Original Article

Cardiometabolic Traits and Systolic Mechanics in the Community

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Background—Obesity and cardiometabolic dysfunction are associated with increased risk of heart failure and other cardiovascular diseases. We sought to examine the association of cardiometabolic traits with left ventricular (LV) cardiac mechanics. We hypothesized that specific obesity-related phenotypes are associated with distinct aspects of LV strain.

Methods and Results—We evaluated the associations of obesity-related phenotypes, including central adiposity, diabetes mellitus, insulin resistance, and circulating adipokine concentrations with echocardiographic measures of LV mechanical function among participants of the Framingham Heart Study Offspring and Third Generation cohorts. Among 6231 participants, the mean age was 51±16 years, and 54% were women. Greater body mass index was associated with worse LV longitudinal strain, radial strain (apical view), and longitudinal synchrony (multivariable-adjusted $P<0.0001$). After accounting for body mass index, we found that central adiposity, as measured by waist circumference, was associated with worse global longitudinal strain and synchrony ($P\leq0.006$). Measures of insulin resistance, dyslipidemia, and diabetes mellitus also were associated with distinct aspects of LV mechanical function. Circulating leptin concentrations were associated with global longitudinal and radial strain (apical view, $P<0.0001$), whereas no such association was found with leptin receptor, adiponectin, or C-reactive protein.

Conclusions—Our findings highlight the association of central obesity and related cardiometabolic phenotypes above and beyond body mass index with subclinical measures of LV mechanical function. Interestingly, obesity-related traits were associated with distinct aspects of LV mechanics, underscoring potential differential effects along specific LV planes of deformation. These findings may shed light onto obesity-related cardiac remodeling and heart failure. **(*Circ Heart Fail*. 2017;10:e003536. DOI: 10.1161/CIRCHEARTFAILURE.116.003536.)**

Key Words: adipokine ■ echocardiography ■ epidemiology ■ left ventricular function ■ obesity

More than 1 in 4 adults are obese in the United States, and more than half of the population is projected to be obese by 2030.[1] Obesity and metabolic disease are closely related, and both represent major risk factors for cardiovascular disease, including heart failure.[2–5] Moreover, subclinical changes in cardiac structure and function are apparent in cardiometabolic disease and may precede the future development of heart failure among obese individuals.[6–8] The underlying mechanisms driving cardiac remodeling in obesity are likely multifaceted and include systemic inflammation and cardiac fibrosis.[9] Obesity may also have direct myocardial effects via circulating adipose-derived hormones such as adiponectin and leptin, which in turn have been linked to clinical heart failure.[10,11]

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Advanced echocardiographic imaging techniques have enabled the assessment of subclinical cardiac dysfunction. Specifically, echocardiographic strain measures have allowed for sensitive quantification of myocardial deformation and mechanics; these measures have been associated with clinical outcomes not only among patients with heart failure but also among asymptomatic community-based populations.[12,13]

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Notably, individual components of left ventricular (LV) deformation may reflect processes affecting specific layers of myofibers oriented anatomically in distinct planes. For example, shortening of the LV long axis as assessed by global longitudinal strain is thought to be a marker of predominantly subendocardial dysfunction, whereas decrease in circumferential strain around the LV short axis is considered a greater reflection of mesomyocardial dysfunction.[13,14] Accordingly, changes in longitudinal strain can occur early along the disease progression of high afterload states, when circumferential and radial strain may initially remain preserved.[15] How adiposity affects LV function along different planes is not well understood. We, therefore, sought to evaluate obesity traits in relation to distinct components of LV systolic mechanics.

Importantly, it is clear that there are many different facets to obesity that are manifest in phenotypes such as central adiposity, diabetes mellitus, insulin resistance, dyslipidemia, and abnormal fasting glucose. Given their complementary nature, we hypothesized that specific obesity-related phenotypes are associated with distinct aspects of LV strain. We, therefore, investigated the association of each of these cardiometabolic traits and circulating adipokine levels with LV mechanics in a large community-based sample of middle-aged and older adults free of overt cardiovascular disease.

