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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)

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ABSTRACT

OBJECTIVES The goal of this study was to investigate the relationship of body mass index (BMI) and its 25-year change to left ventricular (LV) structure and function.

BACKGROUND Longstanding obesity may be associated with clinical cardiac dysfunction and heart failure. Whether obesity relates to cardiac dysfunction during young adulthood and middle age has not been investigated.

METHODS The CARDIA (Coronary Artery Risk Development in Young Adult) study enrolled white and black adults ages 18 to 30 years in 1985 to 1986 (Year-0). At Year-25, cardiac function was assessed by conventional echocardiography, tissue Doppler imaging (TDI), and speckle tracking echocardiography (STE). Twenty-five–year change in BMI (classified as low: <27 kg/m^2 and high: ≥ 27 kg/m^2) was categorized into 4 groups (Low-Low, High-Low, Low-High, and High-High). Multiple linear regression was used to quantify the association between categorical changes in BMI (Low-Low as reference) with LV structural and functional parameters obtained in middle age, adjusting for baseline and 25-year change in risk factors.

RESULTS The mean BMI was 24.4 kg/m^2 in 3,265 participants included at Year-0. Change in BMI adjusted for risk factors was directly associated with incipient myocardial systolic dysfunction assessed by STE (High-High: β-coefficient $=$ 0.67; Low-High: β-coefficient $=$ 0.35 for longitudinal peak systolic strain) and diastolic dysfunction assessed by TDI (High-High: β-coefficient $=$ −074; Low-High: β-coefficient $=$ −0.45 for e′) and STE (High-High: β-coefficient $=$ −0.06 for circumferential early diastolic strain rate). Greater BMI was also significantly associated with increased LV mass/height (High-High: β-coefficient $=$ 26.11; Low-High: β-coefficient $=$ 11.87).

CONCLUSIONS Longstanding obesity from young adulthood to middle age is associated with impaired LV systolic and diastolic function assessed by conventional echocardiography, TDI, and STE in a large biracial cohort of adults age 43 to 55 years. (J Am Coll Cardiol HF 2014;2:500–8) © 2014 by the American College of Cardiology Foundation.

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Longstanding obesity is strongly related to a higher prevalence of clinical heart failure; in most studies, left ventricular (LV) function is assessed by echocardiographic left ventricular ejection fraction (LVEF) (1,2). Obesity has also been associated with adverse LV remodeling and impaired LV diastolic function (2–4); however, although current cross-sectional epidemiological studies do not show an inverse relationship between LVEF and obesity (3), a higher body mass index (BMI) has been associated with more subtle markers of LV dysfunction determined by echocardiography (5). Moreover, the effects of obesity on myocardial deformation during contraction and relaxation have not been investigated among young adults who may be more malleable to lifestyle modification, and may be at greater lifetime risk for developing heart failure.

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LV functional mechanics are complex. LV motion includes longitudinal and circumferential shortening, with radial thickening and cardiac rotation and torsion along the LV long axis. In this regard, myocardial strain is a measure of such myocardial deformation expressed as a fractional or percentage change from an object's original dimension (6). Two-dimensional (2D) speckle tracking echocardiography (STE) is an angle-independent method for deformation assessment that enables strain measurement in the longitudinal, circumferential, and radial directions based on conventional echocardiographic images. Moreover, to assess early changes in diastolic function, tissue Doppler imaging (TDI) takes advantage of the exceptional temporal resolution provided by echocardiography, and is considered the reference method (7). When compared with traditional echocardiographic measurements such as LVEF, myocardial deformation parameters assessed by STE represent earlier indicators of cardiac dysfunction (8).

We hypothesized that higher BMI measured during young adulthood (ages 18 to 30 years) predicts decreased LV function and cardiac remodeling 25 years later. We focused the analysis on the relative associations between young adulthood BMI measured at the CARDIA (Coronary Artery Risk Development in Young Adults) study baseline examination (Year-0), and the 25-year change in BMI with cardiac structure and function measured in mid-life. In addition to the conventional echocardiographic measurements, we investigated how BMI that was measured during young adulthood, as well as the difference in BMI between young adulthood and middle age (ages 43 to 55 years), relates to LV systolic and diastolic deformation assessed as myocardial strain measured by STE, as well as by TDI and conventional echocardiography.

METHODS

PARTICIPANTS. The CARDIA study is a multicenter prospective study that enrolled 5,115 white and black men and women from 4 U.S. Field Centers (Birmingham, Alabama; Oakland, California; Chicago, Illinois; and Minneapolis, Minnesota) in 1985 to 1986 (Year-0) and followed them prospectively at 7 subsequent time periods. Of 3,498 participants attending the Year-25 (2010 to 2011) examination, representing 72.0% of the surviving cohort, 3,474 participants (99.3%) underwent standard echocardiography and STE assessment at Year-25. We excluded participants that were pregnant (n = 8) or missing a covariate (n = 201) at the Year-0 or Year-25 examinations. The remaining 3,265 participants (94.0%) were included in the current analyses.

