Original Article
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Obesity

Association of the Degree of Adiposity and Duration of Obesity with Measures of Cardiac Structure and Function: The CARDIA Study

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Objective: Examine whether there are independent influences of a greater degree of adiposity and longer duration of obesity on cardiac structure and function.

Methods: Participants of CARDIA were 18-30 years when they underwent a baseline examination in 1985-86. Seven follow-up examinations were conducted every 2-5 years.

Results: Among 2,547 participants who underwent an echocardiogram at the year 25 examination and were not obese at baseline, 34.4 and 35.5% were overall (BMI $\geq$ 30 kg m^{-2}) and abdominally obese (waist circumference: men: >102 cm; women: >88 cm) at year 25, respectively. A greater degree of overall and abdominal adiposity at year 25 were each associated with a greater left ventricular (LV) mass ($P < 0.001$), LV volume ($P < 0.001$), LV mass-to-volume ratio ($P < 0.001$), left atrial dimension ($P < 0.001$), and ejection fraction ($P < 0.05$) after adjustment for duration of obesity and other risk factors. In contrast, a longer duration of overall obesity was associated with a greater LV mass ($P = 0.003$) and a trend for a lower ejection fraction ($P = 0.07$).

Conclusions: A greater degree of adiposity is strongly associated with concentric LV remodeling in mid-life, while the cumulative effects of a longer duration of overall obesity during young adulthood contribute to concentric remodeling predominantly by increasing LV mass.

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Introduction

Obesity has been linked to a spectrum of cardiovascular changes ranging from a hyperdynamic circulation, through subclinical cardiac structural changes to overt heart failure (1-3). Existing studies have shown that left ventricular (LV) hypertrophy, LV systolic function, and LV diastolic function worsen with a greater degree of overall and abdominal adiposity (5). Recent evidence also suggests obesity is associated with a greater LV mass to a greater extent than chamber size (6-8). While the pattern of remodeling associated with a greater degree of adiposity has been documented, little information exists on the consequences of a longer duration of obesity.

Understanding the consequences of a longer duration of obesity is critical, given the obesity epidemic. With a doubling of obesity rates for adults and a tripling of rates for children and adolescents over the last three decades, younger individuals are experiencing a greater degree and longer duration of exposure to excess adiposity over their lifetime (9,10). Preliminary data suggest that a longer duration of obesity contributes to a greater LV mass and worse LV function in most (11-13), but not all studies (14). Important limitations of these studies include small clinic-based samples, lack of simultaneous adjustment for the degree of adiposity, and the dependence upon the recall of body weight at previous ages to determine the duration of obesity, a methodology that may be susceptible to a substantial amount of measurement error.

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The present study was conducted to examine whether there are independent influences of a greater degree of adiposity and longer duration of obesity beginning in early adulthood as a result of the obesity epidemic on cardiac structure and function measured via echocardiography in middle-age. Participants were black and white adults recruited in 1985-1986 as part of the Coronary Artery Risk Development in Young Adults (CARDIA) Study. The CARDIA Study provided an ideal setting in which to address this question because participants were recruited and followed largely during the obesity epidemic of the last three decades in the United States as well as during the period of greatest gain in adiposity during the life course (9,15).

Methods

Study sample

CARDIA is a multicenter community-based longitudinal cohort study of the development and determinants of cardiovascular disease over time in 5,115 young adults initially aged 18-30 years in 1985-1986. Black and white adults were recruited from four cities in the United States with population-based samples approximately balanced within center by sex, age, race, and education. To date, participants have been re-examined 2, 5, 7, 10, 15, 20, and 25 years after baseline and retention rates across examinations were 91, 86, 81, 79, 74, 72, and 72%, respectively.

Of the 3,498 participants who completed the year 25 follow-up examination, we excluded those who did not complete an echocardiogram ($n = 24$) and those without available measures of cardiac structure and function ($n = 353$); those who were overall [body mass index (BMI) $\geq$30 kg m^{-2}] or abdominally obese (>102 cm in men and >88 cm in women (16)) at baseline ($n = 341$); were pregnant during any examination ($n = 160$); those who experienced angina, a myocardial infarction, or heart failure during follow-up ($n = 54$); and those who had bariatric surgery ($n = 19$). The remaining 2,547 participants formed the sample population for analysis.

