying fraction; maximum systolic longitudinal strain; and early and late diastolic longitudinal strain rates. Multivariable linear regression analyses stratified by sex assessed the relationship between cBMI and 3D STE-derived LA parameters, adjusting for demographics and traditional cardiovascular.

Results: The mean age of the cohort was 55 ± 3.6 years; 54.8% were women, and 46.5% were black. There were statistically significant additive sex interactions for the association between cBMI and LA minimum contraction value, maximum systolic longitudinal strain, and early and late diastolic longitudinal strain rates. In the fully adjusted model, greater cBMI was associated with lower magnitude LA longitudinal deformation (maximum systolic longitudinal strain and early and late diastolic longitudinal strain rates) in men and with higher LA emptying fraction in women. In addition, greater cBMI was associated with higher LA phasic volumes indices in both men and women.

Conclusions: This study showed that while greater cBMI from early adulthood throughout middle age was associated with higher LA volumes in both genders, differences were found for LA function, with lower longitudinal deformation in men and higher reservoir and active LA function in women. (J Am Soc Echocardiogr 2020;33:878–87.)

Keywords

Body mass index; Left atrium remodeling; 3D echocardiography; Gender

The prevalence of obesity has been increasing in recent decades, reaching pandemic proportions.[1] In the United States, it is a major public health problem, with nearly two-thirds of the adult population classified as overweight or obese.[2] Recently, nationally representative data for U.S. adults from 2001 to 2016 presented significant sex differences in the trend in body mass index (BMI) levels, showing that BMI increase was greater in women compared with men.[3] Moreover, obesity is associated with numerous co-morbidities such as obstructive sleep apnea, nonalcoholic steatohepatosis, dyslipidemia, hyper-tension, diabetes mellitus type 2, and cardiovascular (CV) disease including atrial fibrillation (AF).[4,5]

Three-dimensional (3D) speckle-tracking echocardiography (STE) allows a reproducible and accurate evaluation of left atrial (LA) structure and function, overcoming the limitations of two-dimensional echocardiography such as image foreshortening and geometric inferences.[6] Furthermore, 3D STE supports evaluation of LA phasic volumes, emptying fractions (EFs), and longitudinal strain and strain rates parameters that have shown prognostic information beyond assessments of LA size alone.[7]

Several studies have shown an independent association between central adiposity, long-standing obesity, and steeper trajectories of BMI increase with cardiac systolic and diastolic dysfunction.[8,9] In addition, many investigations have brought a heightened awareness of gender differences in obesity-related cardiac remodeling, showing an increased prevalence of heart failure with preserved ejection fraction in women.[10] Nevertheless, sex differences in the relationship of obesity with LA structure and function are not entirely understood.

This study aimed to evaluate sex differences in the association of cumulative BMI (cBMI), a marker of both severity and duration of obesity, from young adulthood to middle age with LA structure and function assessed by 3D STE in a large longitudinal population study.

METHODS

Study Population

The Coronary Artery Risk Development in Young Adults (CARDIA) study is a multicenter population-based observational cohort study sponsored by the National Heart, Lung, and Blood Institute, initiated between 1985 and 1986, that enrolled 5,115 black and white men and women participants, ages 18–30 years at baseline from four U.S. field centers.[11] After the initial examination (year 0), eight additional visits were performed at years 2, 5, 7, 10, 15, 20, 25, and 30. Written informed consent was obtained from all participants in each visit, and the institutional review boards from each field center and the coordinating center approved the study annually. Of the 3,358 participants presenting at the year 30 examination (2015–16), 11 individuals had missing cBMI data, 162 participants did not undergo echocardiography, and another 1,041 had unsatisfactory 3D images or did not have 3D echo scan performed, leaving 2,144 participants for analyses in this present study (Figure 1).

Episodes of AF during the echo scan or personal history of AF were not considered as exclusion criteria for this study.

Echocardiographic Assessment

Echocardiography exams were accomplished using an Artida ultra-sound system (Toshiba Medical System, Otawara, Japan) by expert sonographers following standardized protocols based on the American Society of Echocardiography guidelines throughout all field centers.[12] In brief, participants were examined in a left lateral decubitus position, using parasternal long-axis, parasternal short-axis, apical four-chamber, apical two-chamber, and apical three-chamber standard views. Electrocardiogram tracing was recorded during all of the exams. Recording and measurements were performed at the end expiration, with a full three cardiac cycle capture, increasing to five entire cardiac cycles if the heart rate was more than 90 beats per minute or in the presence of arrhythmias.

Detailed quality control procedures were carried out during the study period to ensure adequate reproducibility and accuracy of the data.[13] The echocardiograms were stored digitally and transferred electronically from each field center to the Johns Hopkins Hospital cloud server using a protected web-based technology, where experienced readers analyzed the images using standard software (Digiview, Digisonics Systems, Houston, TX).

Acquisition and Analysis of 3D Images

All 3D images were acquired with a matrix array PST-25SX 2.0–4.0 MHz transducer in a single breath hold over four consecutive cardiac cycles. The images were analyzed offline by trained and certified readers using a wall motion tracking software package (UltraExtend, ver. 3.0, Toshiba Medical System) following a standardized protocol.[14]

The analysis of LA 3D parameters was initiated at end-diastolic frame using a multiplane display, including three cross-sectional slices (basal, mid, and roof) and two longitudinal orthogonal planes (plane A = four-chamber view; plane B = a plane orthogonal to the plane A; Figure 2). The endocardial border was traced in a counterclockwise direction, from the medial to the lateral mitral annulus, excluding the LA appendage and the ostium of the pulmonary veins. A semiautomatic border contours detection was performed, with manual adjustments made when necessary. The LA wall thickness was fixed to 3 mm. The 3D endocardial shell of the entire LA was automatically rendered throughout the entire cardiac cycle with quantification of LA phasic volumes, emptying volumes, EF, strain, and strain rate parameters (Figure 2).

Left ventricular (LV) 3D analyses were also initiated at end diastole and shown in multiple simultaneous views, including three cross-sectional slices (base, mid, and apex; planes C1, C2, and C3, respectively) and two longitudinal orthogonal planes (plane A = four-chamber view; plane B = a plane orthogonal to the plane A). Anatomical landmarks were identified in the longitudinal planes (mitral annulus and apex), and a semiautomatic border contour detection was performed, with manual adjustments made when was necessary (Supplemental Figure 1). The 3D endocardial shell of the entire left ventricle (LV) was automatically rendered with measurement of LV volumes, mass, ejection fraction, and strain parameters.

The 3D image quality control score was composed of image quality (poor, fair, good, and excellent), numbers of segments excluded due to unsatisfactory tracking (16 segments model), and the presence of artifacts (blurring, shadowing, stitching, and rib artifacts). Exams with poor image quality, with more than seven segments with inadequate tracking, or having dense artifacts were excluded from the study analysis.