COVARIATES. Standardized protocols were used to measure height, weight, heart rate, blood pressure, lipids, glucose, smoking, educational level, and physical activity (9,10). Information on demographic characteristics, alcohol use (ml/day), smoking status (number of cigarettes/day), educational level (years), physical activity score, and medication use was collected by interview. BMI was calculated as weight (kg) divided by height in meters squared (m^2). Regarding weight status categories, normal weight was defined as BMI between 18.5 and 25.0 kg/m^2, overweight as BMI between 25 and 30 kg/m^2, and obese as BMI ≥30 kg/m^2. Alternative categories investigated were high BMI (≥27 kg/m^2) and low BMI (<27 kg/m^2). The difference in BMI from Year-0 to Year-25 was categorized into 4 groups: 1) high BMI at Year-0 and high BMI at Year-25 (High-High); 2) low BMI at Year-0 and high BMI at Year-25 (Low-High); 3) high BMI at Year-0 and low BMI at Year-25 (High-Low); and 4) low BMI at Year-0 and low BMI at Year-25 (Low-Low). After a 5-min rest, blood pressure was measured 3 times with a random-zero sphygmomanometer and the last 2 values averaged; resting heart rate was also measured. The presence of diabetes was assessed at each examination based on a combination of medication use questions, fasting plasma glucose ≥126 mg/dl (Year-0 and Year-25), 2-h glucose ≥200 mg/dl (Year-25), or HbA_{1c} ≥6.5%

ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional
A = late peak diastolic mitral flow velocity
BMI = body mass index
E = early peak diastolic mitral velocity
e′ = peak early diastolic mitral annular velocity
Ecc = circumferential peak strain
Ecc_SRe = circumferential peak early diastolic strain rate
Ell = 4-chamber longitudinal peak strain
Ell_SRe = 4-chamber longitudinal peak early diastolic strain rate
LAV = left atrial volume
LV = left ventricular
LVEDV = left ventricular end-diastolic volume
LVEF = left ventricular ejection fraction
LVESV = left ventricular end-systolic volume
LVM = left ventricular mass
LVSV = left ventricular stroke volume
STE = speckle tracking echocardiography
TDI = tissue Doppler imaging

(Year-25). New cases of diabetes at the Year-25 examination were computed if the criteria for diabetes were ever met over the period between the Year-0 and Year-25 examinations.

ECHOCARDIOGRAPHIC ASSESSMENT. Doppler echocardiography and 2D-guided M-mode echocardiography were performed using an Artida cardiac ultrasound scanner (Toshiba Medical Systems, Otawara, Japan) by trained sonographers using standardized protocols across all field centers. Experienced sonographers made measurements from digitized images using a standard software offline image analysis system (Digisonics, Houston, Texas). In the conventional echocardiographic parameters, left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were measured from the apical 4-chamber view for the measurement of left ventricular stroke volume (LVSV) and LVEF based on the American Society of Echocardiography recommendations (11). Left atrial volume (LAV) was measured from the apical 4-chamber view (11). Left ventricular mass (LVM) was derived from the Devereux formula (11). LVEDV, LVESV, LVSV, LAV, and LVM were indexed to body height (LVEDV/height, LVESV/height, LVSV/height, LAV/height, and LVM/height). Body surface area was not used to adjust for body size because body surface area is strongly related to BMI—the main input variable of interest in this study. In the diastolic functional parameters, peak velocities of the early phase (E) and late phase (A) of the mitral inflow, and their ratio (E/A ratio) were measured from pulsed-Doppler echocardiography recordings of transmitral flow. Using TDI, early peak diastolic mitral annular velocity (e′) at the septal and lateral mitral annulus were measured (7). The e′ was calculated from the average of the septal and lateral mitral annulus. E/e′ ratio was calculated as an index of LV filling pressures (7).