Clinical measurements

Standardized protocols for data collection were used across study centers and examinations. Participants were asked to fast for at least 12 h and to avoid smoking or engaging in heavy physical activity for at least 2 h before each examination.

Anthropometry

Weight and height were measured with participants wearing light examination clothes and no shoes. Body weight was measured to the nearest 0.2 kg with a calibrated balance-beam scale. Height was measured with a vertical ruler to the nearest 0.5 cm. BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured with a tape in duplicate to the nearest 0.5 cm around the minimal abdominal girth identified laterally midway between the iliac crest and the lowest portion of the rib cage and anteriorly midway between the xiphoid process and the umbilicus.

Duration of overall and abdominal obesity

For each participant, the number of years of overall and abdominal obesity was calculated separately based upon the presence (or absence) of overall or abdominal obesity at each follow-up examination and the preceding examination. For example, a participant who was not overall obese at year 2, but was overall obese at year 5 and all subsequent follow-up examinations was assigned 0 years of overall obesity at year 2, 3 years at year 5, 2 years at year 7, 3 years at year 10, and so on. This scoring methodology was applied at each follow-up examination and the cumulative duration of obesity across examination years for each participant was then calculated (17).

Echocardiography

Echocardiography was performed at year 25 using an Artida cardiac ultrasound machine (Toshiba Medical Systems, Tokyo, Japan) and a previously described protocol (18,19). Briefly, sonographers at each field center underwent initial, centralized training followed by quality assurance and control procedures to assess intra- and inter-sonographer reproducibility. Measurements of LV and left atrium (LA) dimensions were acquired from two-dimensional (2D)-guided M-mode echocardiograms obtained from optimized parasternal short-axis views. Studies were electronically transmitted to a core reading laboratory at Johns Hopkins University. LV mass was calculated using the Devereux formula (20). LV end-diastolic volume was acquired from a 2D four-chamber view. Mass-to-volume ratio was calculated as the ratio of LV mass to end-diastolic volume. Ejection fraction was calculated as the ratio of stroke volume to end-diastolic volume. Heart rate was recorded from the electrocardiogram during the echocardiographic examination. Quality control procedures included participant re-examination and blind re-reading to allow assessment of intra- and inter-sonographer variability and intra- and inter-reader variability, respectively. Technical errors for intra- and inter-sonographer variability ranged from 5 to 11% and 6 to 12%, respectively. Intra- and inter-reader variability ranged from 3 to 9% and 6 to 11%, respectively.

The assessment of other measurements can be found in the Supporting Information.

Statistical analysis

Participant characteristics overall, and according to the degree of adiposity and duration of obesity were described using means, medians, and proportions as appropriate. Differences and trends were tested using linear regression models and χ^2 analyses for continuous and categorical characteristics, respectively. The Kruskal–Wallis test was used for characteristics with skewed distributions. Multivariable linear regression models were used to estimate the association between the degree of adiposity at year 25 and duration of obesity with each of the measures of cardiac structure and function. The degree of adiposity and duration of obesity were modeled in one of two exposure forms: as continuous variables assuming a linear dose-response association, and as five-level categorical variables for overall and abdominal (i.e., sex-specific quintiles) adiposity and a six-level categorical variable for duration of obesity. Models were simultaneously adjusted for degree of adiposity and duration of obesity. Analyses were further adjusted for age, sex, race, educational attainment, CARDIA field center, smoking, and average physical activity and alcohol intake during follow-up. A second model adjusted additionally for use of antihypertensive medication, diabetes, heart rate, and average systolic blood pressure during follow-up. The additional adjustment variables in the second model could be in the causal pathway; we regarded these models as possibly

TABLE 1 Participant characteristics[a] according to duration of overall obesity[b] in 5-year increments, The CARDIA Study ($n = 2,547$)