Methods

Study Sample

Participants of the FHS (Framingham Heart Study) offspring cohort attending the eighth examination (2005–2008) and third generation attending the first examination (2002–2005) were included in this analysis. Details of the cohorts have previously been published.[16,17] In brief, the FHS original cohort was started in 1948 with the overall objective to identify common factors that contribute to cardiovascular disease. In 1971, the offspring cohort was recruited and included 5124 of the original participant's adult children and their spouses. The third-generation cohort in turn included the grandchildren of the original cohort. Of 7714 eligible participants, 883 were excluded (107 because of offsite examination, 183 with prevalent myocardial infarction, 44 with heart failure, 110 with valvular heart disease, 42 with atrial fibrillation, 227 with no strain measures available, and 170 with missing covariates), leaving 6231 participants for analysis.

Clinical Assessment

At the baseline examination, a comprehensive medical history, anthropometrics, assessment of resting blood pressure, and fasting blood work were obtained. Diabetes mellitus was defined as a fasting serum glucose level ≥126 mg/dL and antidiabetic therapy. Metabolic syndrome was defined as meeting ≥3 of 5 accepted criteria:[18] (1) increased waist circumference (≥102 cm in men; ≥88 cm in women); (2) increased fasting triglyceride (≥150 mg/dL); (3) high blood pressure (≥130/85 mm Hg) or treatment for hypertension; (4) decreased high-density lipoprotein (HDL) cholesterol (<40 mg/dL in men; <50 mg/dL in women); and (5) impaired fasting glucose (≥100 mg/dL). All participants provided informed consent, and the study was approved by the Boston University Medical Center Institutional Review Board.

Laboratory Assessment

Fasting blood samples were obtained at the baseline examination and frozen at −80°C until assayed. Glucose and insulin assays have previously been described.[19] The homeostasis model for insulin resistance was calculated as follows: HOMA-IR=(fasting glucose [mmol/L]*fasting insulin [μU/mL]/22.5).[20] Plasma C-reactive protein concentration was measured with Dade Behring BN100 nephelometer (Dade Behring, Deerfield, IL) with intra-assay coefficient of variation of 2.8%.

On samples from third-generation participants included in this study (n=3683), plasma leptin, soluble leptin receptor, and total adiponectin concentrations were measured by ELISA (Quantikine; R&D Systems, Minneapolis, MN). Intra-assay coefficient of variations were 2.9% for leptin, 6.9% for leptin receptor, and 2.2% for adiponectin. Serum aldosterone concentration was measured via radioimmunoassay (Quest Diagnostics), and plasma renin activity was measured using the GammaCoat Plasma Renin Activity RIA Kit (DiaSorin), with interassay coefficient of variation of 12.6%.

Echocardiography

All participants underwent standard 2-dimensional transthoracic echocardiograms using an HP Sonos 5500 ultrasound machine (Phillips Medical Systems, Andover, MA). Digital echocardiographic data were analyzed offline, and conventional LV measures obtained according to standardized techniques by readers blinded to clinical data. Fractional shortening was calculated as follows: ([LV end-diastolic dimension {LVDD}−LV end-systolic dimension]/LVDD)*100, and LV ejection fraction was derived using the Teichholz method.[21] LV mass was calculated as follows: 0.8(1.04[{LVDD+LV posterior wall thickness+LV septal wall thickness}^{3}−LVDD^3])+0.6.[22] LV hypertrophy was defined as LV mass >95 g/m^2 in women and >115 g/m^2 in men. Concentric hypertrophy was defined as LVH and relative wall thickness >0.42 and concentric remodeling as no LVH and relative wall thickness >0.42.

Speckle-tracking–based analyses of LV function were performed offline with excellent reproducibility as previously described (2D Cardiac Performance Analysis v1.1; TomTec Imaging Systems; Unterschleissheim, Germany).[23,24] Primary measures obtained included global longitudinal strain (apical 2- and 4-chamber views), global circumferential strain (mid-LV short-axis view), and longitudinal and radial (apical) segmental synchrony, calculated as the SD of time-to-peak strain.[14] Secondary measures included global radial strain (short-axis view) and global radial strain (apical 2- and 4-chamber views). The interobserver within-subject coefficients of variation for longitudinal and circumferential strain measures ranged from 3.0 to 4.0% and from 4.7 to 7.3% for radial strain (short-axis and apical views) as described previously.[24]

Statistical Analysis

Baseline clinical and echocardiographic characteristics were summarized by sex. Continuous variables that displayed skewed distributions were natural log-transformed (triglyceride concentrations, HOMA-IR, biomarkers, and measures of synchrony). The associations of cardiometabolic traits and echocardiographic measures of LV strain were evaluated using multivariable linear regression models, with a strata term used to indicate cohort. Models were adjusted for age, sex, heart rate, systolic blood pressure, hypertension treatment, body mass index (BMI), diabetes mellitus, HDL cholesterol, and triglyceride concentrations. Primary analyses examined associations of 4 cardiometabolic traits (BMI, triglyceride levels, HOMA-IR, and C-reactive protein) with longitudinal and circumferential strain. Results were deemed significant using a Bonferroni-corrected *P*-value threshold of 0.05/8=0.00625.