2D STE ANALYSIS. STE images for myocardial strain and strain rate measurements were analyzed in a 16-segment basis for LV mid-wall layer, using Wall Motion 2D Tracking software (UltraExtend Version 2.7, Toshiba Medical Systems, Otawara, Japan). Three cardiac cycles from each view were recorded for offline analyses. Strain was calculated as the change in segment length relative to its end-diastolic length from peak systolic values. Longitudinal strain and strain rate curves were assessed from 4-chamber views. Circumferential strain and strain rate were assessed from the short-axis view at the mid-ventricular level. Global strain values were calculated as the average of segmental peak strains. Global strain rate values were also calculated from the average of segmental peak values for each phase (in s^{-1}). The STE image set in each view was excluded if more than 3 segments were improperly tracked. STE indexes of systolic cardiac deformation at the Year-25 examination included 4-chamber longitudinal peak strain (Ell), circumferential peak strain (Ecc), 4-chamber longitudinal systolic strain rate, and circumferential systolic strain rate. Diastolic STE indices were peak early diastolic strain rate in the 4-chamber longitudinal (Ell_SRe) and circumferential (Ecc_SRe) directions.

STATISTICAL ANALYSIS. Descriptive statistics were displayed using means and SD for continuous variables and group proportions for categorical variables. Paired Student's *t* tests were used to compare means between Year-0 and Year-25. The Pearson correlation coefficient was calculated to assess the association of continuous LV functional measures with BMI at the Year-0 and Year-25 examinations.

Unadjusted and multiple linear regression models assessed the cross-sectional associations between Year-0 BMI and Year-25 BMI to STE parameters and conventional echocardiographic parameters measured at the Year-25 examination. Multiple linear regression models were adjusted for the following traditional cardiovascular disease risk factors: age (years), sex (male/female), race (white/African American), diabetes status (yes/no), systolic blood pressure (mm Hg), heart rate (beats/min), total cholesterol (mg/dl), high-density lipoprotein cholesterol (mg/dl), alcohol use (ml/day), physical activity (exercise unit), use of antihypertensive medication (yes/no), educational level (≤12 years/>12 years), and number of cigarettes/day. To better quantify the importance of baseline and Year-25 BMI, the cohort was stratified for BMI into 4 groups at those time points (BMI <27 kg/m^2 = low and BMI ≥27 kg/m^2 = high), and differences between groups for LV structure and function at Year-25 were evaluated, accounting for similar covariates and expressed as β-coefficients in comparison to the Low-Low group. A 2-sided p value of <0.05 was considered for statistical significance and was not adjusted for multiple comparisons. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Cohort characteristics at the baseline and Year-25 examinations are shown in **Table 1**. The mean age at baseline was 25.1 ± 3.6 years; 56.3% of all participants were women, and 53.7% were white. The prevalence of obese and overweight CARDIA participants increased from Year-0 to Year-25 (11.1% to 43.1%, and

23.3% to 31.3%, respectively, $p < 0.0001$ for BMI categories). The High-High group (BMI ≥27 kg/m^2 both at Year-0 and Year-25) included 671 (20.6%) participants; the Low-High group (BMI <27 kg/m^2 at Year-0, but ≥27 kg/m^2 at Year-25) included 1,344 (41.2%) participants; the High-Low group (BMI ≥27 kg/m^2 at Year-0, but <27 kg/m^2 at Year-25) included 22 (0.7%) participants; and the Low-Low group (BMI <27 kg/m^2 both at Year-0 and Year-25) included 1,228 (37.6%) participants. Moreover, the descriptive statistics for conventional echocardiographic and STE parameters at the Year-25 examination are shown in Online Table 1. All conventional echocardiographic parameters were within the normal range based on age.

YEAR-25 EXAMINATION CROSS-SECTIONAL RELATIONSHIPS. For LV structure, when analyzed as a continuous variable, a greater Year-25 BMI was associated with higher LVEDV/height, LVESV/height, LVSV/height, LVM/height, and LVM/LVEDV (Online Table 2). Greater Year-25 BMI was independently associated with higher levels of all cardiac structural indexes in adjusted analyses.

For LV systolic function, Year-25 BMI was not correlated with LVEF (Online Table 2); however, there were positive correlations of Year-25 BMI with speckle tracking deformational indexes reflecting reduced contractile performance such as with Ell and Ecc. Year-25 BMI was also positively correlated with longitudinal systolic strain rate, reflecting less contractile behavior.

For LV diastolic function, greater Year-25 BMI was independently associated with lower E/A ratio, lower e′, higher E/e′ ratio, and greater LAV/height in multiple linear regression models, but the associations between Year-25 BMI and strain rate indexes were not statistically significant (Online Table 2).