The 3D LA STE inter- and intrareader reproducibility was described elsewhere,[14] with four expert readers making the assessments in a random subset of 20 participants. Rereadings were performed 30 days after the initial measurement, blinded to the original analysis (Supplemental Table 1).

LA Parameters

The 3D echocardiography LA volumes assessed were LAVmax: maximum LA volume at end systole (just before the mitral valve opens); LAVpreA: preatrial contraction LA volume at the onset of the P wave on electrocardiogram; and LAVmin: minimum LA volume at end diastole (just after the mitral valve closes). Three EFs were calculated based on those volumes: total EF = [(LAVmax – LAVmin)/LAVmax] * 100, passive EF = (LAVmax – LAVpreA)/ LAVmax) * 100), and active EF = [(LAVpreA – LAVmin)/ LAVpreA] * 100). The LA phasic volumes were indexed by body surface area. The LA global longitudinal strain (LASmax) was measured at end systole. Early LA strain rate (LASre) was defined as the first negative strain rate peak at early diastole, whereas late LA strain rate (LASra) was determined as the second negative strain rate peak at late diastole, after the onset of the P wave on electrocardiogram (Figure 3). In case of AF during the echocardiogram examination, the mean of three measures obtained in consecutive heart beats was calculated.

Covariates

Assessments of CV risk factors were obtained through standard protocols across all field centers and in each examination, as described elsewhere.[15] Body weight was measured with a calibrated balance beam scale to the nearest 0.1 kg. Height was measured with a vertical ruler to the nearest 0.5 cm. The BMI was calculated from these measures in units of kg/m^2. Alcohol consumption, smoking status, and use of medication were assessed by questionnaires. Hypertension was defined as blood pressure ≥ 140/90 mm Hg or use of antihypertensive medications. A physical activity score was obtained using the CARDIA physical activity questionnaire.[16] Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dL or a history of antidiabetic medications. Total cholesterol and high-density lipoprotein (HDL) cholesterol were determined using an enzymatic assay by Northwest Lipids Research Laboratory (Seattle, WA). Low-density lipoprotein (LDL) cholesterol was derived by the Friedewald equation.[17]

Cumulative BMI

The cBMI was defined as the BMI at a given study visit multiplied by the time period measured in years until the next available BMI measurement and summed across exams, over 30 years of follow-up: cBMI = Σ (BMI at visit 1 * years between visit 1 and visit 2) + (BMI at visit 2 * years between visit 2 and visit 3) + … (BMI at visit 8 * time between visit 8 and visit 9) + (BMI at visit 9). Each participant was required to have a baseline BMI

measurement. Missing BMI values were treated using the last observation carried forward method.

Statistical Analysis

Continuous variables are presented as means ± SD or as medians and interquartile ranges and compared using Student's *t* test or Wilcoxon rank-sum test (Mann-Whitney) as appropriate. Categorical variables are presented as absolute values (percentage) and compared using χ^2 statistics. Multivariable linear regression analyses were used to assess the relationship between cBMI with 3D echocardiography LA structure/function parameters, assessed by two analytic models: model 1 was adjusted for demographics at year 30 examination (age and race); model 2 included model 1 with adjustment for traditional CV risk factors at year 30 examination (heart rate, education level, physical activity, systolic blood pressure, smoking status, diabetes, alcohol intake, LDL cholesterol, and HDL cholesterol). Effect modification by sex on the association of cBMI with several LA parameters was observed; therefore, all assessments were stratified by sex. All analyses were conducted using STATA 14.2 version for Windows (StataCorp LP, College Station, TX). A two-tail *P* value < .05 was considered statistically significant.

RESULTS

Participant Characteristics

A total of 2,144 participants were included; their mean age was 55 ± 3.6 years, 54.8% were women, and 46.6% were black. Compared with men, women had lower weight (78.9 6 18.7 vs 89.6 ± 16.1 kg), waist circumference (88.7 ± 14.0 vs 96.9 ± 11.9 cm), moderate-to-vigorous physical activity (246 [115, 432] vs 360 [192, 594] exercise units), alcohol intake (2.4 [0, 12.2] vs 7.3 [0, 21.8] mL/day), and systolic (117.9 ± 16.7 vs 120.4 ± 13.8 mm Hg) and diastolic (71.8 ± 11.2 vs 73.2 ± 10.0 mm Hg) blood pressure; a lower proportion of women were current smokers (12.1% vs 16.4%) or diabetic (9.3% vs 12.5%). Compared with men, women had higher BMI (29.2 ± 6.7 vs 28.5 ± 4.8 kg/ m^2) and higher HDL cholesterol level (67.9 ± 19.2 vs 53.4 ± 15.4 mg/dL). Similarly, a greater proportion of women had education beyond high school than men (60.2% vs 55.1%). The cBMI was not significantly different between women (799.2 ± 175.1 BMI-years) and men (793.7 ± 117.7 BMI-years; Table 1). Only 22 (1.03%) study participants had personal history of AF or had episodes of AF during the echocardiogram examination.

3D LA Echocardiography Variables

The 3D LA frame rate achieved in our study was 25.2 ± 1.7 volume/second. Compared with men, women had better LA function as demonstrated by higher LA passive EF (20.2 ± 11.7 vs 19.8 ± 10.5%), higher LA global longitudinal strain (28.7% ± 7.3% vs 26.3% ± 7.1%), higher magnitude LA early strain rate (−1.3 ± 0.6 vs −1.2 ± 0.5 sec^{-1}), and lower LA active EF (30.4% ± 10.4% vs 31.6% ± 9.3%). However, women and men had similar LA index volumes: LAVmax (24.6 ± 7.0 vs 24.7 ± 7.0 mL/m^2), LAVmin (13.5 ± 4.3 vs 13.5 ± 4.2 mL/m^2), and LAVpreA (19.6 ± 5.9 vs 19.8 ± 5.6 mL/m^2; Table 2).

3D LV Echocardiography Variables

Compared with men, women had lower LV index volumes: end-diastolic volume (47.7 ± 11.1 vs 51.1 ± 12.7 mL/m^2), end-systolic volume (19.4 ± 6.4 vs 21.7 ± 7.5 mL/m^2), SV (28.3 ± 6.8 vs 29.4 ± 7.5 mL/m^2), lower LV index mass (62.6 ± 20.6 vs 68.2 ± 22.3 g/m^2), higher LV ejection fraction (59.6% ± 0.5% vs 57.9% ± 7.4%), and higher magnitude LV deformation: global longitudinal (−17.0% ± 3.1% vs −15.9% ± 2.8%), global circumferential (−29.3% ± 6.4% vs −28.4% ± 5.8%), and global area change strain (−41.7% ± 6.6% vs −40.2% ± 6.3%; Supplemental Table 2).