For significant multivariable-adjusted associations, secondary analyses additionally adjusted for echocardiographic measures (left atrial size, LV mass, and LV fractional shortening). We also examined other clinical traits including waist circumference, fasting glucose, HDL cholesterol, diabetes mellitus, metabolic syndrome, adiponectin, leptin, leptin receptor, and the aldosterone-to-renin ratio in secondary analyses. In an exploratory analysis, we examined age- and sex-adjusted least squares means of strain parameters grouped by number of metabolic syndrome risk factors present (ranging from 0 to 5) and assessed between-group differences using ANCOVA. In additional analyses, we examined Pearson partial correlation coefficients between traditional echocardiographic measures and speckle-tracking measures after adjusting for age and sex. In secondary analyses, we fitted generalized linear models to further adjust primary models for sibling correlations using the GENMOD procedure in SAS. All analyses were performed using SAS v9.2.

Results

Baseline clinical and echocardiographic characteristics of 2843 men (mean age 50±15 years) and 3388 women (mean age 51±16 years) are displayed in Table 1. Among men, the mean BMI was 28.2±4.6 kg/m^2 and 8% had diabetes mellitus. Women had mean BMI of 26.6±6.0 kg/m^2, and 5% had diabetes mellitus. Baseline echocardiographic characteristics included normal mean LV ejection fraction and wall thicknesses, with 9% of the sample meeting LV hypertrophy criteria and 3% with left atrial enlargement. Mean global longitudinal strain was −19±3% in men and −21±3% in women.

Central Adiposity and Other Cardiometabolic Traits Are Associated With LV Strain

We found that higher BMI was associated with worse longitudinal and radial strain (apical). Specifically, each 1-SD increase in BMI was associated with a 0.37% higher longitudinal strain and a 0.52% lower radial strain (apical) after accounting for potential confounders, including age, sex, heart rate, HDL cholesterol, triglyceride concentrations, diabetes mellitus, systolic blood pressure, and antihypertensive therapy (multivariable-adjusted P<0.0001 for both; Table 2). A similar association with worse longitudinal and radial strain (apical) was observed with lower HDL cholesterol (P<0.001 for both).

To examine central obesity specifically, we modeled the association of waist circumference with strain measures after adjusting for BMI among other variables (Table 2). We found that each 1-SD increase waist circumference was associated with a 0.52% higher (worse) longitudinal strain (P<0.0001) after adjusting for BMI and other clinical factors. In contrast, there was no association of waist circumference and other strain measures.

Notably, higher triglyceride concentrations and insulin resistance as assessed by HOMA-IR were also associated with worse longitudinal strain (P<0.0001 for both). In addition, we found that participants with diabetes mellitus had worse circumferential and radial strain (short axis). Specifically, individuals with diabetes mellitus had a 0.84% higher circumferential and 2.91% lower radial strain (short axis) compared with individuals without diabetes mellitus (P≤0.004 for both).

After additionally accounting for traditional echocardiographic measures (left atrial diameter, LV mass, fractional shortening, or LV ejection fraction), all associations of cardiometabolic traits and strain measures highlighted above remained statistically significant (P≤0.007 for all). Additional adjustment for waist circumference and fasting glucose revealed no substantive changes in previous associations, with the exception of BMI, which was no longer associated with strain measures after adjusting for waist circumference (Table I in the Data Supplement). In secondary analyses, we accounted for sibling correlations using generalized linear models, and we found minimal differences in effect sizes (Table II in the Data Supplement).