TABLE 1 Participant Characteristics at the CARDIA Year-0 and Year-25 Examinations (N = 3,265)

	Year-0	Year-25	p Value
Age, yrs	25.1 ± 3.6	50.1 ± 3.6	–
Female, %	1,837 (56.3)	–	–
White, %	1,753 (53.7)	–	–
Height, cm	170.3 ± 9.4	170.4 ± 9.4	–
Weight, kg	70.9 ± 15.8	87.3 ± 22.0	<0.0001
BSA, m^2	1.8 ± 0.2	2.0 ± 0.3	<0.0001
BMI, kg/m^2	24.4 ± 4.9	30.1 ± 7.2	<0.0001
BMI categories, kg/m^2			<0.0001
BMI <18.5 (underweight), %	138 (4.2)	22 (0.7)	–
18.5 ≤ BMI <25.0 (normal), %	2,006 (61.4)	814 (24.9)	–
25.0 ≤ BMI < 30 (overweight), %	760 (23.3)	1,023 (31.3)	–
30 ≤ BMI (obese), %	361 (11.1)	1,406 (43.1)	–
Waist circumference, cm	77.5 ± 11.1	94.3 ± 15.9	<0.0001
Hip circumference, cm	100.0 ± 10.3	110.6 ± 14.3	<0.0001
Waist-hip ratio	0.78 ± 0.07	0.85 ± 0.09	<0.0001
Heart rate, beats/min	69.0 ± 10.7	66.6 ± 10.6	<0.0001
Systolic blood pressure, mm Hg	109.9 ± 10.7	119.7 ± 16.1	<0.0001
Diastolic blood pressure, mm Hg	68.3 ± 9.3	74.8 ± 11.2†	<0.0001
Diabetes mellitus, %	13 (0.4)	464 (14.2)	<0.0001
Number of cigarettes/day	3.4 ± 7.4	1.9 ± 5.2	<0.0001
Antihypertensive medication use, %	22 (0.7)	867 (26.6)	<0.0001
Educational level ≤12 yrs	1,124 (34.4)	726 (22.2)	<0.0001
Physical activity, EU	419.9 ± 297.6	340.8 ± 275.9	<0.0001
Alcohol use, ml/day	11.4 ± 19.7	11.7 ± 23.3	0.460
Total cholesterol, mg/dl	177.2 ± 32.8	192.5 ± 36.6	<0.0001
HDL cholesterol, mg/dl	53.2 ± 12.8	58.1 ± 18.1	<0.0001
LDL cholesterol, mg/dl	109.6 ± 30.4*	112.2 ± 32.5†	<0.0001
Triglycerides, mg/dl	71.4 ± 45.0*	113.0 ± 83.6†	<0.0001

Values are mean ± SD or n (%). *n = 3,181 for LDL cholesterol and n = 3,190 for triglycerides. †n = 3,264 for diastolic blood pressure, n = 3,121 for LDL cholesterol, and n = 3,150 for triglycerides.

BSA = body surface area; BMI = body mass index; CARDIA = Coronary Artery Risk Development in Young Adults study; EU = exercise unit; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

PROSPECTIVE RELATIONSHIPS WITH BMI CHANGES OVER 25 YEARS. LV structure. At the Year-0 CARDIA examination, greater BMI was independently associated with all structural parameters after adjustment for risk factors (**Table 2**). In particular, the relationship between Year-0 BMI and LVM/height remained the strongest association for Year-0 BMI among all structural indexes. When both Year-0 and Year-25 BMI measures were added to the regression model (Online Table 3), both Year-0 BMI and Year-25 BMI remained significantly related to all global LV structural parameters.

The relationship of BMI category at Year-0 and Year-25 to LV structural parameters are shown in **Table 3** and **Figure 1**. Being in the High-High or Low-High group was significantly related to increased LV structural parameters compared with the Low-Low group; because β-coefficients from the High-High group are twice that of Low-High group, the importance of early obesity is emphasized. The model indicates the importance of Year-0 BMI because the β-coefficient for the Low-High group is highly significant and roughly one-half that of the β-coefficient for the High-High group. Similarly, the β-coefficient of LVM/height for the High-Low group is larger than the Low-High group, suggesting that early exposure to obesity is more important than late exposure. We show additional results using a BMI cutoff of 30 to distinguish between the High/Low groups instead of a cutoff of BMI of 27 (Online Table 4). The relationship between change in BMI category and echocardiographic parameters remain consistent irrespective of the BMI cutoff chosen.