Association of cBMI and 3D LA Parameters

In the fully adjusted model, there were statistically significant additive sex interactions for the association between cBMI and LAVmin ($P = .033$), LSmax ($P = .001$), LASre ($P = .029$), and LASra ($P = .008$). Among the LA functional parameters that had significant sex interaction, the associations with cBMI were only significant for men in deformation variables (LASmax: $P_m = .002$ vs $P_w = .941$, LASre: $P_m = .015$ vs $P_w = .823$, LASra: $P_m = .047$ vs $P_w = .174$). Also, for the LA volumetric parameter with effect modification by sex, men had a higher beta coefficient and lower P value than women (LAVmin: $\beta_m = 0.20$, $P < .001$ vs $\beta_w = 0.09$, $P = .006$; Table 3, Figure 4). Also, in the fully adjusted model, cBMI was associated with higher LA total EF ($\beta_m = 0.08$, $P = .029$) and higher LA active EF ($\beta_m = 0.09$, $P = .009$) in women.

Furthermore, in the fully adjusted model, greater cBMI was independently associated with higher 3D LA volume indices in men: Vmax ($\beta_m = 0.18$, $P < .001$), Vmin ($\beta_m = 0.20$, $P < .001$), and VpreA ($\beta_m = 0.23$, $P < .001$); and in women: Vmax ($\beta_w = 0.15$, $P < .001$), Vmin ($\beta_w = 0.09$, $P = .006$), and VpreA ($\beta_w = 0.15$, $P < .001$; Table 3).

In a sensitivity analysis, excluding study participants with AF, the results did not change significantly.

Association of cBMI and 3D LV Parameters

In the fully adjusted model, greater cBMI was associated with lower absolute 3D global LV longitudinal strain in men ($\beta = 0.07$, $P = .047$). On the other hand, greater cBMI was associated with high absolute values of 3D global longitudinal strain in women ($\beta = –0.08$, $P = .012$; Supplemental Table 3).

DISCUSSION

This study demonstrated that in a community-based black and white population free of significant CV disease at the baseline examination, greater cumulative BMI from early adulthood throughout middle age was associated with LA remodeling, as evidenced by higher LA volume indices with greater cBMI in both men and women. Furthermore, we found sex differences in the association of greater cBMI and LA function, as demonstrated by the lower magnitude of LA longitudinal deformation in men and higher reservoir and active LA function in women. These associations were independent of age, race, and other traditional CV risk factors.

LA Remodeling and BMI

Adverse LA remodeling is defined as an adaptive pathophysiologic response to acute or chronic volume, pressure, and neurohumoral stressors, attempting to maintain adequate LV filling.[18] The preponderant adaptive mechanism (change in the LA geometry, chamber enlargement, or abnormal mechanical and electrical function) depends on the onset, severity, and type of the baseline stressor.[19] These LA compensatory adjustments have been classified into four categories based on the principal histologic and pathophysiologic characteristics (cardiomyocyte dependent, fibroblast dependent, mixed cardiomyocyte-fibroblast dependent, and noncollagen deposits-European Heart Rhythm Association class), and it is the foundation of atrial cardiomyopathy.[20]

Traditionally, the LA remodeling assessment performed by echocardiography, cardiac computed tomography, or cardiac magnetic resonance imaging has been concentrated on the reservoir phase, measuring LA maximum anterior-posterior linear diameter, maximum area, or maximum volume.[21] Speckle-tracking analysis is a novel technology that could be applied to images derived from those methods, allowing the evaluation of additional clinically relevant LA parameters, such as phasic volumes, EF, and longitudinal strain and strain rate. These measures have been shown to give robust prognostic information for recurrence of AF, risk of stroke, severity of diastolic dysfunction, myocardium fibrosis, and mortality, beyond the assessment of LA size alone.[22]

The pathophysiologic mechanisms of obesity-related cardiac remodeling are not entirely understood. Evidence suggests that obesity-related inflammation and subsequent neurohormonal activation increases oxidative stress and adipokine concentrations, promoting free fatty acid infiltration in cardiac myocytes.[23] Obesity produces an increase in the circulating blood volume, stroke volume, and cardiac output, as well as a decrease in peripheral vascular resistance, leading to LV enlargement, eccentric hypertrophy, and diastolic dysfunction with preserved ejection fraction.[24] However, more current investigations show a predominance of LV concentric remodeling pattern and small cavity size as a result of chronic exposure to greater BMI.[25]

Previous CARDIA investigations are in agreement with those more recent findings of LV remodeling, demonstrating the association of long-standing obesity, greater degree of adiposity, and a steeper increase in BMI with LV concentric remodeling, diastolic dysfunction, and subclinical systolic dysfunction.[26] Additionally, investigators using long-term prospective data from community-based cohorts showed associations between obesity and LA enlargement, LA dysfunction, prevalence/recurrence of AF, and incidence of heart failure, independent of CV comorbidities and obstructive sleep apnea.[27] In agreement with those prior studies, our research showed that greater cBMI had a significant association with LA adverse remodeling, as reflected by higher LA volume indices in both sexes.

LA Remodeling, Cumulative BMI, and Sex

Strong evidence supports that sex steroids play an essential role not only in the prevalence of obesity but also in adipose tissue location, metabolism, proliferation, and function.[28] Also, sex differences in obesity-related cardiac adverse remodeling have been described.[29] In the

CARDIA year 25 examination, Kishi *et al.*[30] showed that BMI significantly attenuated the differences in conventional LV diastolic parameters among sex and race. Furthermore, in those CARDIA participants without hypertension, dyslipidemia, obesity, former or current smoking, subclinical atherosclerosis, hyperthyroid- ism, or HIV at the year 25 examination, Moreira *et al.*[31] reported that women had higher myocardial systolic and diastolic deformation compared with men. Sex influences on the LV remodeling were also observed in participants of the Multi-Ethnic Study of Atherosclerosis (MESA) study, with women having higher LV circumferential shortening, torsion, and diastolic function compared with men.[32] Additionally, Donekal *et al.*,[33] studying myocardial fibrosis, LV remodeling, and myocardial mechanics, demonstrated that with greater fibrosis, men developed lower LV torsion and ejection fraction compared with women. In a prior investigation, Marques *et al.*[34] had shown gender differences in the association of inflammation and myocardial fibrosis in the MESA study cohort individuals. That study demonstrated an independent association between higher IL-6 and CRP levels with higher interstitial fibrosis just in men.[34] Moreover, Karariga *et al.*[35] demonstrated lower maladaptive LV re- modeling over a pressure overload in women than in men, which was credited to inhibition of inflammatory pathways by gene suppression. Also, Novella *et al.*[36] established that estrogen has a downregulating effect in the aging-associated proinflammatory response, protecting the myocardium from inflammation and fibrosis. Furthermore, Treibel *et al.*[37] described sex dimorphism in the cardiac remodeling on patients with severe aortic valve stenosis, with a higher prevalence of maladaptive patterns in men (LV decompensation, myocardial fibrosis, high levels of N-terminal pro-BNP, and high sensitive troponin) compared with women.[37] Finally, other features such as sex differences in lifestyle, external exposures, and CV risk factors prevalence may affect the cardiac remodeling process.