Variable[a]	Duration of overall obesity (years)						
	0 ($n = 1,552$)	1–5 ($n = 215$)	6–10 ($n = 188$)	11–15 ($n = 203$)	16–20 ($n = 208$)	>20 ($n = 181$)	*P* trend
Selected characteristics							
Baseline age (years)	25.1 (3.5)	24.5 (3.5)	25.1 (3.6)	24.9 (3.8)	24.2 (3.8)	24.8 (3.6)	0.003
Women, % (*n*)	51.7 (802)	54.4 (117)	54.3 (102)	54.7 (111)	54.8 (114)	58.0 (105)	0.07
Black race, %	35.4 (550)	49.3 (106)	53.2 (100)	58.6 (119)	61.5 (128)	70.7 (128)	<0.001
Educational attainment (years)	16.0 (2.6)	15.7 (2.5)	15.5 (2.6)	15.6 (2.6)	15.5 (2.5)	15.1 (2.4)	<0.001
Ever smoker, % (*n*)	39.0 (605)	41.4 (89)	39.4 (74)	34.5 (70)	36.1 (75)	33.7 (61)	0.09
Physical activity (exercise units)[c]	366 (243–524)	324 (200–511)	316 (205–474)	293 (176–477)	289 (186–454)	273 (152–428)	<0.001
Alcohol (ml day^{-1})[c]	7.3 (1.6–17.2)	5.2 (0.7–16.4)	7.1 (1.0–17.0)	4.2 (0.6–11.3)	3.7 (0.4–12.8)	2.9 (0.3–10.6)	<0.001
Clinical and physical characteristics							
Body mass index (kg m^{-2})[c]	23.3 (2.2)	26.5 (1.5)	27.4 (1.4)	28.7 (1.5)	30.6 (2.2)	33.4 (3.1)	<0.001
Waist circumference (cm)[c]	77.7 (7.9)	84.2 (7.1)	86.1 (7.3)	88.2 (7.3)	92.3 (7.6)	96.8 (8.1)	<0.001
Heart rate (bpm)	63.6 (10.4)	66.4 (10.2)	66.9 (9.6)	67.5 (10.3)	67.7 (10.4)	68.1 (10.6)	<0.001
Systolic blood pressure (mm Hg)[c]	109.3 (9.2)	110.9 (9.4)	110.8 (8.5)	113.5 (9.2)	112.9 (8.5)	114.9 (8.7)	<0.001
Diastolic blood pressure (mmHg)[c]	69.1 (7.1)	70.3 (6.6)	70.5 (6.3)	72.6 (7.2)	71.9 (6.6)	74.1 (6.5)	<0.001
Ever antihypertensive medication, % (*n*)	15.7 (243)	28.4 (61)	23.9 (45)	32.5 (66)	31.7 (66)	44.8 (81)	< 0.001
Ever diabetes, % (*n*)[d]	5.4 (83)	12.6 (27)	10.0 (18)	18.2 (37)	21.6 (45)	31.5 (57)	<0.001
Fasting blood concentration[c]							
Glucose (mg dl^{-1})	89.2 (8.4)	91.4 (10.6)	91.7 (10.4)	93.7 (12.1)	93.7 (11.7)	97.7 (15.9)	< 0.001
Insulin (μU ml^{-1})	9.6 (3.8)	12.8 (5.8)	13.2 (4.6)	14.4 (5.6)	16.0 (6.9)	17.9 (7.9)	<0.001

[a]Presented as the mean (SD), median (IQR), or % (*n*) as appropriate.
[b]Overall obesity defined as a body mass index ≥30 kg m^{-2}.
[c]Based upon average values during follow-up.
[d]Diabetes defined as a self-report of oral hypoglycemic medications or insulin at examination years 2, 5, 7, 10, 15, 20, and 25; fasting glucose levels ≥7.0 mmol l^{-1} (≥126 mg dl^{-1}) at examination years 7, 10, 15, 20, or 25; a 2-h postload glucose ≥11.1 mmol l^{-1} (≥200 mg dl^{-1}) at examination years 10, 20, and 25; or a glycated hemoglobin A_{1c} ≥6.5% at years 20 and 25.

explanatory. Models using BMI as an exposure did not additionally adjust for height. Tests for a linear trend were performed by entering the degree of adiposity or duration of obesity into the multivariable models as a continuous variable. Potential effect modification by race-sex was explored in stratified analyses and evaluated by testing the statistical significance of multiplicative interaction terms in models that also included lower-order terms.