LV systolic function. Year-0 BMI was negatively correlated with LVEF (**Table 2**). In the speckle tracking

TABLE 2 Relationship Between Year-0 BMI and Year-25 LV Structural and Functional Indexes

Conventional/STE Parameters	n	r	Year-0 BMI (kg/m²) Unadjusted β-Coefficients (SE)	Partial r*	Multiple Regression β-Coefficients (SE)†
Structural indexes					
LV end-diastolic volume/height, ml/m	3,024	0.27	0.94 (0.06)‡	0.27	0.92 (0.06)‡
LV end-systolic volume/height, ml/m	3,023	0.21	0.45 (0.04)‡	0.20	0.45 (0.04)‡
LV stroke volume/height, ml/m	3,023	0.25	0.49 (0.04)‡	0.23	0.47 (0.04)‡
LV mass/height, g/m	2,935	0.43	2.72 (0.11)‡	0.37	2.33 (0.11)‡
LV mass/LV end-diastolic volume ratio§	2,763	0.19	2.00 (0.20)‡	0.14	2.00 (0.20)‡
Systolic functional indexes					
LV ejection fraction, %	3,023	−0.05	−0.08 (0.03)‖	−0.06	−0.10 (0.03)§
Ell, %	2,855	0.14	0.07 (0.01)‡	0.07	0.04 (0.01)‡
Ecc, %	2,914	0.09	0.05 (0.01)‡	0.06	0.04 (0.01)‖
Diastolic functional indexes					
E/A ratio	3,214	−0.18	−0.01 (0.001)‡	−0.11	−0.01 (0.001)‡
e′, cm/s	3,202	−0.18	−0.09 (0.01)‡	−0.11	−0.05 (0.01)‡
E/e′ ratio	3,178	0.17	0.08 (0.01)‡	0.10	0.05 (0.01)‡
Left atrium volume/height, ml/m	3,226	0.35	0.66 (0.03)‡	0.31	0.63 (0.03)‡
Ell_SRe, s^{-1}	2,843	−0.12	−0.01 (0.001)‡	−0.05	−0.003 (0.001)‖
Ecc_SRe, s^{-1}	2,909	−0.08	−0.01 (0.001)‡	−0.06	−0.005 (0.001)‡

LV end-diastolic volume, LV end-systolic volume, LV stroke volume, left atrium volume, and LV mass were indexed to body height (m). *Partial r is the square root of the partial r^2 in the multiple regression models, corresponding to the β-coefficient. †Year-0 BMI was adjusted for Year-0 age, sex, race + diabetes, systolic blood pressure, heart rate, total cholesterol, high-density lipoprotein cholesterol, alcohol consumption/day, activity level, use of anti-hypertensive medication, educational level, and number of cigarettes/day. ‡$p < 0.001$. §LV mass/LV end-diastolic volume ratio was multiplied by 100. ‖$p < 0.01$.

BMI = body mass index; e′ = peak early diastolic mitral annular velocity; E/A = early to late peak diastolic mitral flow velocity ratio; E/e′ = ratio of early peak diastolic mitral velocity/peak early diastolic mitral annular velocity; Ell = longitudinal peak systolic strain; Ecc = circumferential peak systolic strain; Ell_SRe = longitudinal peak early diastolic strain rate; Ecc_SRe = circumferential peak early diastolic strain rate; LV = left ventricular; STE = speckle tracking echocardiography.

analysis, Year-0 BMI was positively correlated with all strain and strain rate indexes. The Ell-BMI relationship was the strongest among systolic indexes after adjustment for risk factors. Year-0 BMI was independently associated with LVEF. When both Year-0 and Year-25 were added to the regression model (Online Table 3), the association between Year-25 BMI with Ell remained stronger than that of Year-0 BMI with Ell. On the other hand, Year-0 BMI had a stronger association with LVEF and Ecc than did Year-25 BMI.

Table 3 and Figure 1 show no association of BMI categorical changes over the 25 years of follow-up with LV systolic function. LVEF was not associated with categorical changes in BMI over the 25 years of follow-up. Importantly, however, the High-High and Low-High groups had significant associations with Ell when compared with the Low-Low group. The model also indicates the importance of Year-0 BMI because the β-coefficient for the Low-High group was highly significant and roughly one-half that of the β-coefficient for the High-High group. Similarly, the High-High group had worse Ecc (i.e., circumferential shortening) than the Low-Low group.

LV diastolic function. Having a greater Year-0 BMI was associated with low E/A ratio, low e′, high E/e′ ratio, and high LAV/height (Table 2). In the speckle tracking analyses, greater Year-0 BMI also corresponded with a low Ell_SRe and low Ecc_SRe, reflecting slower diastolic filling (Table 2). Year-0 BMI remained significant for all LV diastolic parameters after adjustment for risk factors. When both Year-0 and Year-25 BMI measures were included in the model (Online Table 3), Year-25 BMI exhibited a stronger association with standard and tissue Doppler echocardiographic parameters than Year-0 BMI; however, the associations of Year-0 BMI with both Ell_SRe and Ecc_SRe were stronger than were those for Year-25 BMI.