Our study results are in line with those prior investigations and provide important novel information regarding sex differences in the as- sociation of BMI with LA function. We observed that cBMI was associated with lower LA longitudinal deformation in men, whereas women had a higher reservoir and active LA function. In our view, an interaction of genetic, hormonal, and environmental might be responsible for sex differences in the LA remodeling associated with higher cBMI. Given the cross-sectional design of our study, it is not possible to distinguish a compensatory response from a lack of re- modeling in women.

Potential Clinical Implications

Results from this study provide new insights into sex differences in the long-term associations of weight gain and subclinical LA dysfunction. These results suggest that women from young adulthood to middle age may have a better compensatory adaptation to the burden of weight gain compared with men, possibly leading to a lower incidence of AF and associated stroke. Give the growing prevalence of obesity and heart failure worldwide, further studies to understand the underlying processes related to these pathophysiologic sex differences are needed, especially for elaborating sex-specific target interventions.

Strengths and Limitations

The main strength of the current study is the assessment of LA remodeling associated with 30 years of cumulative BMI from early adult-hood to middle age in a healthy community-

based biracial cohort following rigorous and stringent protocols. Moreover, the assessment of the subclinical LA dysfunction was made using a novel 3D STE method, which seems to be a more sensitive, reproducible, and accurate technique when compared with the traditional two-dimensional measurements.

In term of limitations, 30% of the eligible participants were excluded from our analysis due to unsatisfactory 3D image quality, which leads to selection bias toward the normal range or overweight population. Individuals with unsatisfactory 3D image quality had lower rest heart rate, higher systolic and diastolic blood pressure, and lower HDL cholesterol and were more likely to be obese and diabetic (Supplemental Table 4). Therefore, this study's results cannot be extrapolated to very obese individuals. The proportion of participants excluded in the current study is comparable to other cohort investigations using similar 3D technology, especially when LA assessment is implemented.[38] This may be due to the implicit tracking limitation determined by the LA thinner wall and low temporal and spatial resolution for LA imaging. Because we used the last observation carried forward method for handling missing BMI data (7.6% of the total data points were imputed) and most of the CARDIA participants had increases in BMI over 30 years, cBMI is likely underestimated in those with missing BMI measurements. However, in sensitivity analyses performed without imputation of missing BMI values, the overall results did not change significantly. The incidence/prevalence of AF and related stroke were relatively low in this healthy middle-aged cohort, restricting the study's ability to identify sex differences in the association between those entities. Lastly, due to the observational nature of this study, it was not possible to infer causality between greater cBMI and LA adverse remodeling.

CONCLUSION

Greater cumulative BMI from early adulthood through middle age was associated with higher LA volumes in men and women, lower deformation in men, and higher reservoir and active function in women. Men showed a stronger association of adverse cardiac remodeling with cBMI compared with women. Our results suggest that evaluation of LA structure and function by 3D echocardiography could be a valuable approach to detect subclinical LA remodeling associated with cBMI, highlighting a potential new understanding of the pathways relating BMI with cardiac diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

3D	Three-dimensional
AF	Atrial fibrillation
BMI	Body mass index
CARDIA	Coronary Artery Risk Development in Young Adults
cBMI	Cumulative body mass index
CV	Cardiovascular
EF	Emptying fraction
HDL	High-density lipoprotein
LA	Left atrial
LASmax	Left atrial global longitudinal strain
LASra	Left atrial late diastolic strain rate peak
LASre	Left atrial early diastolic strain rate peak
LAVmax	Maximum left atrial volume at end systole
LAVmin	Minimum left atrial volume at end diastole
LAVpreA	Preatrial contraction left atrial volume at the onset of the P wave on electrocardiogram
LDL	Low-density lipoprotein
LV	Left ventricular, ventricle
MESA	Multi-Ethnic Study of Atherosclerosis
STE	Speckle-tracking echocardiography

REFERENCES

1. Ogden CL, Carroll MD, Fryar CD, Flegal KM. Prevalence of obesity among adults and youth: United States, 2011–2014. NCHS Data Brief 2015;1–8.
2. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. JAMA 2016; 315:2284–91. [PubMed: 27272580]
3. Peters SAE, Muntner P, Woodward M. Sex differences in the prevalence of, and trends in, cardiovascular risk factors, treatment, and control in the United States, 2001 to 2016. Circulation 2019;139:1025–35. [PubMed: 30779652]
4. Neeland IJ, Poirier P, Despres JP. Cardiovascular and metabolic heterogeneity of obesity: clinical challenges and implications for management. Circulation 2018;137:1391–406. [PubMed: 29581366]
5. Vyas V, Lambiase P. Obesity and atrial fibrillation: epidemiology, pathophysiology and novel therapeutic opportunities. Arrhythm Electrophysiol Rev 2019;8:28–36. [PubMed: 30918664]