In a sensitivity analysis, we determined the influence of missing BMI and waist circumference values (7.8% of all measurements for each) on the associations between the degree of adiposity and duration of obesity with measures of cardiac structure and function. Multiple imputation was used to impute missing BMI and waist circumference values using the sequential regression imputation approach that is implemented in the software package IVEware (21). Five datasets were generated using all available BMI and waist circumference data. Each data set was analyzed separately and results from the five analyses were combined using the rules of Little and Rubin (22).

Tests of statistical significance were two-tailed, with an alpha level of 0.05. Because of the increased number of formal tests of interaction, statistical significance for effect modification was defined at an alpha level of 0.01. SAS version 9.3 (SAS Institute, Cary, NC) was used to perform all analyses.

Results

Of the 2,547 eligible participants, 44.4% were black and 53.0% were women. At year 25, the prevalence of a BMI <18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, and ≥35.0 kg m^{-2} was 0.9, 28.8, 35.9, 21.9, and 12.5, respectively. The prevalence of abdominal obesity at year 25 was 35.5%. The average duration of overall and abdominal obesity during follow-up was 14.1 (SD = 6.7) and 12.7 (SD = 6.3) years, respectively. Mean age at onset of obesity was 36.1 (SD = 8.1) and 38.3 (SD = 7.6) years, respectively. The prevalence of overall obesity duration of 1-5, 6-10, 11-15, 16-20, and >20 years was 8.4, 7.4, 8.0, 8.2, and 7.1%, respectively. For abdominal obesity duration, these estimates were 11.3, 8.7, 8.0, 7.9, and 4.4%, respectively.

Those with a longer exposure to overall obesity were more likely to be younger at baseline, black, achieve less education, have a higher average waist circumference during follow-up, and were less physically active and consumed less alcohol during follow-up (Table 1). In addition, a longer duration of obesity was associated with a higher heart rate, average blood pressures, glucose and insulin levels, and were more likely to use antihypertensive medication and have diabetes. Sex and smoking were unrelated to obesity duration. Similar results were observed when the duration of overall obesity was replaced with the degree of overall obesity, degree of

TABLE 2 Mean (standard error) left ventricular mass, left ventricular end-diastolic volume, left atrial dimension, and ejection fraction according to body mass index (BMI) at year 25 and duration of overall obesity[a] during follow-up, The CARDIA Study ($n = 2,547$)

	Left ventricular mass (g)		Left ventricular end-diastolic volume (ml)		Left ventricular mass-to-volume ratio (g ml^{-1})		Left atrial dimension (cm)		Ejection fraction (%)	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
BMI (kg m^{-2})										
<18.5	146.9 (8.7)	149.5 (8.6)	115.4 (6.0)	115.2 (6.0)	1.28 (0.07)	1.30 (0.07)	3.3 (0.09)	3.3 (0.09)	69.5 (1.7)	69.7 (1.7)
18.5–24.9	164.3 (3.7)	163.6 (3.7)	127.5 (2.5)	126.7 (2.6)	1.30 (0.03)	1.31 (0.03)	3.6 (0.04)	3.6 (0.04)	68.4 (0.7)	68.3 (0.7)
25.0–29.9	179.8 (3.3)	178.3 (3.3)	136.4 (2.3)	135.5 (2.3)	1.35 (0.03)	1.35 (0.03)	3.8 (0.03)	3.8 (0.04)	69.1 (0.7)	69.0 (0.7)
30.0–34.9	177.9 (2.0)	177.6 (2.2)	129.3 (1.4)	128.7 (1.5)	1.40 (0.02)	1.40 (0.02)	3.8 (0.02)	3.8 (0.02)	69.8 (0.4)	69.8 (0.4)
≥35.0	186.8 (2.8)	186.2 (3.0)	136.2 (2.0)	136.0 (2.1)	1.40 (0.02)	1.40 (0.02)	3.9 (0.03)	3.9 (0.03)	70.1 (0.6)	70.0 (0.6)
***P* trend**	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.03	0.04
Per 5 kg m^{-2}	11.4 (1.2)	11.2 (1.2)	5.9 (0.8)	6.2 (0.8)	0.04 (0.01)	0.03 (0.01)	0.2 (0.01)	0.2 (0.01)	0.5 (0.2)	0.5 (0.2)
Duration of overall obesity (years)[a]										
0	155.3 (2.6)	156.1 (2.9)	118.5 (1.8)	117.4 (2.0)	1.33 (0.02)	1.35 (0.02)	3.5 (0.03)	3.5 (0.03)	70.1 (0.5)	70.1 (0.6)
1–5	161.9 (3.6)	162.2 (3.6)	126.6 (2.5)	126.2 (2.5)	1.30 (0.03)	1.31 (0.03)	3.6 (0.04)	3.6 (0.04)	70.0 (0.7)	69.9 (0.7)
6–10	169.9 (3.8)	170.7 (3.9)	127.6 (2.6)	127.2 (2.7)	1.34 (0.03)	1.36 (0.03)	3.7 (0.04)	3.7 (0.04)	69.7 (0.7)	69.8 (0.8)
11–15	173.7 (3.8)	172.9 (3.9)	130.8 (2.7)	130.3 (2.7)	1.34 (0.03)	1.34 (0.03)	3.7 (0.04)	3.7 (0.04)	69.4 (0.8)	69.3 (0.8)
16–20	183.9 (4.0)	183.6 (4.1)	133.9 (2.8)	133.5 (2.8)	1.40 (0.03)	1.40 (0.03)	3.7 (0.04)	3.7 (0.04)	68.2 (0.8)	68.3 (0.8)
>20	182.1 (4.4)	180.7 (4.4)	136.4 (3.0)	136.0 (3.0)	1.35 (0.03)	1.35 (0.03)	3.8 (0.05)	3.8 (0.05)	68.8 (0.9)	68.8 (0.9)
***P*-trend**	0.003	0.003	0.17	0.11	0.32	0.46	0.23	0.23	0.05	0.07
Per 5 years	2.5 (0.8)	2.5 (0.8)	0.8 (0.6)	0.9 (0.6)	0.01 (0.01)	0.004 (0.007)	0.01 (0.01)	0.01 (0.01)	−0.3 (0.2)	−0.3 (0.2)