Cardiometabolic Traits Are Associated With Mechanical Synchrony

In addition to LV strain measures, BMI was also associated with worse longitudinal segmental synchrony (multivariable-adjusted P=0.003). After accounting for BMI and other clinical variables, waist circumference and diabetes mellitus status were also associated with worse longitudinal segmental synchrony (P≤0.006 for both; Table 3). However, after adjusting for traditional echocardiographic measures, the association

Table 1. Clinical, Laboratory, and Echocardiographic Characteristics of Sample by Sex

	Men	Women
	n=2843	n=3388
Clinical characteristics		
Age, years	50 (15)	51 (16)
Systolic blood pressure, mm Hg	124 (15)	119 (17)
Body mass index, kg/m^2	28.2 (4.6)	26.6 (6.0)
Waist circumference, cm	100 (13)	92 (16)
Heart rate, beats per min	61 (10)	63 (10)
Diabetes mellitus, n (%)	224 (8)	169 (5)
Antihypertensive medications, n (%)	736 (26)	776 (23)
Metabolic syndrome, n (%)	1286 (45)	1102 (33)
Laboratory characteristics		
HDL cholesterol, mg/dL	48 (13)	62 (17)
Triglycerides, mg/dL	129 (97)	104 (62)
C-reactive protein, mg/L	2.2 (4.5)	3.2 (6.5)
HOMA-IR	1.9 (2.0)	1.6 (1.7)
Fasting glucose, mg/dL	103 (21)	96 (19)
Echocardiographic characteristics		
Left atrial diameter, cm	4.0 (0.5)	3.6 (0.5)
Left atrial enlargement, n (%)	85 (3)	87 (3)
Left ventricular end-diastolic dimension, cm	5.1 (0.4)	4.7 (0.3)
Interventricular septal thickness, cm	1.0 (0.1)	0.9 (0.1)
Posterior wall thickness, cm	1.0 (0.1)	0.9 (0.1)
Relative wall thickness	0.39 (0.05)	0.37 (0.05)
Left ventricular mass, g	192 (38)	135 (29)
Left ventricular hypertrophy, n (%)	244 (9)	321 (10)
Concentric remodeling, n (%)	494 (19)	288 (9)
Concentric hypertrophy, n (%)	109 (4)	100 (3)
Fractional shortening, %	36 (4)	37 (4)
Left ventricular ejection fraction, %	64 (5)	66 (5)
Mitral tissue Doppler e′, cm/s	11.3 (2.8)	11.3 (3.0)
Mitral inflow E/e′ ratio	6.0 (1.6)	6.5 (2.0)
Strain measures		
Longitudinal strain, %	−19 (3)	−21 (3)
Circumferential strain, %	−29 (5)	−30 (5)
Radial strain (short axis), %	45 (17)	47 (17)
Radial strain (apical), %	29 (7)	30 (7)
Longitudinal synchrony, ms	94 (38)	90 (36)
Radial synchrony, ms	124 (49)	121 (48)

Data are means and SDs for continuous variables, unless otherwise indicated.

Table 2. Association of Cardiometabolic Traits and Strain Measures

	Longitudinal Strain		Circumferential Strain		Radial Strain (Short Axis)		Radial Strain (Apical)	
	Estimate (SE)	*P* Value	Estimate (SE)	*P* Value	Estimate (SE)	*P* Value	Estimate (SE)	*P* Value
Primary traits								
Body mass index	0.37 (0.04)	<0.0001	−0.12 (0.07)	0.08	−0.04 (0.26)	0.87	−0.52 (0.10)	<0.0001
Triglycerides	0.20 (0.04)	<0.0001	−0.06 (0.07)	0.39	0.12 (0.27)	0.66	−0.05 (0.11)	0.63
HOMA-IR	0.36 (0.06)	<0.0001	−0.18 (0.11)	0.09	−0.33 (0.38)	0.39	−0.29 (0.15)	0.06
C-reactive protein	0.03 (0.04)	0.51	−0.11 (0.07)	0.11	0.24 (0.25)	0.35	−0.13 (0.10)	0.20
Secondary traits								
Waist circumference	0.52 (0.10)	<0.0001	−0.41 (0.17)	0.01	0.68 (0.61)	0.26	−0.33 (0.24)	0.16
Fasting glucose	0.08 (0.05)	0.10	−0.23 (0.09)	0.01	0.45 (0.32)	0.15	−0.11 (0.12)	0.37
HDL cholesterol	−0.16 (0.05)	0.0006	−0.18 (0.08)	0.02	0.31 (0.28)	0.27	0.37 (0.11)	0.0009
Diabetes mellitus	0.14 (0.16)	0.38	0.84 (0.28)	0.003	−2.91 (1.02)	0.004	−0.51 (0.39)	0.19
Adiponectin	−0.10 (0.05)	0.06	0.17 (0.09)	0.04	0.04 (0.35)	0.90	0.07 (0.14)	0.64
Leptin	0.44 (0.08)	<0.0001	−0.03 (0.12)	0.81	0.66 (0.50)	0.19	−1.15 (0.20)	<0.0001
Leptin receptor	−0.08 (0.05)	0.06	−0.12 (0.07)	0.10	−0.75 (0.29)	0.01	0.32 (0.12)	0.006
Aldosterone/renin ratio	−0.05 (0.04)	0.24	−0.08 (0.07)	0.25	0.09 (0.28)	0.76	0.10 (0.11)	0.37