6. Lang RM, Addetia K, Narang A, Mor-Avi V. 3-Dimensional echocardiography: latest developments and future directions. JACC Cardiovasc Imaging 2018;11:1854–78. [PubMed: 30522687]
7. Wu VC, Takeuchi M, Kuwaki H, Iwataki M, Nagata Y, Otani K, et al. Prognostic value of LA volumes assessed by transthoracic 3D echocardiography: comparison with 2D echocardiography. JACC Cardiovasc Imaging 2013;6:1025–35. [PubMed: 24011776]
8. Reis JP, Allen N, Gibbs BB, Gidding SS, Lee JM, Lewis CE, et al. Association of the degree of adiposity and duration of obesity with measures of cardiac structure and function: the CARDIA study. Obesity 2014;22:2434–40. [PubMed: 25124342]
9. Khan SS, Shah SJ, Colangelo LA, Panjwani A, Liu K, Lewis CE, et al. Association of patterns of change in adiposity with diastolic function and systolic myocardial mechanics from early adulthood to middle age: the Coronary Artery Risk Development in Young Adults Study. J Am Soc Echocardiogr 2018;31:1261–9.e8.
10. Coromilas EJ, Bello NA. Gender differences in obesity-associated cardiac remodeling. Gender Genome 2018;1:76–9.
11. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR, et al. CARDIA—study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol 1988;41:1105–16. [PubMed: 3204420]
12. Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr 2019;32:1–64. [PubMed: 30282592]
13. Armstrong AC, Ricketts EP, Cox C, Adler P, Arynchyn A, Liu K, et al. Quality control and reproducibility in M-mode, two-dimensional, and speckle tracking echocardiography acquisition and analysis: the CARDIA study, year 25 examination experience. Echocardiography 2015;32:1233–40. [PubMed: 25382818]
14. Vasconcellos HD, Moreira HT, Ciuffo L, Nwabuo CC, Yared GS, Ambale-Venkatesh B, et al. Cumulative blood pressure from early adulthood to middle age is associated with left atrial remodelling and subclinical dysfunction assessed by three-dimensional echocardiography: a prospective post hoc analysis from the Coronary Artery Risk Development in Young Adults study. Eur Heart J Cardiovasc Imaging 2018;19:977–84. [PubMed: 29982431]
15. Lewis CE, Jacobs DR Jr., McCreath H, Kiefe CI, Schreiner PJ, Smith DE, et al. Weight gain continues in the 1990s: 10-year trends in weight and overweight from the CARDIA study. Coronary Artery Risk Development in Young Adults. Am J Epidemiol 2000;151:1172–81. [PubMed: 10905529]
16. Gabriel KP, Sidney S, Jacobs DR Jr., Quesenberry CP Jr., Reis JP, Jiang SF, et al. Convergent validity of a brief self-reported physical activity questionnaire. Med Sci Sports Exerc 2014;46:1570–7. [PubMed: 24496119]
17. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clinical Chemistry 1972;18:499–502. [PubMed: 4337382]
18. Vieira MJ, Teixeira R, Goncalves L, Gersh BJ. Left atrial mechanics: echocardiographic assessment and clinical implications. J Am Soc Echocardiogr 2014;27:463–78. [PubMed: 24656882]
19. Mottonen MJ, Ukkola O, Lumme J, Kesaniemi YA, Huikuri HV, Perkiomaki JS. Cardiac remodeling from middle age to senescence. Frontiers Physiol 2017;8:341.
20. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. Heart Rhythm 2017;14:e3–40. [PubMed: 27320515]
21. Armstrong AC, Liu K, Lewis CE, Sidney S, Colangelo LA, Kishi S, et al. Left atrial dimension and traditional cardiovascular risk factors predict 20-year clinical cardiovascular events in young healthy adults: the CARDIA study. Eur Heart J Cardiovasc Imaging 2014;15:893–9. [PubMed: 24534011]
22. Lima JAC, Ambale-Venkatesh B. Left atrial strain to address the cryptogenic puzzle. JACC Cardiovasc Imaging 2018;11:1566–8. [PubMed: 29153565]

23. Franssen WMA, Beyens M, Hatawe TA, Frederix I, Verboven K, Dendale P, et al. Cardiac function in adolescents with obesity: cardiometabolic risk factors and impact on physical fitness. Int J Obesity 2019;43: 1400–10.
24. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol 2009;53: 1925–32. [PubMed: 19460605]
25. Rozenbaum Z, Topilsky Y, Khoury S, Pereg D, Laufer-Perl M. Association of body mass index and diastolic function in metabolically healthy obese with preserved ejection fraction. Int J Cardiol 2019;277: 147–52. [PubMed: 30097335]
26. Reis JP, Allen N, Gunderson EP, Lee JM, Lewis CE, Loria CM, et al. Excess body mass index- and waist circumference-years and incident cardiovascular disease: the CARDIA study. Obesity 2015;23:879–85. [PubMed: 25755157]
27. Chirinos JA, Sardana M, Satija V, Gillebert TC, De Buyzere ML, Chahwala J, et al. Effect of obesity on left atrial strain in persons aged 35–55 years (the Asklepios study). Am J Cardiol 2019;123:854–61. [PubMed: 30563614]
28. Fitzgerald SJ, Janorkar AV, Barnes A, Maranon RO. A new approach to study the sex differences in adipose tissue. J Biomed Sci 2018;25:89. [PubMed: 30509250]
29. Halland H, Lonnebakken MT, Pristaj N, Saeed S, Midtbo H, Einarsen E, et al. Sex differences in subclinical cardiac disease in overweight and obesity (the FATCOR study). Nutr Metab Cardiovasc Dis 2018;28: 1054–60. [PubMed: 30177273]
30. Kishi S, Armstrong AC, Gidding SS, Colangelo LA, Venkatesh BA, Jacobs DR Jr, et al. Association of obesity in early adulthood and middle age with incipient left ventricular dysfunction and structural remodeling: the CARDIA study (Coronary Artery Risk Development in Young Adults). JACC Heart Fail 2014;2:500–8. [PubMed: 25194290]
31. Moreira HT, Nwabuo CC, Armstrong AC, Kishi S, Gjesdal O, Reis JP, et al. Reference ranges and regional patterns of left ventricular strain and strain rate using two-dimensional speckle-tracking echocardiography in a healthy middle-aged black and white population: the CARDIA study. J Am Soc Echocardiogr 2017;30:647–58.e2.
32. Yoneyama K, Gjesdal O, Choi EY, Wu CO, Hundley WG, Gomes AS, et al. Age, sex, and hypertension-related remodeling influences left ventricular torsion assessed by tagged cardiac magnetic resonance in asymptomatic individuals: the Multi-Ethnic Study of Atherosclerosis. Circulation 2012; 126:2481–90. [PubMed: 23147172]
33. Donekal S, Venkatesh BA, Liu YC, Liu CY, Yoneyama K, Wu CO, et al. Interstitial fibrosis, left ventricular remodeling, and myocardial mechanical behavior in a population-based multiethnic cohort: the Multi-Ethnic Study of Atherosclerosis (MESA) study. Circ Cardiovasc Imaging 2014;7: 292–302. [PubMed: 24550436]
34. Marques MD, Nauffal V, Ambale-Venkatesh B, Vasconcellos HD, Wu C, Bahrami H, et al. Association between inflammatory markers and myocardial fibrosis. Hypertension 2018;72:902–8. [PubMed: 30354713]
35. Kararigas G, Dworatzek E, Petrov G, Summer H, Schulze TM, Baczko I, et al. Sex-dependent regulation of fibrosis and inflammation in human left ventricular remodelling under pressure overload. Eur J Heart Fail 2014;16:1160–7. [PubMed: 25287281]
36. Novella S, Heras M, Hermenegildo C, Dantas AP. Effects of estrogen on vascular inflammation: a matter of timing. Arterioscler Thromb Vasc Biol 2012;32:2035–42. [PubMed: 22679310]
37. Treibel TA, Kozor R, Fontana M, Torlasco C, Reant P, Badiani S, et al. Sex dimorphism in the myocardial response to aortic stenosis. JACC Cardio-vasc Imaging 2018;11:962–73.
38. Goncalves A, Hung CL, Claggett B, Nochioka K, Cheng S, Kitzman DW, et al. Left atrial structure and function across the spectrum of cardiovascular risk in the elderly: the Atherosclerosis Risk in Communities Study. Circ Cardiovasc Imaging 2016;9:e004010.