Model 1 simultaneously adjusts for BMI at year 25 (kg m^{-2}) and duration of overall obesity (years) as well as age, sex, race, educational attainment, study center, current smoking, and average physical activity and alcohol intake during follow-up. Model 2 adjusts additionally for use of antihypertensive medication, diabetes, heart rate, and average systolic blood pressure during follow-up.
[a]Overall obesity defined as a body mass index ≥30 kg m^{-2}.

abdominal obesity, and the duration of abdominal obesity except there was no association of age at baseline with the degree of abdominal adiposity or duration of abdominal obesity, and women were more likely to have a longer duration of abdominal obesity (data not shown).

Mean (SD) LV mass, LV end-diastolic volume, LV mass-to-volume ratio, LA dimension, and ejection fraction were 164.0 (48.1) g, 126.0 (30.3) ml, 1.32 (0.32) g/ml, 3.66 (0.47) cm, and 69.6% (7.8), respectively. A greater degree of overall adiposity at year 25 was strongly associated with a greater LV mass, LV end-diastolic volume, LV mass-to-volume ratio, and LA dimension (*P*-trend <0.001, for all) (Table 2). With each 5-U higher BMI, an 11.4 g greater LV mass, a 5.9 ml greater LV end-diastolic volume, a 0.04 g ml^{-1} higher LV mass-to-volume ratio, and a 0.2 cm larger LA was observed. It was also associated with a higher ejection fraction (0.5% higher with each 5-U higher BMI; *P*-trend 0.03). In contrast, the duration of overall obesity was associated with a greater LV mass (*P*-trend 0.003) and a lower ejection fraction that approached statistical significance (*P*-trend 0.05). With each additional 5-years of overall obesity, a 2.5 g greater LV mass and a 0.3% lower ejection fraction was observed. Adjustment for antihypertensive medication use, heart rate, average systolic blood pressure, and diabetes during follow-up had minimal influence on these associations (Table 2; model 2). Results were also consistent when LV mass was indexed to height$^{2.7}$ (data not shown).