The relationships of categorical 25-year changes in BMI to LV diastolic function are shown in Table 3 and Figure 1. Being in the High-High or the Low-High group was significantly associated with lower E/A ratio; e′, E/e′ ratio, and LAV index were higher relative to the Low-Low group. This model indicates the importance of becoming obese for diastolic function because the coefficient for the Low-High group was highly significant for all standard and tissue Doppler echocardiographic parameters. The β-coefficient of diastolic parameters for the High-High group was almost 1.7 times larger than the β-coefficient for the Low-High group. Furthermore, the High-High group

TABLE 3 Relationship of BMI Status at Year-0 and Year-25 With Year-25 LV Structural and Functional Indices

Conventional/STE Parameters	n	High-High (n = 671) β-Coefficients (SE)	Low-High (n = 1,344) β-Coefficients (SE)	High-Low (n = 22) β-Coefficients (SE)
Structural indices				
LV end-diastolic volume/height, ml/m	3,024	10.61 (0.82)*	5.54 (0.63)*	2.52 (3.05)
LV end-systolic volume/height, ml/m	3,023	4.80 (0.54)*	2.01 (0.41)*	2.16 (2.01)
LV stroke volume/height, ml/m	3,023	5.78 (0.48)*	3.52 (0.36)*	0.32 (1.78)
LV mass/height, g/m	2,935	26.11 (1.40)*	11.87 (1.06)*	15.52 (5.21)†
LV mass/LV end-diastolic volume ratio‡	2,763	19.1 (3.00)*	9.60 (2.20)*	14.0 (10.6)
Systolic functional indices				
LV ejection fraction, %	3,023	−0.63 (0.41)	0.30 (0.32)	−1.12 (1.53)
Ell, %	2,855	0.67 (0.134)*	0.35 (0.102)*	−0.24 (0.510)
Ecc, %	2,914	0.50 (0.165)‡	0.06 (0.125)	0.53 (0.657)
Diastolic functional indices				
E/A ratio	3,214	−0.12 (0.018)*	−0.07 (0.014)*	−0.10 (0.071)
e′, cm/s	3,202	−0.74 (0.114)*	−0.45 (0.088)*	−0.70 (0.450)
E/e′ ratio	3,178	0.64 (0.117)*	0.43 (0.091)*	1.16 (0.462)§
Left atrium volume/height, ml/m	3,226	7.78 (0.46)*	4.11 (0.36)*	2.12 (1.78)
Ell_SRe, s^{-1}	2,843	−0.03 (0.014)	−0.008 (0.011)	−0.03 (0.055)
Ecc_SRe, s^{-1}	2,909	−0.06 (0.019)†	−0.02 (0.015)	−0.100 (0.076)

β-Coefficients represent the difference between the group listed and the Low-Low group after adjustment for covariates structural and functional indices. LV end-diastolic volume, LV end-systolic volume, LV stroke volume, left atrium volume, and LV mass were indexed to body height (in meters). High-High = Year-0 BMI ≥27 and Year-25 BMI ≥27; High-Low = Year-0 BMI ≥27 and Year-25 BMI <27; Low-High = Year-0 BMI <27 and Year-25 BMI ≥27. Model: Categorical BMI groups were included as covariates and were adjusted for baseline age, sex, race + both Year-0 and 25-year change in diabetes, systolic blood pressure, heart rate, total cholesterol, high-density lipoprotein cholesterol, alcohol consumption/day, activity level, use of antihypertensive medication, educational level, and number of cigarettes/day. *$p < 0.001$ versus Low-Low (n = 1,228) as the reference among 4 BMI groups; †$p < 0.01$ versus Low-Low (n = 1,228) as the reference among 4 BMI groups; ‡LV mass/LV end-diastolic volume ratio was multiplied by 100. §$p < 0.05$ versus Low-Low (n = 1,228) as the reference among 4 BMI groups.

Abbreviations as in Table 2.

was also associated with worse Ecc_SRe; however, Ell_SRe was not associated with BMI groups.

DISCUSSION

BMI measured at age 18 to 30 years and change in BMI over 25 years were consistently related to LV structural remodeling and incipient LV dysfunction 25 years later. In our study, both cross-sectional and 25-year changes in BMI show that higher BMI in young adults is independently associated with future decreased LV systolic and diastolic function, as well as increased LV volumes, LVM, and LAV.

RELATIONSHIP OF BMI WITH GLOBAL LV STRUCTURE. Obesity contributes to the development and progression of myocardial remodeling by multiple mechanisms (12,13). Greater adiposity is associated with hemodynamic volume overload, leading to LV dilation and hypertrophy (2,3,12–14). The Framingham Offspring Study, performed in middle-aged adults (mean age of 45 years), reported that high BMI was associated with increased LV volume and LVM over a 16-year period (15,16). We show that a higher BMI in healthy young adults 18 to 30 years of age, as well as 25 years later, was strongly associated with larger LV volume, greater LVM/height, and greater LVM/LVEDV ratio, independent of other risk factors over a 25-year time period. Our results are based on data from a much younger cohort (the CARDIA study) than the Framingham Offspring Study.