HIGHLIGHTS

- Greater cBMI is associated with LA adverse remodeling.
- Higher cBMI and LA impairment are more correlated in men than in women.
- 3D echocardiography detects subclinical LA remodeling associated with cBMI.

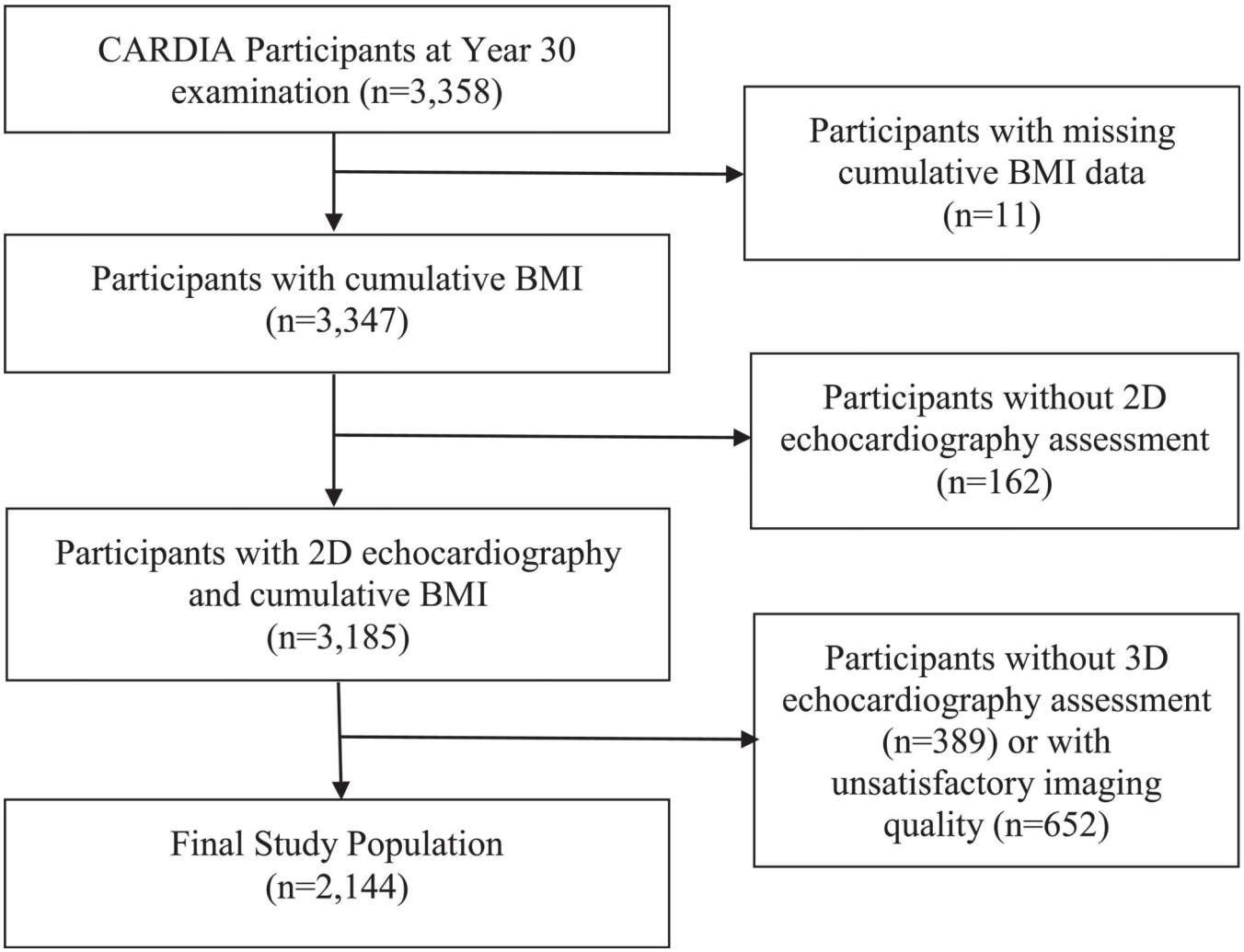

Figure 1.
Study enrollment flow chart.