A greater degree of abdominal adiposity at year 25 was strongly associated with a greater left ventricular mass, LV end-diastolic volume, LV mass-to-volume ratio, and LA dimension (*P*-trend <0.001, for all) (Table 3). With each 10 cm higher waist circumference, an 11.0 g greater LV mass, a 4.0 ml greater LV end-diastolic volume, a 0.05 g ml^{-1} higher LV mass-to-volume ratio, and a 0.2 cm larger LA was observed. Similarly, a greater degree of abdominal adiposity was associated with a higher ejection fraction that approached statistical significance (0.4% higher with each 10 cm higher waist circumference; *P*-trend 0.06). In contrast, the duration of abdominal obesity was associated with a greater LV end-diastolic volume only (*P*-trend 0.03). Adjustment for antihypertensive medication use, heart rate, average systolic blood pressure, and diabetes during follow-up had minimal influence on these associations (Table 3; model 2).

Associations did not vary by race-sex except for the association of the duration of overall obesity with LV mass-to-volume ratio (*P*-interaction 0.007) and the degree of overall adiposity with LA dimension (*P*-interaction <0.001). However, similar to findings in the total sample, no association of the duration of overall obesity with LV mass-to-volume ratio was observed within each race-sex group [slope: 0.01, −0.02, 0.01, and 0.01 for black men, black women, white men, and white women, respectively (*P* >0.2, for all), per 5-year longer duration of overall obesity]. Measures of association were in a similar direction for the association of the

TABLE 3 Mean (standard error) left ventricular mass, left ventricular end-diastolic volume, left atrial dimension, and ejection fraction according to waist circumference at year 25 and duration of abdominal obesity[a] during follow-up, The CARDIA Study ($n = 2,547$)

	Left ventricular mass (g)		Left ventricular end-diastolic volume (ml)		Left ventricular mass-to-volume ratio (g ml^{-1})		Left atrial dimension (cm)		Ejection fraction (%)	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Waist circumference quintiles[b]										
I	151.6 (3.3)	150.7 (3.4)	124.8 (2.3)	123.2 (2.4)	1.23 (0.03)	1.24 (0.03)	3.5 (0.03)	3.4 (0.04)	68.5 (0.7)	68.2 (0.7)
II	166.1 (3.2)	164.6 (3.3)	133.7 (2.2)	132.1 (2.3)	1.26 (0.03)	1.27 (0.03)	3.6 (0.03)	3.6 (0.04)	69.6 (0.7)	69.3 (0.7)
III	170.3 (2.9)	168.8 (3.0)	133.9 (2.0)	132.7 (2.1)	1.30 (0.02)	1.30 (0.02)	3.8 (0.03)	3.7 (0.03)	69.7 (0.6)	69.5 (0.6)
IV	175.6 (2.1)	174.8 (2.3)	131.7 (1.5)	131.2 (1.6)	1.36 (0.02)	1.36 (0.02)	3.8 (0.02)	3.8 (0.02)	69.5 (0.4)	69.3 (0.5)
V	189.0 (2.1)	189.1 (2.2)	132.8 (1.4)	133.2 (1.6)	1.44 (0.02)	1.44 (0.02)	3.9 (0.02)	3.9 (0.02)	70.0 (0.4)	70.0 (0.5)
***P*-trend**	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.06	0.04
Per 10 cm	11.0 (1.0)	11.1 (1.0)	4.0 (0.7)	4.6 (0.1)	0.05 (0.008)	0.04 (0.008)	0.2 (0.01)	0.2 (0.01)	0.4 (0.2)	0.5 (0.2)
Duration of abdominal obesity (years)[b]										
0	163.5 (1.7)	163.8 (2.1)	122.2 (1.2)	121.6 (1.4)	1.36 (0.01)	1.37 (0.02)	3.6 (0.02)	3.6 (0.02)	69.7 (0.3)	69.5 (0.4)
1–5	169.9 (2.6)	169.2 (2.8)	129.4 (1.8)	128.5 (1.9)	1.33 (0.02)	1.34 (0.02)	3.7 (0.03)	3.7 (0.03)	69.7 (0.5)	69.5 (0.6)
6–10	164.9 (3.0)	164.4 (3.2)	126.9 (2.1)	126.1 (2.2)	1.32 (0.02)	1.32 (0.03)	3.7 (0.03)	3.7 (0.03)	69.7 (0.6)	69.6 (0.7)
11–15	168.3 (3.4)	167.4 (3.5)	131.7 (2.4)	130.9 (2.4)	1.29 (0.03)	1.30 (0.03)	3.7 (0.04)	3.7 (0.03)	69.3 (0.7)	69.1 (0.7)
16–20	177.7 (3.7)	175.8 (3.7)	137.4 (2.5)	136.0 (2.6)	1.33 (0.03)	1.33 (0.03)	3.8 (0.04)	3.7 (0.04)	68.3 (0.7)	68.1 (0.8)
>20	178.9 (4.5)	176.8 (4.5)	140.7 (3.1)	139.8 (3.1)	1.29 (0.04)	1.29 (0.04)	3.8 (0.05)	3.7 (0.05)	69.9 (0.9)	69.8 (0.9)
***P*-trend**	0.13	0.19	0.03	0.04	0.38	0.32	0.90	0.94	0.15	0.17
Per 5 years	1.4 (0.9)	1.2 (0.9)	1.3 (0.6)	1.3 (0.6)	−0.006 (0.01)	−0.007 (0.01)	0.001 (0.01)	−0.001 (0.01)	−0.3 (0.1)	−0.2 (0.2)