RELATIONSHIP OF BMI WITH LV SYSTOLIC FUNCTION. Cross-sectional analysis at Year-25 showed that higher BMI was associated with lower longitudinal myocardial deformation, but not with reduced LVEF. Similar to our findings in cross-sectional analysis, Turkbey et al. (3) reported that LVEF assessed by magnetic resonance imaging was not significantly associated with BMI in the older population cohort of the MESA (Multi-Ethnic Study of Atherosclerosis) study. Furthermore, a prior smaller cross-sectional study—which assessed the relationship of BMI with LV function using deformation parameters—showed an inverse relationship of obesity to systolic strain and strain rate measured by tissue Doppler, but not to LVEF (17).

Prospective longitudinal studies based on repeated examinations may produce more meaningful findings than cross-sectional analyses. Higher BMI in healthy young adulthood or increase in BMI between young

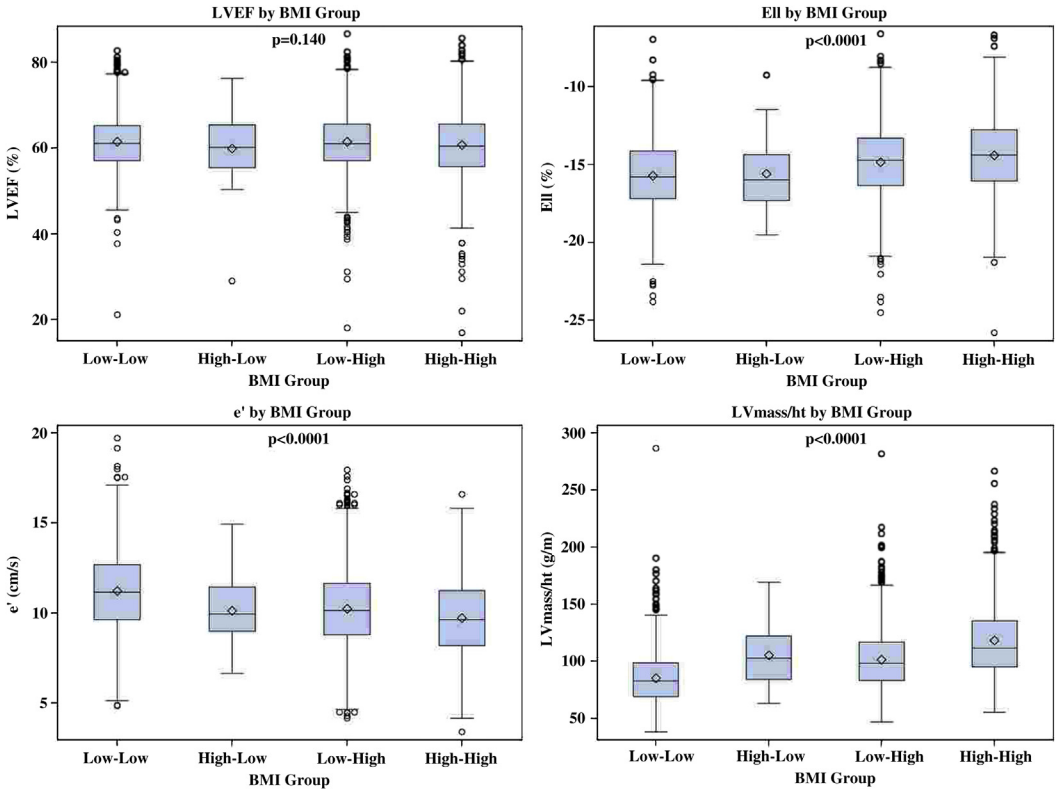

FIGURE 1 Mean LV Structural and Functional Parameters in Each BMI Group

Comparisons across categorical changes in the body mass index (BMI) groups were by Student *t* test from analysis of variance. e′ = peak early diastolic mitral annular velocity; Ell = 4-chamber longitudinal peak strain; LV = left ventricular; LVEF = left ventricular ejection fraction; $LV_{mass/ht}$ = left ventricular mass divided by body height.

adulthood and middle age was associated with early decreased systolic myocardial deformation by STE in the CARDIA study. These analyses suggest that early obesity and chronic exposure to obesity are stronger predictors of LV dysfunction. Longitudinal strain and strain rate were altered to a greater extent than circumferential strain/strain rate among the STE parameters.