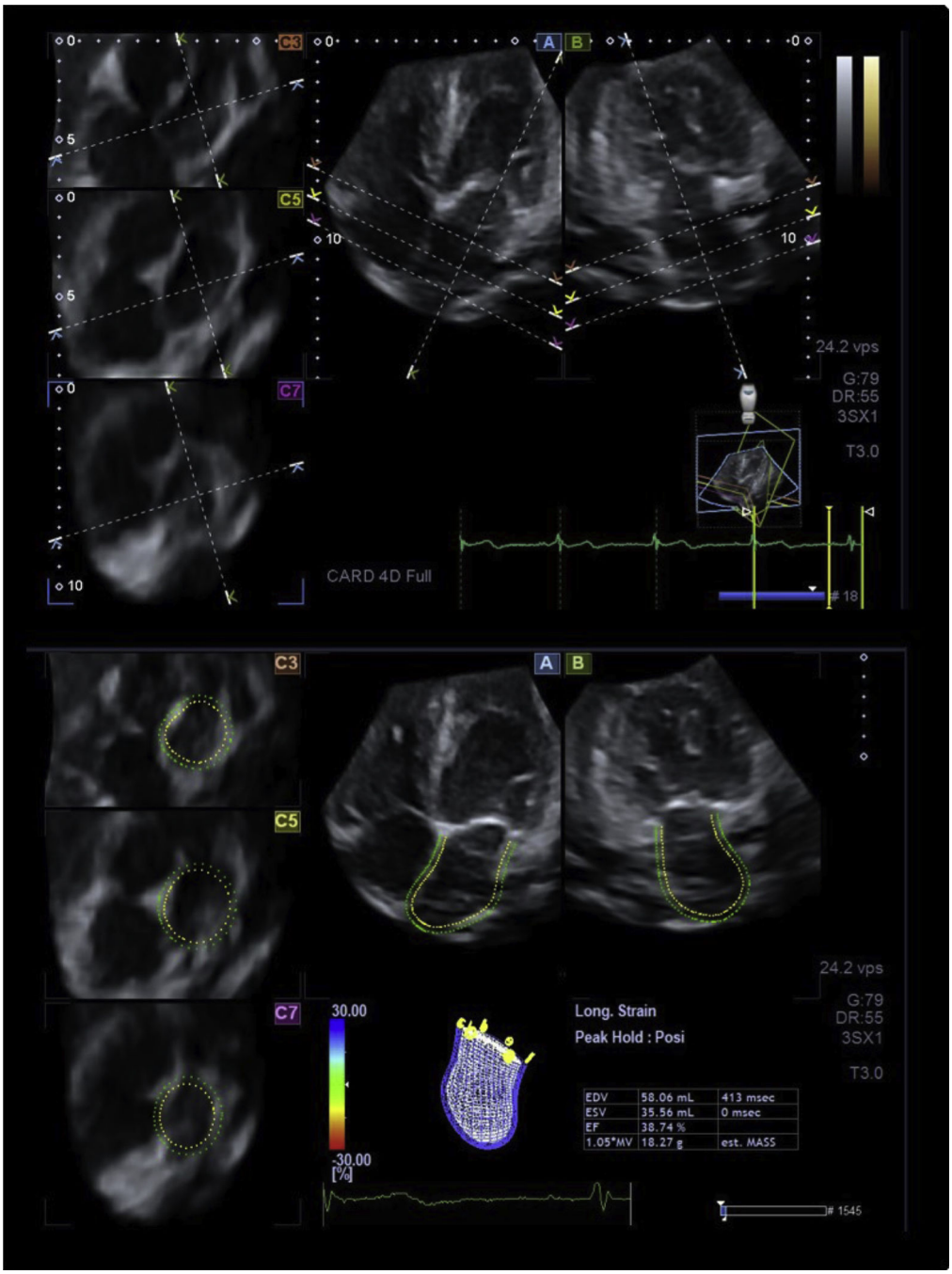

Figure 2.

Multiplane display of the LA 3D full volume showing five plane views composed of three cross-section slices ([C7], [C5], and [C3]), and two longitudinal orthogonal planes (four-chamber **[A]** and two-chamber **[B]** views).

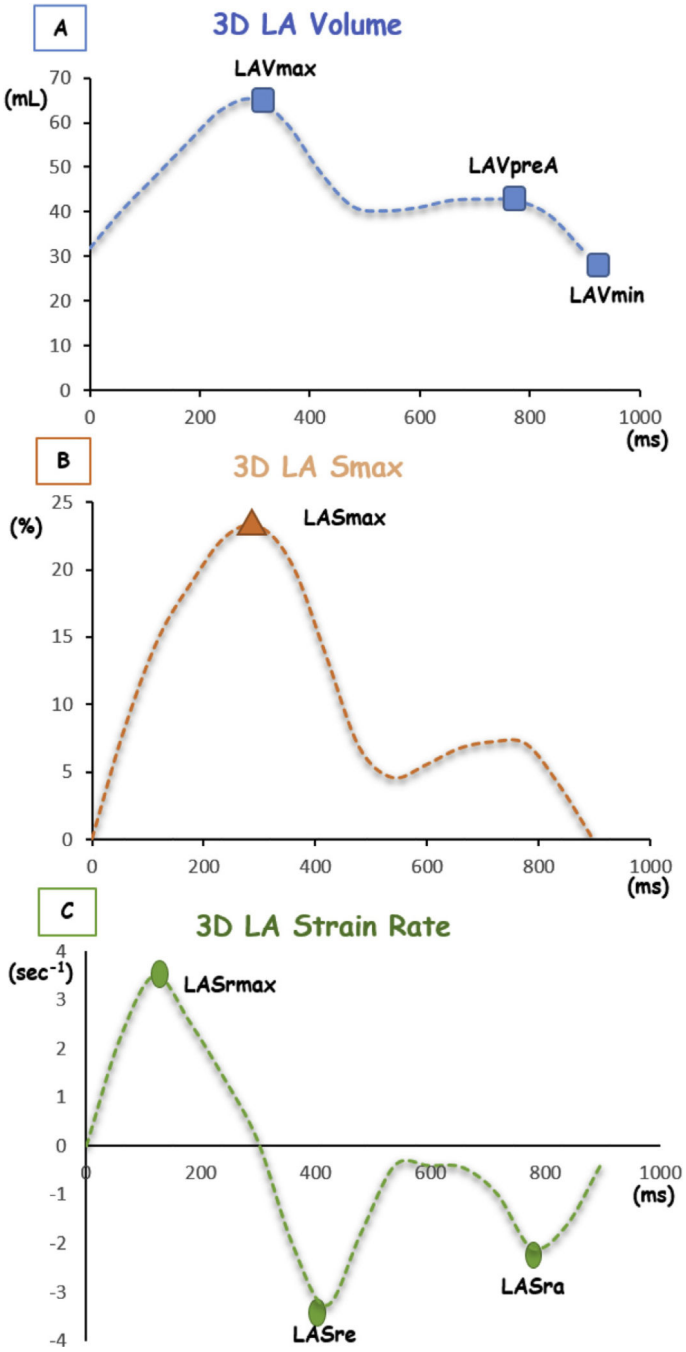

Figure 3.

Three-dimensional speckle-tracking volume analysis (**A**, *blue line*), strain analysis (**B**, *brown line*), and strain rate analysis (**C**, *green line*).