Model 1 simultaneously adjusts for waist circumference at year 25 (cm) and duration of abdominal obesity (years) as well as age, sex, race, educational attainment, height, study center, current smoking, and average physical activity and alcohol intake during follow-up.
[a]Abdominal obesity defined as a waist circumference >102 cm in men and >88 cm in women.
[b]Cut-points were 86.0, 92.5, 98.3, and 105.5 cm for men and 74.3, 81.5, 89.5, and 97.5 cm for women.

degree of overall adiposity with LA dimension [slope: 0.17, 0.09, 0.01, 0.19 for black men, black women, white men, and white women, respectively (P <0.001, for all), per 5-U higher BMI].

We observed similar results when we further adjusted for weight change over the follow-up period (quintiles) and when we imputed missing values using all available measures of BMI and waist circumference during follow-up on the sample of 2,547 participants (data not shown).

Discussion

In this community-based sample of adults recruited and followed largely during the obesity epidemic in the United States, a greater degree of overall and abdominal adiposity were each strongly associated with numerous measures of cardiac structure, including a greater left ventricular mass, left ventricular end diastolic volume, and left atrial dimension. A greater LV mass-to-volume ratio suggested an adverse pattern of concentric LV remodeling with a greater degree of adiposity. A longer duration of overall obesity, on the other hand, was strongly associated with a greater LV mass. These findings were independent of sociodemographic characteristics, lifestyle behaviors, and other cardiovascular risk factors. In addition, results did not vary consistently between white and black men and women. These results suggest that a greater degree of adiposity is strongly associated with concentric LV remodeling in midlife, while the cumulative effects of a longer duration of overall obesity during young adulthood may contribute to concentric remodeling predominately by increasing LV mass.

Findings of the current study suggest that the degree of adiposity may be a more important determinant of cardiac structure than a longer duration of obesity. This was evidenced by strong dose-response associations of the degree of overall and abdominal adiposity with nearly all measures of LV structure and LA size. Obesity has long been considered as a state of chronic volume overload because the heart is required to circulate blood through the large depot of adipose tissue (23). A greater degree of adiposity contributes to a higher cardiac output and workload, and a greater LV mass (24,25). Early studies suggested that a greater degree of adiposity was associated with eccentric LV remodeling (26). However, the results of the current study as well as a number of other recent studies suggest a pattern of concentric LV remodeling whereby the LV mass may increase to a greater extent than cavity size (higher LV mass-to-volume ratio) (8,27).

Studies estimating the association of a longer duration of obesity on cardiac structure have been mixed. These studies have relied exclusively on the self-report of body weight at previous ages to determine the duration of obesity as opposed to the objective assessment

in the current study, and did not account for the degree of adiposity. In a small, clinic-based sample of morbidly obese patients prior to weight loss surgery, Alpert *et al*. (11) showed the duration of morbid obesity correlated significantly with a higher LV mass and poorer LV systolic function. In a sample of 35 obese patients, a longer duration of obesity was associated with LV enlargement and wall thickening independent of body weight (12). However, among 109 overweight and obese adults attending a weight management center, the duration of obesity showed no association with numerous measures of LV structure and function (14). In the current study, we found a longer duration of overall obesity was associated with a greater LV mass independent of the degree of adiposity, potential confounders, and intermediate factors. Our findings suggest that while the degree of adiposity may be a more important determinant of cardiac structure in midlife, the long-term cumulative effects of sustained obesity and metabolic dysregulation during young adulthood may also contribute to concentric remodeling primarily by increasing LV mass.