β estimate represents the change in echo variable (strain expressed in %) per 1-SD change in continuous clinical traits and for the presence vs absence of dichotomous traits. Multivariable model adjusted for age, sex, body mass index, heart rate, systolic blood pressure, hypertension treatment, diabetes mellitus, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations. Biomarkers are log transformed. HOMA-IR indicates homeostatic model assessment of insulin resistance.

of BMI and waist circumference with longitudinal segmental synchrony was attenuated (P>0.05 for both). There were no significant associations between cardiometabolic traits and radial (apical) segmental synchrony.

Adipokines, Aldosterone, and LV Mechanical Function

Higher circulating leptin concentrations were associated with worse longitudinal and radial strain (apical), even after accounting for BMI and other clinical covariates (multivariable-adjusted P<0.0001 for both; Table 3). This finding persisted even after additionally accounting for traditional echocardiographic measures (P<0.0001 for both).

Higher soluble leptin receptor concentrations were associated with higher radial strain (apical; P=0.006) but not longitudinal strain or other strain measures. Adiponectin concentrations were not associated with strain parameters (P≥0.04 for both). None of the adipokines measured were associated with synchrony measures.

We found no association of aldosterone concentrations or aldosterone-to-renin ratio and measures of LV strain. Further, the association of leptin and longitudinal and radial strain (apical) measures was not attenuated after adjusting for aldosterone concentrations in multivariable analyses (P<0.0001).

Association of Metabolic Syndrome and Strain Measures

Among the sample studied, 45% of men and 33% of women met criteria for metabolic syndrome. The presence of metabolic syndrome was associated with worse longitudinal and radial strain (apical) in age- and sex-adjusted analyses (P<0.0001 for both). Specifically, individuals with metabolic syndrome had a 1% higher longitudinal strain compared with those without metabolic syndrome (β estimate 1.06; SE 0.09). The Figure displays longitudinal strain by number of metabolic syndrome risk factors (between 0 and 5).

Association of Traditional Echocardiographic Measures With Speckle-Tracking Strain

We observed modest correlations between traditional echocardiographic measures and strain measures in age- and sex-adjusted analyses. All 4 strain measures were correlated with LV ejection fraction (Table 4). Traditional measures of diastolic function included mitral e′ velocity, with worse mitral e′ correlated with worse longitudinal strain, and the mitral inflow E/e′ ratio, with higher E/e′ ratio correlated with worse longitudinal and better circumferential strain.

Discussion

Among 6231 participants of the FHS, we found that greater BMI, and specifically central adiposity as measured by waist circumference, was associated with worse global longitudinal strain, as well as worse longitudinal synchrony. Beyond BMI itself, other phenotypes accompanying obesity including insulin resistance, dyslipidemia, and diabetes mellitus were associated with distinct aspects of LV mechanical function. Interestingly, we also found that the adipose-derived hormone leptin was associated with global longitudinal and radial strain (apical), whereas no such association was found with adiponectin or C-reactive protein. These findings may shed light onto obesity-related cardiac remodeling and heart failure.

The association of obesity and diastolic dysfunction is well described, whereas the effects of obesity on systolic function are less clear.[8] Previous data support normal LV ejection fraction in obesity,[25] whereas recent studies examining global