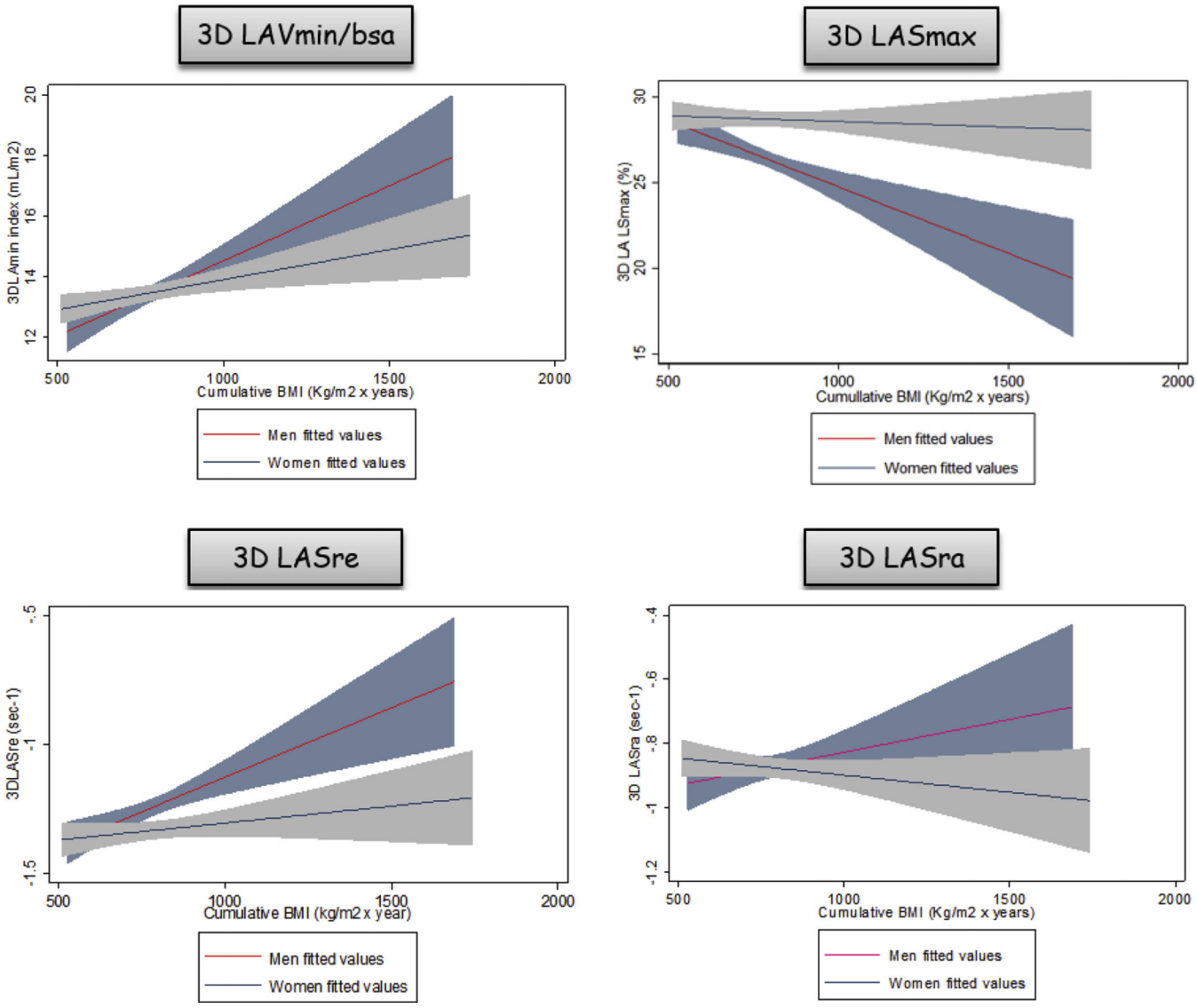

Figure 4.

Plots showing linear regression fits for men and women with the 3D echo variables on the y-axis and cumulative BMI on the *x*-axis. The shaded regions around the fitted value lines represent 95% CIs. *BSA*, Body surface area.

Table 1

Clinical characteristics of the CARDIA study participants by gender at year 30 follow-up examination (N = 2,144)

Clinical characteristics	Men (n = 965)	Women (n = 1,168)	p value*
Age, years	54.9 (3.6)	55.1 (3.7)	.362
Weight, kg	89.6 (16.1)	78.9 (18.7)	<.001
Waist circumference, cm	96.9 (11.9)	88.7 (14.0)	<.001
BMI, kg/m^2	28.5 (4.8)	29.2 (6.7)	.003
cBMI, BMI-years	793.7 (117.7)	799.2 (175.1)	.403
Resting heart rate, bpm	65.0 (9.9)	65.7 (10.0)	.084
Education > high school, n (%)	527 (55.1)	702 (60.2)	.018
Physical activity, exercise units	360 (192, 594)	246 (115, 432)	<.001
Current smokers, n (%)	155 (16.4)	140 (12.1)	.001
Alcohol intake, mL/day	7.3 (0, 21.8)	2.4 (0, 12.2)	<.001
Hypertension, n (%)	118 (35.2)	161 (39.5)	.235
Systolic blood pressure, mm Hg	120.4 (13.8)	117.9 (16.7)	<.001
Diastolic blood pressure, mm Hg	73.2 (10.0)	71.8 (11.2)	.002
Diabetes mellitus, n (%)	120 (12.5)	107 (9.3)	.016
LDL cholesterol, mg/dL	110.6 (33.1)	111.1 (31.9)	.499
HDL cholesterol, mg/dL	53.4 (15.4)	67.9 (19.2)	<.001

Data are presented as mean (SD) or median (interquartile range) unless otherwise indicated.

*P values were calculated by Student's t test, Wilcoxon rank-sum test, or χ^2 test.

Table 2

3D echocardiogram parameters of the CARDIA study participants by gender at year 30 follow-up examination ($N = 2,144$)*

3D echocardiogram LA parameters	Men (n = 965)	Woman (n = 1,168)	P value†
3D LAVmax index, mL/m^2	24.7 (7.0)	24.6 (7.0)	.617
3D LAVmin index, mL/m^2	13.5 (4.2)	13.5 (4.3)	.874
3D LAVpreA index, mL/m^2	19.8 (5.6)	19.6 (5.9)	.624
3D LA total EF, %	45.1 (9.5)	44.4 (10.2)	.132
3D LA passive EF, %	19.8 (10.5)	20.2 (11.7)	.374
3D LA active EF, %	31.6 (9.3)	30.4 (10.4)	.006
3D LASmax, %	26.3 (7.1)	28.7 (7.3)	<.001
3D LASre, sec^{-1}	−1.2 (0.5)	−1.3 (0.6)	<.001
3D LASra, sec^{-1}	−0.9 (0.5)	−0.9 (0.5)	.728

*Data are presented as mean (SD).

†P values were calculated by Student's t test.

Table 3

Association between cumulative BMI and LA structure and function by gender

	Model 1				Model 2			
	Men		Women		Men		Women	
3D LA echo parameters	*β*	*P* value	*β*	*P* value	*β*	*P* value	*β*	*P* value
3D LAVmax index, mL/m^2	0.15	<.001	0.16	<.001	0.18	<.001	0.15	<.001
3D LAVmin index*, mL/m^2	0.13	<.001	0.09	.007	0.20	<.001	0.09	.006
3D LAVpreA index, mL/m^2	0.18	<.001	0.15	<.001	0.23	<.001	0.15	<.001
3D LA total EF, %	0.17	.603	0.09	.005	−0.05	.237	0.08	.029
3D LA passive EF, %	−0.02	.589	−0.02	.631	−0.05	.220	0.03	.932
3D LA active EF, %	0.03	.459	0.11	.001	−0.03	.390	0.09	.009
3D LSmax, *%	−0.13	<.001	0.001	.977	−0.12	.002	−0.003	.941
3D LASre, *sec^{-1}	0.12	<.001	0.02	.474	0.09	.015	0.01	.823
3D LASra, *sec^{-1}	0.05	.142	−0.05	.144	0.08	.047	−0.05	.174

The multivariable linear regression model is showing coefficients per 117.7 BMI-years in men and per 175.1 BMI-years in women for cumulative BMI. Model 1 is adjusted for age and race at year 30 examination. Model 2 is model 1 with adjustment for heart rate, education level, physical activity, systolic blood pressure, smoking status, diabetes, alcohol intake, LDL cholesterol, and HDL cholesterol at year 30 examination.

*Statistically significant additive sex interactions (LAVmin [*P* = .033], LASmax [*P* = .001], LASre *[P* = .029], and LASra *[P* = .008]).