In the current study, we found significant, positive associations of the degree of overall and abdominal adiposity with ejection fraction that were independent of the duration of obesity, potential confounders, and risk factors. Conversely, we observed an inverse association of a longer duration of overall obesity with a lower ejection fraction that approached statistical significance. Findings from available studies of the degree of adiposity with LV systolic function have varied considerably suggesting that ejection fraction is lower (28), similar (29), or higher (30) among obese subjects as compared to those who are not obese. Existing studies of the duration of obesity have generally shown consistent inverse associations of prolonged obesity with reduced fractional shortening (11), stroke volume (12), and ejection fraction (13). Findings from the current study suggest that there may be a compensatory increase in systolic function in middle-age with a greater degree of adiposity that may subsequently become impaired with a longer duration of obesity. Future studies are needed to confirm these findings particularly with more sensitive indicators of LV contractile function.

In addition to the increased cardiac work load and resultant increased LV mass that occurs to meet the enhanced metabolic demands of both lean and fat mass with obesity, a number of other potential mechanisms may help to explain the association of a greater degree of adiposity with structural and functional changes in the heart. Intra-abdominal fat located in close proximity to the portal circulation may mediate concentric LV remodeling by secreting a number of proinflammatory cytokines that may play a role in the myocardial remodeling process by directly influencing hypertrophy, fibrosis, and ultimately contractility (31,32). Hyperinsulinemia and insulin resistance, which may promote myocardial hypertrophy via the growth-stimulating effects of insulin, may also mediate the increased LV mass and LA size in obesity (14,33). Obstructive sleep apnea may also contribute to LV structural changes by exacerbating daytime and nighttime hypertension, increased sympathetic tone, and chronic hypoxemia (34). Additional mechanisms that may explain, at least in part, the association of a greater degree of adiposity with LV concentric remodeling include increases in leptin and angiotensin II, and reductions in adiponectin (35-37). The cumulative effects of these hemodynamic and metabolic changes as a result of prolonged obesity may also help to at least partially explain the association of a longer duration of overall obesity with increases in LV mass and impaired systolic function over time.

Strengths of the current study include a community-based sampling method; cohort recruitment and follow-up largely during the obesity epidemic of the last three decades; a biracial cohort; extensive data on potential confounders; a large sample size well balanced with respect to age, sex, race, and education that increased precision and permitted simultaneous adjustment and stratification by multiple variables; repeated assessments of BMI, waist circumference, and potential confounding factors; a high retention rate; and the standardized data collection protocols and rigorous quality control of the CARDIA study. Nevertheless, three limitations deserve mention. First, our study relied on relatively simple estimates of anthropometry that are unable to distinguish between fat and fat-free mass. However, these measures are reliable, efficient, cost-effective, and widely applicable for research in large studies and clinical practice. Second, our estimation of the duration of overall and abdominal obesity during follow-up was based on the measurement of BMI and waist circumference, respectively, every 2-5 years. It is likely that a more frequent number of assessments would have led to a more accurate estimation of the duration of obesity during follow-up. Third, since our study collected data over a 25-year follow-up period, some participants were missing at least one eligible measurement of BMI and waist circumference. However, we noted similar results between our multiple imputed datasets and our primary dataset.

In conclusion, in this community-based longitudinal cohort study of adults recruited and followed during the obesity epidemic over the last three decades in the United States, we found the degree of overall and abdominal adiposity to be important factors associated with a greater LA dimension and a pattern of LV concentric remodeling. These findings were independent of the duration of obesity and numerous potential confounding factors and cardiovascular risk factors. A longer duration of overall obesity, on the other hand, was associated with a greater left ventricular mass and a trend for a lower ejection fraction. Thus, these findings suggest that cardiac remodeling throughout young adulthood results largely as a consequence of a greater degree of adiposity, while the cumulative effects of a longer duration of overall obesity may contribute to concentric remodeling predominately by increasing LV mass. Future public health interventions focused on cardiovascular disease prevention should focus on younger populations in order to prevent or at least delay the onset of obesity. O

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