Table 3. Association of Cardiometabolic Traits and Synchrony Measures

	Longitudinal Segmental Synchrony		Radial (Apical) Segmental Synchrony	
	Estimate (SE)	*P* Value	Estimate (SE)	*P* Value
Primary traits				
Body mass index	0.02 (0.005)	0.003	0.01 (0.006)	0.11
Triglycerides	−0.003 (0.005)	0.59	−0.003 (0.006)	0.63
HOMA-IR	0.02 (0.008)	0.05	0.02 (0.009)	0.05
C-reactive protein	0.0003 (0.005)	0.96	−0.006 (0.006)	0.31
Secondary traits				
Waist circumference	0.03 (0.01)	0.006	0.01 (0.01)	0.42
Fasting glucose	−0.008 (0.006)	0.20	−0.01 (0.007)	0.09
HDL cholesterol	−0.007 (0.006)	0.21	−0.02 (0.007)	0.008
Diabetes mellitus	0.08 (0.02)	<0.0001	0.05 (0.02)	0.02
Adiponectin	0.0006 (0.005)	0.90	0.004 (0.006)	0.54
Leptin	0.01 (0.007)	0.15	0.01 (0.008)	0.07
Leptin receptor	−0.001 (0.004)	0.76	−0.006 (0.005)	0.20
Aldosterone/ renin ratio	0.006 (0.004)	0.14	−0.007 (0.005)	0.14

β estimate represents the change in echo variable (synchrony expressed in ms) per 1-SD change in continuous clinical traits and for the presence versus absence of dichotomous traits. Multivariable model adjusted for age, sex, body mass index, heart rate, systolic blood pressure, hypertension treatment, diabetes mellitus, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations. Biomarkers are log transformed. HOMA-IR indicates homeostatic model assessment of insulin resistance.

longitudinal strain show an association of BMI and central adiposity with LV systolic dysfunction using this more sensitive measure.[26–28] Our study extends these findings to a large community-based population of middle-aged and older adults and demonstrates a robust association of BMI and central adiposity with global longitudinal strain. Further, our results support an association of metabolic phenotypes, including insulin resistance and hypertriglyceridemia with strain measures, above and beyond obesity itself.

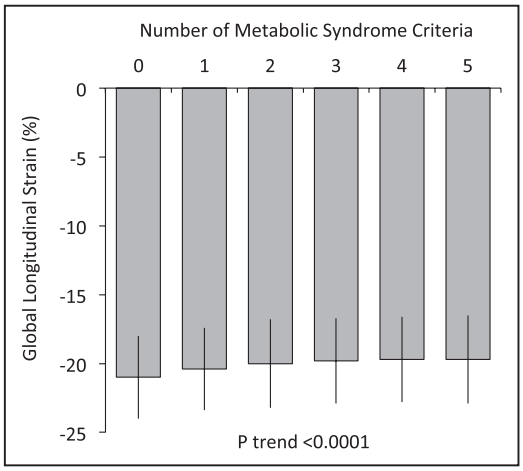

Figure. Least-squared means of global longitudinal strain by number of metabolic syndrome criteria, adjusted for age and sex. Error bars represent SE.

Of note, we show a distinct association of BMI, central adiposity, insulin resistance, and hypertriglyceridemia with global longitudinal strain, whereas there were no significant associations with circumferential strain. This mirrors the early decline in longitudinal deformation with relative preservation of radial deformation in models of ischemia and increased afterload states.[29,30] In addition, we found that diastolic function as assessed by mitral inflow E/e′ ratio correlated with worse longitudinal and better circumferential strain. Indeed, increasing left atrial to LV gradients in an animal model of pacing-induced heart failure result in greater diastolic lengthening rate of the LV in the anteroposterior and septolateral dimensions but progressive decline in long-axis lengthening.[31]

Of note, diabetes mellitus was associated with circumferential but not longitudinal strain after adjusting for BMI. Interestingly, circumferential strain previously was found to be more strongly predictive of incident heart failure compared with longitudinal strain.[13] These results are distinct from previous analyses from the ARIC study (Atherosclerosis Risk in the Community), which showed an association of dysglycemia and diabetes mellitus with global longitudinal strain.[32] This difference in results may be because of the older mean age of the ARIC participants compared with our study population. Cardiac effects of age-related changes in body composition are often difficult to separate from inherent effects of obesity,[33] and it may be that in our younger cohort, we observe more direct associations of cardiometabolic dysfunction on cardiovascular phenotypes, whereas in older samples, age-related effects may be at play. In fact, an earlier study on a subsample of older FHS participants showed a similar association of diabetes mellitus with longitudinal strain,[23] which we no longer observe in a younger sample with more than double the number of participants, and after accounting for BMI differences.