Moreover, our findings suggest the activation of compensatory structural mechanisms to preserve cardiac output through maintaining a stable LVEF and enlarged LV cavity size (14,18). Even if longitudinal and circumferential myocardial shortening were lower at higher levels of BMI, higher BMI was associated with higher LVSV/height, higher LVM/height, and greater LV volume. Greater LV volume with LV remodeling leads to increased LVSV, thus preserving the cardiac output (2,18). Systolic radial thickening results from longitudinal and circumferential shortening, as well as LV torsion (19). Mechanisms of increased radial thickening to compensate for decreased circumferential shortening and to preserve cardiac output have been suggested previously (20). Moreover, longitudinal strain and strain rate parameters, to assess cardiac deformation, are known to be more sensitive parameters in the early stage of worsening LV systolic function than LVEF (5,17). In our study, 25-year changes in BMI were associated with STE-derived systolic dysfunction, but not with LVEF reduction.

RELATIONSHIP OF BMI WITH LV DIASTOLIC FUNCTION. Previous studies have shown relationships of SRe with pre-load, LV relaxation, and regional myocardial stiffness (21). Identifying which SRe parameter is the most sensitive index of LV diastolic function in obesity has been controversial (22,23). The potential reasons for discrepancy in recent studies include sample size, population characteristics, and methodological differences in the assessment of myocardial deformation. In our study, lower longitudinal and

circumferential SRe were significantly associated with higher BMI.

Importantly, higher BMI also related significantly to standard measurements of diastolic dysfunction such as LAV enlargement, higher E/e′, and lower e′ values as indicators of impaired LV filling (18). Similarly, in the CABL (Cardiac Abnormalities and Brain Lesion) study—a cohort with an average age of 70 years—a higher BMI was cross-sectionally associated with LV diastolic dysfunction, independent of LVM or the presence of cardiovascular risk factors (4). The relationship of higher BMI or differences in BMI across a 25-year period with lower LV diastolic mechanics among young adults and over 25 years into early adulthood, however, has not been previously investigated. Our study indicates that higher BMI is associated with lower LV diastolic function, independent of other risk factors using both standard measurements and STE. The pathophysiological mechanisms underlying this relationship have yet to be elucidated in detail.

STUDY LIMITATIONS. We did not attempt to address any contribution of regional adipose distribution through the use of anthropometric measures such as waist circumference or noninvasive imaging techniques; therefore, we cannot identify specific fat depots associated with the demonstrated alterations of LV structure and function. Close correlations between BMI and measures of fat mass or waist circumference, however, have been demonstrated previously in other populations ($r = 0.97$ to 0.98 for fat mass and $r = 0.86$ to 0.89 for waist circumference) (3). Finally, we could not assess torsion, rotation, twist, or untwist as LV functional parameters in the CARDIA study, given its large magnitude as a prospective longitudinal study of cardiovascular risk factors and subclinical disease in young adults.

CLINICAL IMPLICATIONS AND PUBLIC HEALTH. The prevalence of obesity for adults has more than doubled in the world since 1980 (24,25). At least 2.8 million adults die each year as a result of being overweight or obese (24). Current policies regarding prevention of heart failure recommend maintaining normal body weight because excess BMI in young adulthood is a risk factor for heart failure antecedents, such as hypertension and diabetes (24,25). We have shown in this cohort that young adults who maintain appropriate weight or obese adult lose weight over 25 years have favorable LV remodeling; however, this analysis suggests that early obesity still has a residual adverse effect (26).

Myocardial deformation parameters represent incipient indicators of cardiac dysfunction compared with traditional echocardiographic measurements (8,27). Additionally, myocardial deformation may predict clinical heart failure with either depressed or preserved LVEF (27,28). Our study findings indicate that obesity in early adulthood or developed during the first 25 years of early adulthood is related to early measures of systolic and diastolic dysfunction in middle-aged individuals, emphasizing the importance of prevention of obesity development early in life (29). These findings suggest that, left unchecked, the ongoing obesity epidemic may increase the lifetime risk of incident heart failure in the general population (30).

CONCLUSIONS

Greater BMI during young adulthood and middle age is associated with reduced LV systolic and diastolic function assessed by myocardial deformation in the CARDIA study comprising a large biracial cohort of adults 43 to 55 years of age. Greater BMI in early adulthood is also associated with LV hypertrophy, LV dilation, and preserved LVEF. Our study is the first to demonstrate the significant structural and functional effects of obesity on the heart in early adulthood and middle age in an otherwise healthy population.

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KEY WORDS **echocardiography, left ventricular function, left ventricular remodeling, obesity, risk factors, speckle tracking echocardiography, tissue Doppler imaging**

APPENDIX **For supplemental tables, please see the online version of this article.**