The mechanisms underlying obesity-associated cardiac remodeling are likely multifaceted. Previous experimental studies support the potential role of circulating adipose-derived hormones. For example, circulating leptin can have direct myocardial effects on fatty acid metabolism, hypertrophy, and fibrosis and may also influence cardiac function indirectly via vascular and hypothalamic effects.[11] Soluble leptin receptor is the predominant leptin-binding protein in the blood and thus may directly modulate leptin action.[34] Circulating adiponectin binds to adiponectin receptor 1 on cardiac myocytes, with downstream cardioprotective effects on cardiac fatty acid and glucose metabolism, hypertrophy, fibrosis, and apoptosis.[10] We found that circulating leptin but not adiponectin concentrations were associated with global longitudinal strain. Interestingly, previous studies have suggested that leptin may be linked to increased aldosterone secretion.[35] However, leptin remained associated with longitudinal strain even after adjusting for aldosterone concentrations, and there was no association of aldosterone or the aldosterone-to-renin ratio and measures of LV strain. Similarly, we did not find an association of C-reactive protein and measures of cardiac strain.

Table 4. Correlation Between Traditional Echocardiographic and Strain Measures

	Longitudinal Strain	Circumferential Strain	Radial Strain (Short Axis)	Radial Strain (Apical)
	*R** *P* Value	*R** *P* Value	*R** *P* Value	*R** *P* Value
LA diameter	0.03	−0.11	0.04	0.003
	0.05	<0.0001	0.002	0.85
LV mass	0.12	0.007	−0.001	−0.03
	<0.0001	0.58	0.93	0.06
RWT	0.11	−0.07	−0.07	0.03
	<0.0001	<0.0001	<0.0001	0.03
LVEF	−0.19	−0.44	0.13	0.19
	<0.0001	<0.0001	<0.0001	<0.0001
Mitral e′	−0.23	−0.02	−0.02	0.05
	<0.0001	0.08	0.26	<0.0001
Mitral E/e′ ratio	0.07	−0.13	0.02	−0.02
	<0.0001	<0.0001	0.27	0.12

*Partial Pearson correlation coefficient adjusted for age and sex. LA indicates left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; and RWT, relative wall thickness.

Previous population-based data show that higher leptin concentrations are associated with diastolic dysfunction.[36] We now extend previous findings to also highlight a role for leptin in relation to LV systolic mechanics in humans, which corroborates previous findings in leptin receptor–deficient animal models.[37] It is important to note that data linking circulating leptin concentrations to clinical outcomes in population-based studies have shown conflicting results, with some studies suggesting higher risk and others a null or even protective effect.[38–40]

Several limitations of our study should be considered. The observational, cross-sectional nature of our study precludes causal inferences, and the clinical value of strain measures remains unclear. Although strain measures have been associated with cardiovascular events among Framingham participants,[13] these analyses were limited in power, and further studies are needed to elucidate clinical implications. We acknowledge that effect sizes were modest in our study and that the clinical significance of observed associations remains unclear. Specifically, although strain measures have been shown to improve with interventions such as bariatric surgery, exercise training, and spironolactone therapy in small trials of select patient groups with cardiometabolic disease,[41–43] the clinical impact of improving LV systolic mechanics with regard to disease prevention remain unknown. We measured radial strain along 2 different imaging planes (short-axis and apical views) and note that the mechanistic value or differences between the 2 imaging planes is not established. Given greater reproducibility for longitudinal and circumferential strain measurements,[24] we examined radial strain measures as secondary points of interest. Global longitudinal strain was measured in the apical 4- and 2-chamber views. This may have excluded the anterior septum and inferolateral wall and decreased accuracy of our measurements. However, we expect that this would have biased our results toward the null. Speckle-tracking analyses were performed on previously acquired images that had been obtained without specific focus on optimal endocardial border definition. However, image quality was acceptable for the vast majority of participants, and reproducibility was good for strain measures across different planes.[24] It would have been interesting to examine pericardial fat depots; however, this was not assessed contemporaneous with strain measures, given variability in echocardiographic images. Finally, our study sample was predominantly white, limiting potential generalizability to other populations.

In sum, our findings highlight the association of central obesity and related cardiometabolic phenotypes above and beyond BMI with subclinical measures of LV systolic function and mechanics. We also found that obesity-related traits were associated with distinct aspects of LV mechanics, suggesting potential differential effects along specific LV planes of deformation. Finally, leptin was associated with global longitudinal strain, suggesting a potential role for circulating adipokines in obesity-related cardiac remodeling. Further work is needed to investigate the possible mechanisms underlying the link between cardiometabolic traits and subclinical alterations in cardiac mechanical dysfunction.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Obesity and cardiometabolic dysfunction are associated with increased risk of heart failure and other cardiovascular diseases. We evaluated the associations of obesity-related phenotypes with echocardiographic measures of left ventricular mechanical function among 6231 participants of the Framingham Heart Study. Greater body mass index and central adiposity were associated with worse global longitudinal strain and synchrony. Measures of insulin resistance, dyslipidemia, and diabetes mellitus also were associated with distinct aspects of left ventricular mechanical function. Our findings highlight the association of central obesity and related cardiometabolic phenotypes above and beyond body mass index with subclinical measures of left ventricular mechanical function and may shed light onto obesity-related cardiac remodeling and heart failure.

Cardiometabolic Traits and Systolic Mechanics in the Community

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Supplemental Material

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Supplemental Table 1. Association of strain measures and clinical traits after additional adjustment for waist circumference and fasting glucose.

Echo measure	**Clinical Trait**	**Multivariable model (prior)**		**Multivariable model with WC and FG***	
		estimate (s.e.)	P	estimate (s.e.)	P
Longitudinal strain	Body mass index	0.37 (0.04)	<0.0001	-0.06 (0.09)	0.48
	Triglycerides	0.20 (0.04)	<0.0001	0.18 (0.04)	<0.0001
	HOMA-IR	0.36 (0.06)	<0.0001	0.33 (0.06)	<0.0001
	Waist circumference	0.52 (0.10)	<0.0001	0.51 (0.10)	<0.0001
	HDL cholesterol	-0.16 (0.05)	0.0006	-0.14 (0.05)	0.002
	Leptin	0.44 (0.08)	<0.0001	0.38 (0.08)	<0.0001
Circumferential strain	Diabetes mellitus	0.84 (0.28)	0.003	1.39 (0.35)	<0.0001
Radial strain (short)	Diabetes mellitus	-2.91 (1.02)	0.004	-4.01 (1.27)	0.002
Radial strain (apical)	Body mass index	-0.52 (0.10)	<0.0001	-0.24 (0.22)	0.28
	HDL cholesterol	0.37 (0.11)	0.0009	0.36 (0.11)	0.001
	Leptin	-1.15 (0.20)	<0.0001	-1.08 (0.21)	<0.0001
Longitudinal segmental synchrony	Body mass index	0.02 (0.005)	0.003	-0.01 (0.01)	0.31
	Waist circumference	0.03 (0.01)	0.006	0.03 (0.01)	0.006
	Diabetes mellitus	0.08 (0.02)	<0.0001	0.10 (0.03)	0.0001

Supplemental Table 2. Associations of cardiometabolic traits and strain parameters, before and after accounting for sibling correlations

	Primary Analysis		Adjusting for Sibling Correlations	
	estimate (s.e.)	P	estimate (s.e.)	P
Longitudinal strain				
Body mass index	0.37 (0.04)	<0.0001	0.36 (0.04)	<0.0001
Triglycerides	0.20 (0.04)	<0.0001	0.20 (0.04)	<0.0001
HOMA-IR	0.36 (0.06)	<0.0001	0.37 (0.06)	<0.0001
Waist circumference	0.52 (0.10)	<0.0001	0.50 (0.10)	<0.0001
HDL cholesterol	-0.16 (0.05)	0.0006	-0.16 (0.05)	0.0009
Leptin	0.44 (0.08)	<0.0001	0.44 (0.08)	<0.0001
Circumferential strain				
Diabetes mellitus	0.84 (0.28)	0.003	0.82 (0.33)	0.01
Radial strain (short axis)				
Diabetes mellitus	-2.91 (1.02)	0.004	-2.94 (1.06)	0.005
Radial Strain (apical)				
Body mass index	-0.52 (0.10)	<0.0001	-0.51 (0.11)	<0.0001
HDL cholesterol	0.37 (0.11)	0.0009	0.37 (0.12)	0.002
Leptin	-1.15 (0.20)	<0.0001	-1.17 (0.21)	<0.0001
Leptin receptor	0.32 (0.12)	0.006	0.33 (0.13)	0.009

Beta estimate represents the change in echo variable (strain expressed in %) per 1-standard deviation change in continuous clinical traits, and for the presence versus absence of dichotomous traits. Multivariable model adjusted for age, sex, body mass index, heart rate, systolic blood pressure, hypertension treatment, diabetes mellitus, HDL cholesterol, triglyceride concentrations. Biomarkers are log-transformed.